Australian and New Zealand College
of Anaesthetists and Faculty of Pain Medicine

ACUTE PAIN MANAGEMENT: SCIENTIFIC EVIDENCE

Fourth Edition 2015

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Copyright information for Tables 10.1 and 10.2

Disclaimer

This document aims to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice recommendations. It is designed to provide information based on the best evidence available at the time of publication to assist in decision-making. The information provided is not intended to over-ride the clinical expertise of health care professionals and its use is subject to the clinician's judgement and the patient's preference in each individual case. There is no substitute for the skilled assessment of each individual patient's health status, circumstances and perspectives, which health care practitioners will then use to select the treatments that are relevant and appropriate to that person.

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ACUTE PAIN MANAGEMENT: SCIENTIFIC EVIDENCE

AUSTRALIAN AND NEW ZEALAND
COLLEGE OF ANAESTHETISTS AND
FACULTY OF PAIN MEDICINE

4TH EDITION

FOREWORD

Mounting evidence that tissue injury often results in changes to the nervous system function has provided a new understanding of mechanisms that explain how acute pain can often lead to chronic pain (Gilron 2014; Shipton 2014b). Most patients will recover and return to their normal life after an acute injury or surgery, yet others will suffer chronic pain and long-lasting disabilities (Lavand'homme 2011).

There are many short-term and long-term consequences of inadequately treated acute pain. These include hyperglycaemia, insulin resistance, an increased risk of infection, decreased patient comfort and satisfaction and the development of chronic pain (Reardon 2015). The transition of acute postoperative or post-traumatic pain to pathological chronic pain is a complex and poorly understood process (Shipton 2014a). Biological, psychological, and social-environmental factors and the known polymorphisms in human genes are all involved in perpetuating the pain (Walsh 2011).

Anaesthetists and other physicians treating acute trauma play a pivotal role in the identification of factors that may lead to suboptimal pain control in the perioperative or post-traumatic period (Shipton 2014a). Following acute trauma or surgery, multimodal pharmacological strategies, psychological strategies, modified surgical techniques, procedure-specific postoperative pain management, and enhanced postoperative recovery programs are all used to prevent persistent acute postprocedure pain (Shipton 2014b).

According to modern practice standards, clinical activity is expected to be reliable based on the current best evidence (Vidaeff, in press). Evidence, in general, is anything presented in support of an assertion or endeavour (Vidaeff, in press). In medicine this is usually based on peer-reviewed, published scientific literature. Evidence-based medicine provides a framework for clinical decision-making processes. It integrates the evidence with clinical experience and individualised patient factors (Macintyre 2011). However, evidence can be constrained due to its quality, clinical significance and application.

Acute pain management has moved away from symptom management to the creation of the discipline of acute pain medicine. This discipline is rapidly changing. Valid and pragmatic assessment of acute pain is essential for effective pain management (Gordon 2015).

This is the fourth edition of Acute Pain Management: Scientific Evidence. The first three were published in 1999, 2005 and 2010, respectively. The first edition was written by a multidisciplinary committee headed up by Professor Michael Cousins of the University of Sydney. The second and third editions were edited by working parties chaired by Associate Professor Pam Macintyre from the University of Adelaide. The third edition was endorsed internationally by the International Association for the Study of Pain, and by Colleges, Societies and Associations from the United Kingdom, Ireland, Hong Kong, Singapore and Malaysia, and recommended to its members by the American Academy of Pain Medicine.

The Australian National Pain Strategy grew out of the Australian National Pain Summit in March 2010. Two of its key goals are best-practice evidence-based care and quality improvement and evaluation (painaustralia 2010). This book promotes both these goals.

In August, 2010 the Faculty of Pain Medicine's foundation dean and a past ANZCA president, Professor Cousins, chaired the first International Pain Summit in conjunction with the International Association for the Study of Pain's World Congress in Montreal in Canada (Cousins 2011). An important outcome of this summit was the "Declaration of Montreal", which called for "access to pain management as a fundamental human right" (Cousins 2011). This included the management of acute pain.

This fourth edition sums up the evidence currently available to assist health professionals in the management of acute pain. Additional literature has been reviewed from August 2009 to August 2014. Levels of evidence have been documented according to the National Health and Medical Research Council (NHMRC) designation (NHMRC 1999). The Jadad scoring instrument was used to score the quality of all randomised controlled trials (RCTs) (Jadad 1996). Key

messages for each topic are specified with the highest level of evidence available to support them, or with a symbol showing that they are based on clinical experience or expert opinion.

The volume of medical knowledge is doubling every 8 years (Carroll 2011). Such was the enormity of the challenge faced by Prof Stephan Schug and the other members of the editorial subgroup of the working group (A/Prof Greta Palmer, A/Prof David A Scott, Dr Richard Halliwell and Dr Jane Trinca).

This fourth edition is a tribute to their efforts and to the fortitude and strategic leadership of their chair, Prof Stephan Schug. The contributions of Dr Mark Rockett (Faculty of Pain Medicine, Royal College of Anaesthetists), Professor Karen Grimmer (University of South Australia), the members of the multidisciplinary consultative committee and the large panel of contributors are acknowledged as well.

The third edition has created demand from healthcare professionals across the globe. It is widely used in western Europe, and in North America and South America. It has set the standard in acute pain medicine, and is recognised as probably the finest text on this subject in the world. Both the Australian and New Zealand College of Anaesthetists and its Faculty of Pain Medicine are immensely proud of its prestige.

In its milestone report Crossing the Quality Chasm, the United States Institute of Medicine defined patient-centred care as ''care that is respectful of and responsive to individual patient preferences, needs and values'' (National Research Council 2001; Meissner 2015). This reminds us that despite the best available evidence, patient values and involvement should always guide all our clinical decisions (National Research Council 2001; Meissner 2015).

These remain exciting times in acute pain medicine. This fourth edition has emphasised the role played by acute pain management as a vital component of perioperative and post-traumatic care. Our responsibility as anaesthetists and specialist pain medicine physicians is to understand and modify the pathogenic mechanisms of the undesirable responses to surgical and traumatic injury (Kehlet, in press). Only in this way will we optimise acute pain management and boost recovery and improve safety.

We are indebted to Professor Schug and his team for providing us with an update of the scientific evidence. The challenge is for acute pain services around the world to develop their own policies and standard operating procedures for acute pain management based on this book.

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INTRODUCTION

This is the fourth edition of the document *Acute Pain Management: Scientific Evidence*. The first edition was written by a multidisciplinary committee headed by Professor Michael Cousins and published by the National Health and Medical Research Council (NHMRC) in 1999.

The second edition was written by multiple contributors and a working group chaired by A/Prof Pam Macintyre. It was approved by the NHMRC and published by the Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) in 2005. It was also endorsed by other major organisations worldwide.

The third edition was written by multiple contributors and a working group chaired by A/Prof Pam Macintyre. It was approved by the NHMRC and published by ANZCA and its FPM in 2010. It was also endorsed by other major organisations — the International Association for the Study of Pain (IASP), the Royal College of Anaesthetists and its Faculty of Pain Medicine, the Australian Pain Society, the Australasian Faculty of Rehabilitation Medicine, the College of Anaesthesiologists of the Academies of Medicine of Malaysia and Singapore, the College of Intensive Care Medicine of Australia and New Zealand, the Faculty of Pain Medicine of the College of Anaesthetists of Ireland, the Hong Kong College of Anaesthesiologists, the Hong Kong Pain Society, the Malaysian Association for the Study of Pain, the New Zealand Pain Society, the Pain Association of Singapore, the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Psychiatrists and the Royal Australasian College of Surgeons — and recommended to its members by the American Academy of Pain Medicine.

Guidelines should be revised as further evidence accumulates (ideally every 5 years), and as there has been a continuing and substantial increase in the quantity and quality of information available about acute pain management, it was seen as timely to reassess the available evidence aiming for a release of the new document in 2015. ANZCA and the FPM therefore again took responsibility for revising and updating the document to its fourth edition. As for the third edition of this document, endorsement will be sought from a number of key organisations.

A working group was convened to coordinate and oversee the development process (see Appendix A). An editorial subgroup of the working group (Prof Stephan A Schug [Chair], A/Prof Greta M Palmer, A/Prof David A Scott, Dr Richard Halliwell, Dr Jane Trinca) coordinated the development process and edited and/or wrote the sections. The working group also included Dr Mark Rockett, nominated by the Faculty of Pain Medicine, Royal College of Anaesthetists in the United Kingdom, and Prof Karen Grimmer from the University of South Australia, who had been the NHMRC-appointed Guidelines Assessment Register representative for the second edition and provided expert advice on the methodology including the use of evidence-based findings and the application of NHMRC criteria for this edition.

A large panel of contributors was appointed to draft sections of the document and a multidisciplinary consultative committee was chosen to review the draft of the document and contribute more broadly as required (see Appendix A). To ensure general applicability and inclusiveness, there was a very wide range of experts among the contributors and on the multidisciplinary committee, including medical, nursing, allied health and complementary medicine professionals and consumers.

Acute Pain Management: Scientific Evidence covers a wide range of clinical topics. The aim of the document is, as with the first three editions, to combine a review of the best available evidence for acute pain management with current clinical and expert practice, rather than to formulate specific clinical practice guidelines. Accordingly, the document aims to summarise the substantial amount of evidence currently available for the management of acute pain in a concise and easily readable form. New and updated content has been incorporated into the content of the previous edition of the book.

This document has been written primarily for medical practitioners and clinicians who are engaged with managing and supporting patients with acute pain. It may also be accessed by consumers who may find the content useful. As always, we would encourage patients

to discuss the management of their individual health needs with their doctor and to seek specialist pain advice and treatment if appropriate.

A detailed description of the methodology used to generate this document can be found in Appendix B. The following summarises the most important information on the methodology.

Review of the evidence

This document is a revision of the third edition of *Acute Pain Management: Scientific Evidence* published in 2010. Therefore most of the new evidence included in this fourth edition has been published from August 2009 onwards, which was the cut-off date for literature inclusion in the third edition. Literature was considered when published between this date and the cut-off date for this fourth edition (August 2014). However, in rare circumstances, references published after this cut-off were considered but only if of high relevance and encountered in the editorial process. Moreover, evidence-based guidelines had been published independently by a number of organisations in the areas of acute back and musculoskeletal pain and recommendations relevant to the management of acute pain were drawn directly from these.

Levels of evidence

Levels of evidence were documented according to the NHMRC designation (NHMRC 1999 **GL**).

Levels of evidence	
I	Evidence obtained from a systematic review of all relevant randomised-controlled trials (RCTs)
II	Evidence obtained from at least one properly designed randomised-controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post test or pretest and post-test
Clinical practice points	
☑	Recommended best practice based on clinical experience and expert opinion

Quality scoring

In refinement of the methodology used for the third edition, evidence was subjected to quality scoring and other types of references identified to enhance the value of the information provided.

Systematic reviews and meta-analyses

- Reviews performed by the Cochrane Collaboration are identified as [Cochrane] in the text eg (Derry 2013 **Level I** [Cochrane]);
- Reviews that overtly state that the review conformed with an evidence-based minimum set of items for reporting referred to as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati 2009 **GL**) are identified as PRISMA eg (Moore 2014 **Level I** [PRISMA]);
- Reviews that overtly state that the review conformed with standards previously published as Quality of Reporting of Meta-analyses (QUOROM) (Moher 1999 **GL**), a precursor of PRISMA, are identified as QUOROM eg (Macedo 2006 **Level I** [QUOROM]);
- Non-Cochrane meta-analyses that did not provide evidence of using PRISMA or QUOROM quality and reporting methods are only labelled Level I eg (Thorlund 2014 **Level I**).

For all systematic reviews and meta-analyses, the number of RCTs for Level I and the number of studies for all other levels is reported as well as the number of subjects included in these,

if reported or immediately obvious eg (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473); if this is not the case, the term unspecified is used eg (Hughes 2011 **Level IV SR**, 5 studies, n unspecified).

Randomised-controlled trials

The Jadad scoring instrument was used to score the quality of all RCTs (Jadad 1996). The Jadad Score (JS) ranges from 0 (lowest quality) to 5 (highest quality) and is based on randomisation and blinding methods used and accurate accounting of study participants.

In addition to the Jadad score, the number of patients randomised (prior to dropouts) is reported for all Level II references eg (Chan 2010 **Level II**, n=4,484, JS 5) including those carried forward from the third edition.

Other evidence

No quality evaluation was undertaken for lower ranked evidence (**Level III** and **Level IV**), when this was the highest available level of evidence. However, the number included is reported if the size of the study subtracts from, or adds to the quality of, the evidence eg (Morton 2010 **Level IV**, n=5,065).

Identification of other types of references

Narrative reviews containing such evidence are identified by "NR" following the reference eg (Graham 2013 **NR**). Other studies were included where relevant and identified by a research identifier following the reference. Thus readers will find CR (for case report) eg (Madadi 2010 **CR**), GL for clinical practice guidelines eg (Kowalski 2011 **GL**), BS if presenting basic science or animal data eg (LaCrois-Fralish 2011 **BS**), PK if presenting pharmacokinetic studies eg (Holford 2012 **PK**) and EH if presenting human experimental data eg (Saxena 2013 **EH**). The latter two were also assigned an evidence level in line with NHMRC hierarchy if suitable eg (Williams 2002 **Level II PK**, n=96, JS 4).

Conflicting evidence

If evidence was consistent, the most recent, highest hierarchy and highest quality references were used. If evidence was conflicting, the same approach was taken (identifying highest level, highest quality evidence); however examples were given of differences within the literature so that readers could appreciate the ongoing debate. In some instances, particularly in acute pain management in various patient populations, evidence was limited to case reports only, which was made clear in the document as the best available evidence in this instance.

Key messages

Key messages for each topic are given with the highest level of evidence available to support them, with levels of evidence documented according to the NHMRC designation. As for the previous two editions of this document, clinical practice points have been added with a symbol indicating that they are based on clinical experience or expert opinion. .

Key messages are presented in order of level of evidence from the highest to the lowest. Key messages referring to information extracted from Cochrane meta-analyses were marked "Level I [Cochrane Review]", and these were listed first, followed by those marked "Level I [PRISMA]" and "Level I [QUOROM]".

There is no standard approach to updating wording or strength of evidence of existing guideline recommendations (Vernooij 2014 **GL**). As in the third edition, an indication of how the key messages in this fourth edition relate to those in the third edition is provided. An adapted version of the system used by Johnston et al (Johnston 2003) to reflect the implications of new evidence on clinical recommendations was therefore used as previously. Where the new evidence led to reversal of a conclusion and key message, this was noted in the text.

Review and revision of key messages

New	New evidence leads to new key message(s).
Unchanged	The new evidence is consistent with the data used to formulate the original key message. The key message in the previous edition remains unchanged.
Strengthened	The new evidence is consistent with the data used to formulate the original key message. The key message in the previous edition remains unchanged or expanded. The level of evidence and/or content of the key message in the previous edition has been strengthened to reflect this additional evidence.
Weakened	The new evidence is inconsistent with the data used to inform the original key message(s). However, the new evidence does not alter the key message but weakens the level of evidence.
Qualified	The new evidence is consistent with the data used to formulate the original key message. The key message in the previous edition remains unchanged but applicability may be limited to specific patient groups/ circumstances.
Reversed	The new evidence is inconsistent with the data used to inform the original key message(s). The strength of the new evidence alters the conclusions of the previous edition.
NB	*Clinical and scientific judgement informed the choices made by the Working Group members; there was no mandatory threshold of new evidence (eg number of studies, types of studies, magnitude of statistical findings) that had to be met before classification to categories occurred.* *The first letter of each of the words (**N**ew, **U**nchanged etc) was used to denote the changes (if any) from the previous edition of this document.*

Acknowledgements

The production of a document such as this requires a considerable amount of time over a long period and the generous input of many. All contributions were honorary and the time contributed freely by the members of the Working Group and the many contributors needs to be acknowledged in particular. Although institutional support in terms of time and resources came from a number of centres, special thanks need to go to the School of Medicine and Pharmacology of the University of Western Australia and the Department of Anaesthesia and Pain Medicine of Royal Perth Hospital for providing sabbatical leave to the Chair of the Working Group; without this support the development of this edition would have not been possible. The support of many hospital departments, including Departments of Anaesthesia throughout Australia and New Zealand, is difficult to quantify but gratefully acknowledged.

Special thanks are also extended to Peta Gjedsted at the Anaesthesiology Unit of the University of Western Australia for her extensive reference management, Jenny Ramson at Ampersand Health Science Writing for her expert editorial input and the staff at ANZCA and the FPM. The ANZCA library was a valuable resource, in particular for provision of difficult to access references. Finally, thanks to Faculty staff Helen Morris, Penny McMoran and Cassandra Sparkes for their ongoing input to the process.

Stephan Schug

On behalf of the Working Group of the Australian New Zealand College of Anaesthetists and its Faculty of Pain Medicine

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SUMMARY OF KEY MESSAGES

A description of the levels of evidence and associated symbols can be found in the Introduction (see pages viii to ix).

1. PHYSIOLOGY AND PSYCHOLOGY OF ACUTE PAIN

Psychological aspects of acute pain

1. High fear avoidance beliefs in patients with back pain of less than 6 months duration are associated with poor outcomes, which may be improved by treatment approaches aimed at fear avoidance (**N**) (**Level I** [PRISMA]).
2. There is significant association between anxiety, pain catastrophising (**N**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**N**) (**Level IV SR)** and the subsequent development of chronic postsurgical pain.
3. There is a significant association between high levels of catastrophising in acute and subacute back pain and pain and disability at later points of time (**N**) (**Level III-2 SR**).
4. Preoperative anxiety (**S**) (**Level IV SR**), catastrophising (**S**) (**Level IV SR**) and depression (**U**) (**Level IV**) are associated with higher postoperative pain intensity.
5. Preoperative anxiety and depression are associated with an increased number of PCA demands and dissatisfaction with PCA (**U**) (**Level IV**).

☑ Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope **(U).**

Placebo and nocebo effects in acute pain

1. Placebo effects for all clinical conditions are small but consistently positive. They are more prominent, although highly variable, in studies of pain (**N**) (**Level I** [Cochrane Review]).
2. Nocebo effects in studies of pain are of moderate to large size and of high variability (**N**) (**Level I** [PRISMA]).
3. Trials aimed at studying placebo effects demonstrate larger placebo effects than those assessing responses in placebo-control groups (**N**) (**Level I** [QUOROM]).
4. Analgesic placebo effects are based upon multiple neurobiological mechanisms, including involvement of endogenous opioid, cholecystokinin (**N**) (**Level II**) and endogenous cannabinoid systems (**N**) (**Level III-1**).
5. Analgesic placebo effects are based upon multiple psychological determinants including expectancy, classical conditioning and social and observational learning (**N**) (**Level II**).
6. Placebo and nocebo effects have significant influence on the efficacy of analgesics (**N**) (**Level II**)

☑ Placebo effects are the consequence of the psychosocial context (or treatment ritual) on the patient's mind, brain and body (**N**).

☑ Placebo effects occur in routine clinical care even when no placebo is given. The outcome of a treatment is attributable to both the treatment itself and the contextual (or placebo) component (**N**).

☑ Nocebo effects occur in routine clinical care and are seen as an increased pain response to a painful stimulus or the development of adverse effects not caused by, or separate from, the intervention (**N**).

☑ Ethical harnessing of placebo and minimisation of nocebo effects will improve response to clinical management interventions (**N**).

Progression of acute to chronic pain

1. Perioperative ketamine reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
2. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review]).
3. Following breast cancer surgery, paravertebral block reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
4. Sparing of the intercostobrachial nerve during mastectomy does not decrease chest wall hypersensitivity (**N**) (**Level I** [PRISMA]).
5. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain but an increase in chronic pain (**S**) (**Level I**).
6. There is significant association between anxiety, pain catastrophising (**N**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**N**) (**Level IV SR**) and the subsequent development of chronic postsurgical pain.
7. Other risk factors that predispose to the development of chronic postsurgical pain include the severity of presurgical chronic pain and postsurgical acute pain and intraoperative nerve injury (**S**) (**Level IV SR**).
8. Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean delivery (**U**) (**Level III-2**).
9. Chronic postsurgical pain is common and may lead to significant disability (**S**) (**Level IV**).
10. Chronic postsurgical pain often has a neuropathic component (**S**) (**Level IV**).

☑ Although pregabalin and gabapentin may have an effect in preventing chronic postsurgical pain, considerable uncertainty exists regarding efficacy with contradictory meta-analyses of few, usually small studies with a large degree of heterogeneity (**N**).

Pre-emptive and preventive analgesia

1. The timing of a single analgesic intervention (preincisional rather than postincisional), defined as pre-emptive analgesia, has a significant effect on postoperative pain relief as seen with epidural analgesia (**U**) (**Level I**).
2. There is evidence that some analgesic interventions have an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the medicine, defined as preventive analgesia (**S**) (**Level I**).
3. NMDA-receptor antagonists (ketamine) show preventive analgesic effects (**S**) (**Level I**).
4. Local anaesthetic administration, either perineural or systemic, shows preventive analgesic effects (**S**) (**Level I**)

☑ In clinical trials assessing acute postoperative pain for many systemic medicines, the range of doses administered, the variable durations of follow-up and variable half-lives following infusion or repeated dosing means that “early” preventive effects, although possible, are difficult to discern from persistence of direct pharmacological effects (**N**).

Adverse physiological and psychological effects of acute pain

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**S**) (**Level I** [PRISMA]).

☑ Acute pain and injury of various types are inevitably interrelated and, if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (**U**).

Genetics and acute pain

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine, oxycodone and tramadol (**Q**) (**Level II**).
2. The mu opioid receptor OPRM1 polymorphism is unlikely to be clinically relevant as a single gene mutation in Caucasian populations and is more likely to be of clinical relevance in Asian populations (**N**) (**Level III-2** SR).
3. CYP2D6 ultrarapid metabolisers are at increased risk of codeine and tramadol toxicity (**N**) (**Level IV**).

☑ Genetic polymorphisms contribute to the wide interindividual variability in plasma concentrations of a given dose of methadone (**U**).

2. ASSESSMENT AND MEASUREMENT OF PAIN AND PAIN TREATMENT

Assessment and measurement

1. Regular assessment of pain leads to improved acute pain management (**U**) (**Level III-3**).
2. There is good correlation between the visual analogue and verbal numerical rating scales (**S**) (**Level IV SR**).
3. Appropriate assessments (including screening tools) are required to determine the presence of neuropathic pain (**N**) (**Level IV**).

☑ Self-reporting of pain should be used whenever appropriate as pain is by definition a subjective experience (**U**).

☑ The pain measurement tool chosen should be appropriate to the individual patient and the clinical context (eg intensive care, ward, community). Developmental, cognitive, emotional, language and cultural factors should be considered (**S**).

☑ Scoring should incorporate different components of pain including the functional capacity of the patient. In the postoperative patient this should include static (rest) and dynamic (eg pain on sitting, coughing) pain (**U**).

☑ Uncontrolled or unexpected pain requires a reassessment of the diagnosis and consideration of alternative causes for the pain (eg new surgical/ medical diagnosis, neuropathic pain) (**U**).

Outcome measures in acute pain management

☑ Multiple outcome measures are required to adequately capture the complexity of the pain experience and how it may be modified by pain management interventions (**U**).

3. PROVISION OF SAFE AND EFFECTIVE ACUTE PAIN MANAGEMENT

Education

1. There is no good evidence in favour of general education for acute neck pain having significant effects on any relevant outcomes (**N**) (**Level I** [Cochrane Review]).
2. Short educational interventions in acute whiplash injury reduce pain and disability and enhance recovery and mobility (**N**) (**Level I** [PRISMA])
3. There is no good evidence in favour of preoperative education having significant effects on outcomes such as pain, length of stay, patient satisfaction, postoperative complications, mobility and expectations in most postoperative settings (**N**) (**Level I**).
4. There is no good evidence in favour of general education for acute back pain having significant effects on any relevant outcomes (**N**) (**Level III-1 SR**).
5. Targeted reassurance in acute back pain by physicians in primary care can result in improved changes in psychological factors such as fear, worry, anxiety, catastrophisation and healthcare utilisation (**N**) (**Level III-1 SR**).

6. Educational interventions in cancer pain patients improve knowledge, attitudes and pain control (**N**) (**Level III-1 SR**).
7. Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief (**U**) (**Level II**).
8. Specific pain education in specific surgical settings may result in decreased pain, opioid use and less healthcare utilisation (**N**) (**Level II**).
9. Written information given to patients is better than verbal information given at the time of the interview (**S**) (**Level III-2**).
10. While evidence for the benefit of patient education in terms of better pain relief is inconsistent, structured preoperative education may be better than routine information (**S**) (**Level III-2**).
11. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**S**) (**Level III-3**).

☑ Successful management of acute pain requires close liaison between all personnel involved in the care of the patient (**U**).

☑ More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

Organisational requirements

1. Implementation of an acute pain service may improve pain relief and reduce the incidence of adverse effects (**U**) (**Level III-3**).
2. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**U**) (**Level III-3**).
3. Even "simple" techniques of pain relief can be more effective if attention is given to education, documentation, patient assessment and provision of appropriate guidelines and policies (**U**) (**Level III-3**).
4. Implementation of root-cause analysis to follow up critical incidents improved the safety of patients under care of an acute pain service (**N**) (**Level III-3**)

☑ Successful management of acute pain requires close liaison between all personnel involved in the care of the patient (**U**).

☑ More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

☑ Appropriate institutional support and engagement is important for the effective implementation of an acute pain service (**N**).

☑ Procedure-specific analgesic protocols can help optimise analgesia for the individual patient while reducing adverse effects (**N**)**.**

Economic considerations in acute pain management

☑ Patients value well-controlled pain highly (**N**).

☑ Long-term economic consequences from the progression of acute to chronic pain can be significant (**N**).

☑ Costs from PCA errors can be considerable; the most common high-cost errors arise from staff communication error and operator error (**N**).

☑ There are different measures of economic assessment and analysis used in healthcare; no one method is most appropriate (**N**).

4. ANALGESIC MEDICINES

Opioids

Systemic

1. Dextropropoxyphene has low analgesic efficacy (**U**) (**Level I** [Cochrane Review]).
2. Tramadol is an effective treatment for neuropathic pain (**U**) (**Level I** [Cochrane Review]).
3. Droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron are effective in the prevention of postoperative nausea and vomiting (**S**) (**Level I** [Cochrane Review]).
4. PC6 acupuncture, PC6 acupressure and PC6 electroacupoint stimulation reduce postoperative nausea and vomiting (**N**) (**Level I** [PRISMA]).
5. Opioids in high doses, in particular remifentanil, can induce hyperalgesia and/or acute tolerance (**S**) (**Level I** [PRISMA]).
6. Paracetamol given intravenously preoperatively and intraoperatively reduces postoperative nausea and vomiting; this effect is associated with improved analgesia, not reduced opioid requirements (**N**) (**Level I** [PRISMA]).
7. Alvimopan, methylnaltrexone (**S**) (**Level I** [QUOROM]) and naloxegol (**N**) (**Level II**) reduce opioid-induced slowing of gastrointestinal transit time and constipation; alvimopan is an effective treatment for postoperative ileus.
8. NMDA-receptor antagonists reverse the acute tolerance and/or hyperalgesia induced by remifentanil (**N**) (**Level I** [QUOROM]).
9. Haloperidol, perphenazine and transdermal scopolamine are effective in the prevention of postoperative nausea and vomiting (**N**) (**Level I**).
10. The incidence of clinically meaningful adverse effects (nausea, vomiting) of opioids is dose-related (**S**) (**Level I**).
11. Gabapentin, pregabalin, nonselective NSAIDs, systemic lignocaine and ketamine are opioid-sparing medications and reduce opioid-related adverse effects (**S**) (**Level I**).
12. Paired combinations of $5HT_3$ antagonist, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**U**) (**Level I**).
13. Naloxone, naltrexone, nalbuphine and droperidol are effective treatments for opioid-induced pruritus (**U**) (**Level I**).
14. Opioids administered by PCA, in particular morphine, show higher analgesic efficacy in females than in males (**N**) (**Level I**).
15. Tapentadol has similar efficacy to opioids with a reduced rate of gastrointestinal adverse effects (nausea, vomiting, constipation) (**N**) (**Level I**).
16. Neurokinin-1 receptor antagonists (fosaprepitant, aprepitant) are effective in the prevention of postoperative nausea and vomiting (**N**) (**Level II**).
17. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
18. Pethidine is not superior to morphine or hydromorphone in treatment of pain of renal colic (**S**) (**Level II**).
19. Morphine-6-glucuronide is an effective analgesic (**U**) (**Level II**).
20. In the management of acute pain, one opioid is not superior to others but some opioids are better in some patients (**U**) (**Level II**).
21. High doses of methadone can lead to prolonged QT interval (**U**) (**Level II**).

22. Opioid antagonists are effective treatments for opioid-induced urinary retention (**N**) (**Level III-1**).
23. Pethidine use was associated with an increased risk of delirium in the postoperative period compared to other opioids (**N**) (**Level III-2 SR**)
24. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**U**) (**Level III-2**).
25. Tapentadol has lower rates of abuse and doctor shopping than oxycodone (**N**) (**Level III-2**).
26. Opioid-related adverse effects in the postoperative period result in increased length of hospital stay, costs and rates of readmission (**N**) (**Level III-2**).
27. Assessment of sedation is a more reliable way of detecting early opioid-induced ventilatory impairment than a decreased respiratory rate (**U**) (**Level III-3**).
28. The evidence for significant QT prolongation and risk of cardiac arrhythmias following low-dose droperidol, haloperidol and dolasetron is weak (**N**) (**Level III-3**).
29. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).
30. Impaired renal function and the oral route of administration result in higher levels of the morphine metabolites morphine-3-glucuronide and morphine-6-glucuronide with increased risk of sedation and respiratory depression (**S**) (**Level IV**).
31. CYP2D6 ultrarapid metabolisers are at increased risk of codeine toxicity (**N**) (**Level IV**).

☑ Opioid-induced ventilatory impairment is a more appropriate term to describe the effects of opioids on ventilation as it encompasses the central respiratory depression caused by opioids and also the depressed consciousness and the subsequent upper airway obstruction resulting from excessive opioid use (**N**).

☑ The use of pethidine and dextropropoxyphene should be discouraged in favour of other opioids (**S**).

Intrathecal

1. Intrathecal morphine and intrathecal fentanyl prolong spinal local anaesthetic block, with fentanyl being associated with fewer adverse effects (**N**) (**Level I** [PRISMA]).
2. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl or sufentanil after Caesarean delivery (**U**) (**Level I**).
3. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**U**) (**Level I**).

Epidural

4. Epidural morphine provides similar analgesia to epidural fentanyl when combined with local anaesthetic, although the incidence of nausea is greater with morphine (**N**) (**Level I** [PRISMA]).
5. Extended-release epidural morphine provides analgesia for up to 48 hours (**U**) (**Level II**), however it is associated with more respiratory depression than IV PCA following abdominal surgery (**S**) (**Level I**)
6. Epidural pethidine produces better pain relief and less sedation than IV pethidine after Caesarean delivery (**U**) (**Level II**).

☑ No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil (**U**).

☑ Neuraxial administration of bolus doses of hydrophilic opioids carries an increased risk of delayed sedation and respiratory depression compared with lipophilic opioids (**U**).

Peripheral

1. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo when administered after surgery (**U**) (**Level I**).
2. Peripheral opioids administered with local anaesthetics perineurally have no analgesic effects (**N**) (**Level I**).
3. Evidence for a clinically relevant peripheral opioid effect with topical administration is inconclusive (**S**) (**Level I**).

Paracetamol

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects is comparable to placebo (**U**) (**Level I** [Cochrane Review]).
2. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related adverse effects (**U**) (**Level I**).
3. Hepatotoxicity with therapeutic doses of paracetamol is extremely rare (**N**) (**Level IV**) and not associated with alcohol consumption (**N**) (**Level I** [PRISMA]).

Nonselective NSAIDs and coxibs

Systemic

1. Nonselective NSAIDs are effective in the treatment of acute postoperative pain, renal colic, migraine, primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]), acute ankle sprain (**N**) (**Level I**) and chronic low-back pain (**N**) (**Level I** [PRISMA]).
2. Coxibs are effective in the treatment of acute postoperative pain (**U**) (**Level I** [Cochrane Review]) and chronic low-back pain (**N**) (**Level I** [PRISMA]).
3. Nonselective NSAIDs and coxibs are effective analgesics of similar efficacy for acute pain (**U**) (**Level I** [Cochrane Review])
4. Nonselective NSAIDs given in addition to paracetamol improve analgesia compared with either medicine given alone (**S**) (**Level I**), in particular ibuprofen combined with paracetamol (**N**) (**Level I** [Cochrane Review]).
5. The risk-benefit ratio for coxibs as a discharge medication after orthopaedic surgery is superior to that for nonselective NSAIDs (**N**) (**Level I** [PRISMA]).
6. Nonselective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea and vomiting (**W**) (**Level I**).
7. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related adverse effects (**U**) (**Level I**), except after total knee arthroplasty, where they reduce pain scores and adverse effects and improve outcomes (**N**) (**Level I**).
8. With careful patient selection and monitoring, the incidence of NSAID-induced perioperative renal impairment is low (**S**) (**Level I** [Cochrane Review]).
9. Nonselective NSAIDs may increase the risk of any bleeding-related outcome after tonsillectomy in adults (**W**) (**Level I**) but not in children (**U**) (**Level I** [Cochrane Review]); in particular, there is an increase in bleeding complications with aspirin in adults and children (**U**) (**Level I**) and with ketolorac in adults only (**N**) (**Level III-2** [PRISMA]).
10. Nonselective NSAIDS, but not coxibs, may cause bronchospasm in individuals known to have NSAID-exacerbated respiratory disease (**S**) (**Level I** [PRISMA]).
11. Coxibs and nonselective NSAIDs are associated with similar rates of adverse cardiovascular effects, in particular myocardial infarction; naproxen may be associated with a lower risk than other nonselective NSAIDs and celecoxib may be associated with a lower risk than other coxibs and nonselective NSAIDs overall (**U**) (**Level I**).

12. Short-term use of parecoxib (**U**) (**Level I**) and other NSAIDs (**N**) (**Level III-2**) compared with placebo does not increase the risk of cardiovascular adverse effects after noncardiac surgery.
13. Use of parecoxib followed by valdecoxib after coronary artery bypass graft surgery increases the incidence of cardiovascular and cerebrovascular effects and is therefore contraindicated (**S**) (**Level I**).
14. Perioperative nonselective NSAIDs increase the risk of minor and major bleeding after surgery compared with placebo (**S**) (**Level I**).
15. Coxibs do not impair platelet function; this leads to perioperative blood loss being reduced in comparison with nonselective NSAIDs (**U**) (**Level II**) and comparable to placebo after total knee arthroplasty (**N**) (**Level I**).
16. Coxibs and nonselective NSAIDs have similar adverse effects on renal function (**U**) (**Level I**), although increased COX-2 selectivity may be associated with less risk of acute kidney injury (**N**) (**Level III-2**), which is confirmed for celecoxib (**N**) (**Level I**).
17. Short-term use (5–7 days) of coxibs results in gastric ulceration rates similar to placebo and lower than nonselective NSAIDs (**U**) (**Level II**).
18. The protective effects of low-dose aspirin are reduced by concomitant administration of some NSAIDs, in particular ibuprofen (**N**) (**Level III-2**).
19. The risk of adverse renal effects of nonselective NSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension and use of other nephrotoxic agents including angiotensin-converting enzyme inhibitors (**S**) (**Level IV**).

☑ Adverse effects of nonselective NSAIDs are significant and may limit their use (**U**).

☑ The effects of NSAIDs on bone healing and anastomotic leakage (after colorectal surgery) remain unclear (**N**).

Nonsystemic

1. Topical NSAIDs (except indomethacin) are effective in treating acute strains, sprains or sports injuries with systemic adverse effects comparable to placebo (**S**) (**Level I** [Cochrane Review]).
2. The efficacy of nsNSAIDs for peri or intra-articular injection as a component of local infiltration analgesia compared with systemic administration remains unclear (**N**) (**Level I** [PRISMA]).
3. Topical NSAIDs are effective analgesics for traumatic corneal abrasions (**U**) (**Level I**).
4. Intra-articular nonselective NSAIDs may provide more effective analgesia following arthroscopy than with IV administration (**N**) (**Level I**).

Local anaesthetics and other membrane stabilisers

Systemic

1. Perioperative intravenous lignocaine reduces pain and opioid requirements following abdominal surgery as well as nausea, vomiting, duration of ileus and length of hospital stay (**S**) (**Level I** [PRISMA]).
2. Perioperative intravenous lignocaine has a preventive analgesic effect (extending beyond 5.5 half-lives of lignocaine, ie > 8 hrs after cessation of administration) after a wide range of operations (**N**) (**Level I**).
3. Both IV lignocaine and mexiletine are effective in the treatment of chronic neuropathic pain. (**U**) (**Level I** [Cochrane]).

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use membrane stabilisers including systemic lignocaine in the management of acute neuropathic pain (**U**).

Regional local anaesthetics

1. Lignocaine intrathecal is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**U**) (**Level I** [Cochrane Review]).
2. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level I**).
3. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blocks (**S**) (**Level I**).
4. Continuous perineural infusions of lignocaine (lidocaine) result in less effective analgesia and more motor block than long-acting local anaesthetic agents (**U**) (**Level II**).
5. There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine in terms of quality of analgesia or motor block, when given in low doses for regional analgesia (epidural and peripheral nerve block) (**U**) (**Level II**).
6. Cardiovascular and central nervous system toxicity of the stereospecific isomers ropivacaine and levobupivacaine is less severe than with racemic bupivacaine (**U**) (**Level II**).
7. Local anaesthetic systemic toxicity is reduced by the use of ultrasound guidance for regional anaesthesia (**N**) (**Level IV**).
8. Local anaesthetic systemic toxicity is increased in paravertebral and upper limb blocks, with the use of lignocaine and higher doses of local anaesthetics (**N**) (**Level IV**).
9. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity (**S**) (**Level IV**); however uncertainties relating to dosage, efficacy and adverse effects still remain; therefore it is appropriate to administer lipid emulsion only once advanced cardiac life support has begun and convulsions are controlled (**U**) (**Level IV**).

☑ Case reports following accidental overdose with ropivacaine, levobupivacaine and bupivacaine suggest that resuscitation is less likely to be successful with bupivacaine (**Q**).

Inhalational agents

1. Nitrous oxide has some analgesic efficacy in labour pain (**S**), increases maternal adverse effects (nausea, vomiting, dizziness) (**N**), with no adverse effects on the newborn (**S**) (**Level I** [Cochrane Review]) and increases maternal satisfaction compared to pethidine and epidural analgesia (**N**) (**Level IV SR**).
2. Nitrous oxide has equivalent effectiveness and more rapid recovery compared with intravenous sedation in patients having lower gastrointestinal endoscopy (**N**) (**Level I**).
3. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations (**U**) (**Level II**).
4. Methoxyflurane, in low doses, is an effective analgesic with rapid onset in the prehospital setting, and a range of procedures in the hospital setting with good safety data (**S**) (**Level II**).

☑ Neuropathy and bone marrow suppression are rare but potentially serious complications of nitrous oxide use, particularly in at-risk patients, including those abusing nitrous oxide (**S**).

☑ The information about the complications of nitrous oxide for procedural pain is from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to nitrous oxide in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to nitrous oxide. The suggestions for the use of nitrous oxide are extrapolations only from the information above. Consideration should be given to the duration of exposure and supplementation with vitamin B_{12}, methionine, and folic or folinic acid (**U**).

☑ If nitrous oxide is used with other sedative or analgesic agents, appropriate clinical monitoring should be used (**U**).

NMDA-receptor antagonists

Systemic

1. Perioperative ketamine reduces the incidence of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review]).
2. Perioperative IV ketamine reduces opioid consumption, time to first analgesic request and postoperative nausea and vomiting compared to placebo (**S**) (**Level I** [PRISMA]); these benefits are limited to patients after thoracic surgery, when ketamine is added to the opioid in the PCA pump (**N**) (**Level I**).
3. Morphine/ketamine compared with higher doses of morphine alone improves analgesia and reduces sedation and postoperative nausea and vomiting in postoperative patients (**S**) (**Level I).**
4. NMDA-receptor antagonists reduce the development of acute tolerance/opioid-induced hyperalgesia associated with remifentanil use (**N**) (**Level I**).
5. IV ketamine does not increase intracranial pressure or reduce cranial perfusion pressure compared to opioids (**N**) (**Level I**).
6. IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect and improves pain scores (**R**) (**Level I**).
7. Ketamine is a safe and effective analgesic in the prehospital setting (**S**) (**Level II**).
8. Ketamine reduces postoperative pain in opioid-tolerant patients (**U**) (**Level II**).
9. IV magnesium extends the duration of sensory block with spinal anaesthesia and reduces subsequent postoperative pain (**N**) (**Level II**).

☑ Increasing rates of ketamine abuse are reported, in particular from South-East Asia and China (**N**).

☑ Ketamine toxicity leads to cognitive impairment and abuse to chronic organ toxicity (bladder, liver) (**N**).

Regional

1. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing adverse effects (**U**) (**Level I**).
2. Caudal ketamine in children, in combination with local anaesthetic or as the sole medicine, improved and prolonged analgesia with few adverse effects (**N**) (**Level I**).

Antidepressant medicines

1. In chronic neuropathic pain and fibromyalgia, tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitor are effective analgesics and more effective than selective serotonin-reuptake inhibitors (**S**) (**Level I** [Cochrane Review]).
2. Tricyclic antidepressants are effective in the treatment of chronic headaches (**S**) (**Level I** [PRISMA]).
3. Duloxetine is as effective as other first-line treatments for pain and disability of osteoarthritis (**N**) (**Level I**).
4. There is evidence that some antidepressants, in particular duloxetine, may be effective in the treatment of chronic low-back pain (**S**) (**Level I**).
5. Perioperative serotonin-noradrenaline reuptake inhibitors reduce acute pain and opioid requirements in a limited number of studies (**N**) (**Level II**).

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitors in the management of acute neuropathic pain (**S**).

☑ To minimise adverse effects, it is advisable to initiate treatment with tricyclic antidepressants at low doses (**Q**).

Anticonvulsant medicines

1. Alpha-2-delta ligands (gabapentin and pregabalin) are the only anticonvulsants with well-proven efficacy in the treatment of chronic neuropathic pain (**S**) (**Level I** [Cochrane Review]).
2. Pregabalin is the only anticonvulsant with proven but limited efficacy in chronic pain due to fibromyalgia (**N**) (**Level I** [Cochrane Review]).
3. Perioperative alpha-2-delta ligands (gabapentin/pregabalin) reduce postoperative pain and opioid requirements (**S**) and reduce the incidence of vomiting (**S**), pruritus (**U**) and urinary retention (**U**) but increase the risk of sedation (**U**) (**Level I** [QUOROM]).

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use alpha-2-delta ligands (gabapentin, pregabalin) in the management of acute neuropathic pain (**Q**).

Alpha-2 agonists

Systemic

1. The perioperative use of systemic alpha-2-agonists (clonidine and dexmedetomidine) reduces postoperative pain intensity, opioid consumption and nausea without prolonging recovery times, but the frequency and severity of adverse effects (bradycardia and hypotension) may limit their clinical usefulness (**S**) (**Level I** [PRISMA]).

Regional

1. Intrathecal clonidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics (**S**) (**Level I)** or morphine (**N**) (**Level I** [PRISMA]).
2. Dexmedetomidine when added to local anaesthetics for brachial plexus block prolongs anaesthesia and analgesia (**N**) (**Level I** [PRISMA]).
3. Intrathecal adrenaline (epinephrine) when combined with local anaesthetic, but not with intrathecal opioids, prolongs analgesia duration (**N**) (**Level I** [PRISMA]).
4. Intrathecal dexmedetomidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics (**S**) (**Level I** [QUOROM]).
5 Clonidine improves duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for peribulbar, peripheral nerve and plexus blocks but is associated with increased hypotension and bradycardia (**Q**) (**Level I**).
6. Dexmedetomidine added to intravenous regional anaesthesia improves and prolongs analgesia (**S**) (**Level II**).
7. Epidural clonidine may reduce postoperative systemic opioid requirements (**W**) (**Level II**).
8. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).

Salmon calcitonin and bisphosphonates

1. Bisphosphonates reduce bone pain associated with metastatic breast cancer and multiple myeloma (**Q**) (**Level I** [Cochrane Review]).
2 Salmon calcitonin reduces pain and improves mobilisation in the acute phase after osteoporosis-related vertebral compression fractures (**S**) (**Level I** [PRISMA]).
3. Salmon calcitonin reduced acute, but not chronic, phantom limb pain (**U**) (**Level II**).
4. Pamidronate reduced pain associated with acute osteoporotic vertebral compression fractures (**S**) (**Level II**).

Cannabis, cannabinoids and cannabimimetics

1. Current evidence does not support the use of cannabinoids in acute pain management (**U**) (**Level I**).
2. Cannabinoids appear to be mildly effective when used in the treatment of chronic neuropathic pain, including that associated with multiple sclerosis and HIV (**U**) (**Level I**).
3. Adverse effects including dizziness, cognitive changes and psychosis may limit the usefulness of cannabinoids in pain treatment in some patients (**N**) (**Level I**).

Corticosteroids

Systemic

1. Dexamethasone reduces postoperative pain and opioid requirements to a limited extent but also reduces nausea and vomiting, fatigue, and improves the quality of recovery compared with placebo (**S**) (**Level I** [PRISMA]).
2. Preoperative administration of dexamethasone appears more effective than intraoperative or postoperative administration (**N**) (**Level I** [PRISMA).
3. Mild hyperglycaemia may follow the perioperative administration of corticosteroids (**N**) (**Level II**).

☑ The risks of using corticosteroids in surgical populations remain to be evaluated (**N**).

Regional

1. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**U**) (**Level I** [QUOROM]).
2. Lumbar epidural (or transforaminal) corticosteroid administration is effective for short-term relief of acute radicular pain (**U**) (**Level I**).
3. Addition of dexamethasone to local anaesthetic prolongs the duration of sensory and motor block in brachial plexus block similar to systemic administration (**N**) (**Level II**).
4. Addition of dexamethasone to intravenous regional anaesthesia with lignocaine improves analgesia for up to 24 hours (**U**) (**Level II**).
5. Addition of corticosteroid to periarticular injection of local anaesthetic does not improve pain relief or range of movement following total knee arthroplasty (**N**) (**Level II**).
6. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**U**) (**Level II**).
7. There is a risk of septic arthritis with intra-articular steroids (**S**) (**Level IV**).

☑ Concerns have been raised regarding the safety of epidural steroids (**N**).

☑ There is little data in humans regarding the neurotoxicity of perineural corticosteroids (**N**).

Other regional analgesic medicines

1. Intrathecal neostigmine improves perioperative and peripartum analgesia in combination with other spinal medications but is associated with significant adverse effects (**U**) (**Level I**).
2. Epidural neostigmine combined with local anaesthetics improves postoperative analgesia without increasing the incidence of adverse effects (**S**) (**Level I**).
3. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).
4. Intrathecal midazolam combined with a local anaesthetic prolongs the time to first analgesia and reduces postoperative nausea and vomiting (**U**) (**Level I**).

Complementary and alternative medicine

1. White willow bark (*Salix alba*) and devil's claw (*Harpagophytum procumbens*) are effective in treating acute episodes of low-back pain (**N**) (**Level I** [Cochrane])
2. Homeopathic preparations of arnica (*Arnica montana*) (**N**) (**Level I** [PRISMA]) and St John's wort (*Hypericum perforatum*) (**N**) (**Level I** [QUOROM]) are not effective in treating acute postoperative pain
3. St John's wort (*Hypericum perforatum*) induces metabolism of oxycodone reducing its plasma concentrations and efficacy (**N**)(**Level II**).
4. A variety of complementary medicines show efficacy in prevention and treatment of primary dysmenorrhoea (**N**)(**Level II**).

☑ There is some evidence that some complementary and alternative medicines may be effective in some acute pain states. Adverse effects and interactions with medications have been described with complementary and alternative medicines and must be considered before their use (**U**).

5. ADMINISTRATION OF ANALGESIC MEDICINES

Oral route

1. Oral paracetamol combined with codeine is more effective than either medicine alone and shows a dose-response effect (**U**) (**Level I** [Cochrane Review]).
2. Oral paracetamol combined with tramadol is more effective than either medicine alone and shows a dose-response effect (**U**) (**Level I**).
3. NSAIDs given parenterally or rectally are not more effective and do not result in fewer adverse effects than the same medicines given orally (**U**) (**Level I**).
4. Early postoperative oral administration of paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (**U**) (**Level II**).

☑ Other than in the treatment of severe acute pain, and providing there are no contraindications to its use, the oral route is the route of choice for the administration of most analgesic medicines (**U**).

☑ Controlled-release oral opioid preparations should only be given at set time intervals (**U**).

☑ Immediate-release oral opioids should be used for breakthrough pain and for titration of controlled-release opioids (**U**).

☑ The use of controlled-release opioid preparations as the sole agents for the early management of acute pain is discouraged because of difficulties in short-term dose adjustments needed for titration (**U**).

Intravenous route

1. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
2. Continuous intravenous infusion of opioids in the general-ward setting is associated with an increased risk of respiratory depression compared with other methods of parenteral opioid administration (**U**) (**Level IV**).

☑ Titration of opioids for severe acute pain is best achieved using intermittent intravenous bolus doses as it allows more rapid titration of effect and avoids the uncertainty of medicine absorption by other routes (**U**).

Intramuscular and subcutaneous routes

1. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance (**U**) (**Level II**).

Transdermal route

1. Transdermal fentanyl (except for Iontophoretic patient-controlled transdermal devices) should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration (**Q**) (**Level IV**).

☑ Transdermal fentanyl preparations should not be used in the management of acute pain in opioid-naïve patients because of safety concerns and, in most countries, the lack of regulatory approval for use in other than opioid-tolerant patients (**S**).

Transmucosal routes

1. Intranasal, sublingual and buccal fentanyl preparations are effective treatments for breakthrough pain in cancer patients (**S**) (**Level I** [Cochrane Review]) with similar efficacy to IV administration (**N**) (**Level I** [PRISMA]) and superior to oral morphine (**N**) (**Level I**)
2. Intranasal fentanyl provides faster and better analgesia for breakthrough pain in cancer patients than oral transmucosal fentanyl and fentanyl buccal tablets (**N**) (**Level I**).

☑ Neither buccal nor transdermal fentanyl preparations should be used in the management of acute pain in opioid-naïve patients because of safety concerns and, in most countries, the lack of regulatory approval for use in other than opioid-tolerant patients (**S**).

Epidural analgesia

1. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**U**) (**Level I** [Cochrane Review]); except epidural analgesia using a hydrophilic opioid only (**U**) (**Level I**).
2. Thoracic epidural analgesia for open abdominal aortic surgery reduces the duration of tracheal intubation and mechanical ventilation, as well as the incidence of myocardial infarction, acute respiratory failure, gastrointestinal complications and renal insufficiency when compared with IV opioids (**S**) (**Level I** [Cochrane Review]).
3. High thoracic epidural analgesia used for coronary artery bypass graft surgery reduces postoperative pain, risk of dysrhythmias, pulmonary complications and time to extubation when compared with intravenous opioid analgesia (**S**) (**Level I** [Cochrane Review]).
4. Thoracic epidural analgesia for thoracotomy reduces the risk of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review]).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery) (**S**) (L**evel I** [Cochrane Review]).
6. Epidural analgesia provided with local anaesthetics for at least 24 hours compared to systemic opioid analgesia reduces perioperative mortality and multiple morbidities (including ileus, pneumonia, respiratory depression and arrhythmias) but increases hypotension (**N**) (**Level I** [PRISMA]).
7. After laparoscopic colectomy, initial pain scores and postoperative nausea and vomiting are reduced by thoracic epidural analgesia compared to intravenous PCA with reduced time to first bowel motion, without any further improved outcomes (**N**) (**Level I** [PRISMA]) and at the expense of longer hospital stay and increased urinary tract infection rates (**Level III-2**).
8. Combinations of low concentrations of local anaesthetic agents and opioids for epidural analgesia provide consistently superior pain relief compared with either of the medicines alone; epidural opioids alone have no advantage over parenteral opioids (**N**) (**Level I**).
9. Epidural local anaesthetic administration improves oxygenation and reduces pulmonary infections and other pulmonary complications compared with parenteral opioids (**U**) (**Level I**).
10. Thoracic epidural analgesia extended for more than 24 hours reduces the incidence of postoperative myocardial infarction (**U**) (**Level I**).

11. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**S**) (**Level I**).
12. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**U**) (**Level I**).
13. Thoracic epidural analgesia reduces need for ventilation in patients with multiple rib fractures (**U**) (**Level I**) and reduces incidence of pneumonia (**U**) (**Level II**) and mortality (**N**) (**Level III-2**).
14. The combination of thoracic epidural analgesia with local anaesthetics and nutritional support leads to preservation of total body protein after upper abdominal surgery (**U**) (**Level II**).
15. The incidence of permanent neurological damage in association with epidural analgesia is extremely low, especially in the obstetric population, but increases with various comorbidities and risk factors; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV**).
16. Immediate decompression of an epidural haematoma (within 8 hours of the onset of neurological signs) increases the likelihood of partial or good neurological recovery (**U**) (**Level IV**).

☑ The provision of epidural analgesia by continuous infusion or patient-controlled administration of local anaesthetic-opioid mixtures is safe on general hospital wards, as long as supervised by an anaesthesia-based pain service with 24-hour medical staff cover and monitored by well-trained nursing staff (**U**).

☑ Magnetic resonance imaging investigation may be warranted to assess for possible epidural abscess if patients, who have had an epidural catheter inserted, develop a fever and infection at the catheter insertion site; urgent investigation is especially indicated if other signs are present that could indicate an abscess, such as back pain or neurological change (**U**).

☑ Prior to insertion of an epidural catheter, thorough handwashing with surgical scrub solution, the use of barrier precautions including the wearing of a cap, mask, sterile gown and gloves and use of chlorhexidine in alcohol (0.5%) for skin preparation are recommended; but meticulous care must be taken to avoid the chlorhexidine solution from reaching epidural space or cerebrospinal fluid (**N**).

Intrathecal analgesia

1. Intrathecal morphine improves analgesia and is opioid-sparing for up to 24 hours with a low risk of major adverse effects, especially following abdominal surgery (**S**) (**Level I** [PRISMA]).
2. After major surgery, the incidence of opioid-induced ventilatory impairment and pruritus is higher with intrathecal morphine compared with intravenous PCA opioids (**S**) (**Level I**).
3. There is an increase in the incidence of urinary retention (**N**) (**Level I)**, nausea and vomiting with intrathecal opioids in comparison to systemic opioids for minor but not major surgery (**Q**) (**Level I**).
4. Pruritus with intrathecal opioids can be effectively managed with $5HT_3$ antagonists (**N**) (**Level I**).
5. The addition of intrathecal clonidine to intrathecal morphine results in slightly longer analgesia and reduced opioid requirements (**N**) (**Level I**).
6. The addition of intrathecal magnesium to opioids and/or local anaesthetics results in slightly longer analgesia in nonobstetric patients (**N**) (**Level I**).

☑ The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids and the increase in adverse effects with higher doses suggests that the lowest effective dose (less than 300 mcg morphine) should be used (**Q**).

- ☑ Patients receiving intrathecal opioids should be monitored for opioid-induced ventilatory impairment for the anticipated duration of opioid effects, eg 18 to 24 hours after intrathecal morphine (**N**).
- ☑ Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**), however caution is recommended in patients who are at risk of spinal cord ischaemia **(N)**.

Other regional and local analgesic techniques

1. Topical EMLA® cream (eutectic mixture of lignocaine [lidocaine] and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (**U**) (**Level I** [Cochrane Review]).
2. Paravertebral block provides superior analgesia for up to 48 hours following breast surgery when compared to systemic analgesia, with a lower incidence of postoperative nausea and vomiting (**N**) (**Level I** [PRISMA])
3. In thoracic surgery, compared with thoracic epidural analgesia, continuous thoracic paravertebral analgesia results in comparable analgesia but has a better adverse effect profile (less urinary retention, hypotension, nausea and vomiting) than epidural analgesia and leads to a lower incidence of postoperative pulmonary complications (**S**) (**Level I** [PRISMA]).
4. Continuous peripheral nerve block, compared with single-injection peripheral nerve block, results in improved pain control, decreased need for opioid analgesics, reduced nausea and improved patient satisfaction (**N**) (**Level I**).
5. Femoral nerve block, either single-injection or continuous, provides better analgesia and decreased nausea compared with parenteral opioid-based techniques after total knee arthroplasty (**S**) (**Level I**).
6. Compared with opioid analgesia, continuous peripheral nerve block (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**U**) (**Level I**).
7. Transversus abdominis plane blocks improve short-term analgesia compared to controls in Caesarean delivery and in laparoscopic surgery (**N**) (**Level I**).
8. Blocks performed using ultrasound guidance are more likely to be successful, faster to perform, with faster onset and longer duration compared with localisation using a peripheral nerve stimulator (**S**) (**Level I**).
9. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**U**) (**Level I**).
10. Following total knee arthroplasty, local infiltration analgesia reduces postoperative pain for up to 32 hours when compared to systemic analgesics alone (**S**); however, there is limited benefit in comparison to femoral nerve block (**N**) (**Level I**).
11. Following total hip arthroplasty, there is no additional analgesic benefit for local infiltration analgesia over conventional multimodal analgesia (**N**) (**Level I**).
12. Following either knee or hip arthroplasty, there is insufficient evidence to support the use of postoperative administration of local infiltration analgesia via catheter (**N**) (**Level I**).
13. Local anaesthetic injections through wound catheters provide analgesic benefits following gynaecological and obstetric surgery but not other nonorthopaedic surgery (**Q**) (**Level I**).
14. Intraperitonal local anaesthetic after laparoscopic cholecystectomy improves early postoperative pain relief (**N**) (**Level I**).
15. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**N**) (**Level I**).
16. The benefit of routine sciatic nerve block in addition to femoral nerve block for analgesia following total knee joint arthroplasty remains unclear (**N**) (**Level I**).

17. Continuous interscalene analgesia provides better analgesia, reduced opioid-related adverse effects and improved patient satisfaction compared with intravenous PCA or single-injection interscalene block after open shoulder surgery (**Q**) (**Level II**).
18. Adductor canal block provides postoperative analgesia that is noninferior to single-injection femoral nerve block for 8 hours and is associated with reduced quadriceps weakness **(N)** (**Level II**).
19. Lumbar plexus block results in similar pain scores following total hip arthroplasty compared to femoral nerve block; lumbar plexus block results in modest improvements in postoperative pain following hip arthroscopy (**N**) (**Level II**).
20. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**N**) (**Level IV**).
21. Postoperative neurologic dysfunction is often related to patient and surgical factors and the incidence of neuropathy directly related to peripheral regional anaesthesia is rare (**N**) (**Level IV**).

☑ Continuous peripheral nerve blocks carry a risk of infection; skin preparation with alcohol-based chlorhexidine and full barrier precautions (including face masks) are recommended for insertion of peripheral nerve catheters (**N**).

☑ Ultrasound-guided techniques should be practiced with a high degree of skill and care, including aseptic techniques, as they do not eliminate the risks of injury to tissues and structures, local anaesthetic toxicity or site contamination (**N**).

Regional analgesia and concurrent anticoagulant medications

1. Anticoagulation and coagulopathy are the two most important risk factors for the development of epidural haematoma after neuraxial block (**U**) (**Level IV**).

☑ Consensus statements of experts guide the timing and choice of regional anaesthesia and analgesia in the context of anticoagulation but do not represent a standard of care and will not substitute the risk/benefit assessment of the individual patient by the individual anaesthetist (**U**).

6. PATIENT-CONTROLLED ANALGESIA

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**U**) (**Level I** [Cochrane Review]).
2. Opioid administration by IV PCA leads to higher opioid consumption, a higher incidence of pruritus and no difference in other opioid-related adverse effects or hospital stay compared with traditional methods of intermittent parenteral opioid administration (**U**) (**Level I** [Cochrane Review]).
3. Patient satisfaction with intravenous PCA is higher when compared with conventional regimens (**U**) (**Level I** [Cochrane Review]).
4. Iontophoretic transdermal fentanyl PCA is not as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**U**) (**Level I** [QUOROM]).
5. When ketamine is added to the opioid in the PCA pump, benefits with regard to analgesia and adverse effects are limited to patients after thoracic surgery (**Q**) (**Level I**).
6. In settings where there are high nurse:patient ratios, there may be no difference in effectiveness of PCA and conventional parenteral opioid regimens (**N**) (**Level I**).
7. Tramadol via intravenous PCA provides effective analgesia comparable to morphine by intravenous PCA **(N) (Level I**).
8. The addition of a background infusion to intravenous PCA morphine increases the incidence of respiratory depression **(S) (Level I)** and does not improve pain relief or sleep, or reduce the number of PCA demands (**U**) (**Level II**).

9. There is little evidence that one opioid via PCA is superior to another with regards to analgesic or adverse effects in general; although on an individual patient basis, one opioid may be better tolerated than another (**U**) (**Level II**).
10. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however the incidence of nausea and pruritus may be decreased (**U**) (**Level II**).
11. Subcutaneous PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
12. Intranasal PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
13. In the emergency department, PCA morphine compared with IV morphine administered by nursing staff, provides more effective analgesia with more rapid onset and with higher patient satisfaction (**N**) (**Level II**).
14. The safety of PCA use can be significantly improved by hospital-wide safety initiatives (equipment, guidelines, education, monitoring) (**N**) (**Level III-3**).
15. The adoption of "smart pump" technologies in PCA design can reduce programming errors and improve safety (**N**) (**Level IV SR**).
16. Operator-error remains a common safety problem with PCA use, in particular programming error, often leading to patient harm (**S**) (**Level IV**).

☑ Adequate analgesia needs to be obtained prior to commencement of PCA. Initial orders for bolus doses should take into account individual patient factors such as a history of prior opioid use and patient age. Individual PCA prescriptions may need to be adjusted (**U**).

☑ The routine addition of antiemetics to PCA opioids is not encouraged, as it is of no benefit compared with selective administration (**U**).

☑ PCA infusion systems must incorporate antisiphon valves and, in nondedicated lines, antireflux valves (**U**).

☑ Drug concentrations, prescription and observation forms should be standardised to improve patient safety (**S**).

☑ The pharmacokinetics of morphine (long equilibration half-time and active metabolites) may make it less suitable for PCA use than other opioids (**N**).

☑ Pethidine when used in PCA may cause central nervous system toxicity due the accumulation of norpethidine (**N**).

7. NONPHARMACOLOGICAL TECHNIQUES

Psychological interventions

1. Listening to music produces a small reduction in postoperative pain and opioid requirement (**S**) (**Level I** [Cochrane Review]).
2. Distraction reduces pain (**Q**) (**Level I** [Cochrane Review]) and hypnosis reduces both pain and distress associated with needle-related procedures in children and adolescents (**S**) (**Level I** [Cochrane Review]).
3. Procedural information has no effect on postoperative pain (**Q**) (**Level I**), in particular when provided before joint replacement surgery (**Q**) (**Level I** [Cochrane Review]).
4. Active and passive music therapy reduces pain and anxiety associated with needle-related procedures in children (**N**) (**Level I**).
5. The evidence that sensory and combined sensory-procedural information is effective in reducing procedure-related pain is equivocal and not sufficient to make recommendations (**Q**) (**Level I**).
6. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative affect and analgesic use (**U**) (**Level I**).
7. Hypnosis is not effective in the management of postoperative and labour pain (**Q**) (**Level I**).

8. Evidence for any benefit of relaxation techniques in the treatment of acute pain is weak and inconsistent (**U**) (**Level I**).
9. Immersive virtual reality distraction is effective in reducing pain in some clinical situations (**U**) (**Level III-2**).

Transcutaneous electrical nerve stimulation

1. Transcutaneous electrical nerve stimulation (TENS) compared to sham TENS reduces acute pain (procedural and nonprocedural) (**N**) (**Level I** [Cochrane Review]), including pain after thoracic surgery (**N**) (**Level I** [PRISMA).
2. High-frequency transcutaneous electrical nerve stimulation is effective in primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
3. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour with the exception of a reduction of reports of severe pain when applied to acupuncture points (**Q**) (**Level I** [Cochrane Review]).

Acupuncture and acupressure

1. Acupuncture and acupressure for labour pain reduces pain, use of pharmacological pain relief, Caesarean delivery rates and may increase satisfaction with pain management compared to standard care or placebo (**S**) (**Level I** [Cochrane Review]).
2. For oocyte retrieval, electroacupuncture when added to conscious sedation reduces procedural and postoperative pain more than sedation plus placebo or sedation alone, but not when added to paracervical block (**N**) (**Level I** [Cochrane Review]).
3. Acupuncture or acupressure may be effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).
4. Acupuncture may be effective in other acute pain settings (**S**) (**Level I** [PRISMA]), including acute burns and back pain (**N**) (**Level I** [PRISMA]), tension-type headaches and migraine (**N**) (**Level I** [Cochrane Review]).
5. Acupuncture (**S**) (**Level I**), specifically auricular acupuncture (**N**) (**Level I** [PRISMA] reduces postoperative pain, opioid requirements as well as opioid-related adverse effects compared to a variety of controls.
6. Beneficial effects of acupuncture on postoperative pain have been confirmed after back surgery and ambulatory knee surgery (**N**) (**Level I** [PRISMA]) and total knee joint replacement (**N**) (**Level II**).

Physical therapies

☑ Conclusions regarding the efficacy of physical therapies in postoperative pain are not possible at present due to limited, poor quality evidence and the inability to conduct blinded trials (**N**).

8. SPECIFIC CLINICAL SITUATIONS

Postoperative pain

Multimodal postoperative pain management

1. Multimodal analgesia compared to mainly opioid-based analgesia improves pain control and reduced opioid consumption ("opioid-sparing") and adverse effects (**N**) (**Level II**).

☑ The concept of multimodal (or "balanced") analgesia suggests the use of combinations of analgesics with different mode or site of action (**N**).

Procedure-specific postoperative pain management

1. An analgesic may have different efficacy in different surgical settings (**N**) (**Level I**).

☑ Pooling of data from different postoperative pain states may ignore the specific effects of a specific analgesic in a specific postoperative pain state (**N**).

☑ Different surgical procedures cause different pain states (eg musculoskeletal vs visceral) of different severity in different locations, thereby requiring a procedure-specific approach (**N**).

Enhanced recovery after surgery

1. Adherence to multimodal enhanced recovery after surgery protocols results in reduced hospital stay and complication rates (**N**) (**Level I**).

☑ Provision of appropriate analgesia is only one of several elements of enhanced recovery after surgery protocols (**N**).

☑ Analgesic techniques, which permit early mobilisation and early enteral feeding, in particular those that are opioid-sparing, may contribute to early recovery after surgery protocols (**N**).

Postoperative neuropathic pain

1. Acute neuropathic pain occurs after trauma and surgery (**S**) (**Level IV**).

☑ Treatment of acute neuropathic pain should follow guidelines for chronic neuropathic pain; ketamine, opioids (including tramadol and tapentadol in particular) and alpha-2-delta ligands may offer faster onset of effect than other treatment options (**N**).

☑ Diagnosis and subsequent appropriate treatment of acute neuropathic pain might prevent development of chronic pain (**U**).

Acute postamputation pain syndromes

1. Morphine, gabapentin, ketamine and dextromethorphan reduce phantom limb pain compared to placebo (**S**) (**Level I** [Cochrane Review]).
2. Calcitonin reduces phantom limb pain in the acute (<7 days post amputation) but not the chronic setting (**Q**) (**Level I** [Cochrane Review]).
3. Continuous regional block via nerve sheath catheters provides postoperative analgesia after amputation but has no preventive effect on phantom limb pain (**S**) (**Level I**).
4. Treatments aiming at cortical reorganisation such as mirror therapy (**S**) (**Level I**), sensory discrimination training and motor imagery reduce chronic phantom limb pain (**S**) (**Level II**).
5. Perioperative epidural analgesia reduces the incidence of severe phantom limb pain (**U**) (**Level III-2**).

☑ Perioperative ketamine may prevent severe phantom limb pain (**U**).

Other postoperative pain syndromes

1. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
2. Following breast cancer surgery, paravertebral block reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
3. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain, but an increase in chronic pain (**S**) **(Level I**).
4. Post-thoracotomy, postmastectomy, postherniotomy and posthysterectomy pain syndromes occur frequently (**N**) (**Level IV**).

Day-stay or short-stay surgery

1. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia, but not motor block (**N**) (**Level I** [PRISMA]); however concerns regarding neurotoxicity remain.
2. Wound infiltration and intraperitoneal instillation with local anaesthetics for short-stay laparoscopic cholecystectomy has good analgesic efficacy, in particular when administered prior to trocar insertion and at commencement of pneumoperitoneum respectively (**N**) (**Level I**).
3. Intraperitoneal instillation with local anaesthetic provides good analgesia for up to 6 hours after short-stay gynaecologic laparoscopy (**N**) (**Level I**).
4. In the short-stay surgery setting, anti-inflammatories (nonselective NSAIDs, coxibs and dexamethasone) contribute to reduced pain and improved recovery (**N**) (**Level II**).
5. Infiltration of the wound with local anaesthetic provides effective and long-lasting analgesia after many short-stay procedures (**S**) (**Level II**).
6. Single-injection peripheral nerve blocks with long-acting local anaesthetics provide long-lasting postoperative analgesia after short-stay surgery (**S**) (**Level II**).
7. Continuous peripheral nerve blocks provide extended analgesia after short-stay surgery, leading to reduced opioid requirements, earlier achievement of discharge criteria, less sleep disturbance and improved early rehabilitation (**S**) (**Level II**).
8. Paravertebral block improves pain-related outcomes after short-stay major breast surgery and hernia repair (**N**) (**Level II**).
9. Buprenorphine or dexmedetomidine added to local anaesthetics for peripheral nerve blocks prolongs duration of analgesia after short-stay surgery (**N**) (**Level II**).
10. Dexamethasone added to local anaesthetics or given systemically in peripheral nerve blocks prolongs duration of analgesia after short-stay surgery (**N**) (**Level II**).
11. Pain relief after short-stay surgery remains poor (**U**) (**Level IV**) and is a common cause of unplanned re-presentation (**U**) (**Level III-3**).
12. Continuous peripheral nerve blocks have been shown to be safe at home after short stay surgery, if adequate resources and patient education are provided (**U**) (**Level IV**).

Cranial neurosurgery

1. Local anaesthetic infiltration of the scalp provides early analgesia after craniotomy (**S**) (**Level I** [PRISMA]).
2. Morphine is more effective than codeine and tramadol for pain relief after craniotomy (**U**) (**Level II**).
3. Craniotomy leads to significant pain in the early postoperative period (**U**) (**Level IV**), which is however not as severe as pain from other surgical interventions (**U**) (**Level III-2**).
4. Craniotomy can lead to significant chronic headache (**U**) (**Level IV**).

☑ Acute pain following craniotomy is underestimated and often poorly treated (**N**).

Spinal surgery

1. Perioperative use of gabapentin or pregabalin improves analgesia and reduces opioid requirements after spinal surgery (**N**) **(Level I)** [PRISMA].
2. NSAIDs provide analgesic benefits as well as opioid-sparing effects after spinal surgery (**N**) (**Level I** [QUOROM]).
3. Perioperative pregabalin improves functional outcome after laminectomy at 3 months (**N**) (**Level II**).

4. Local infiltration anaesthesia improves analgesia and reduces opioid requirements after spinal surgery; this benefit is enhanced with preincision infiltration compared to infiltration at wound closure (**N**) (**Level II**).
5. Perioperative systemic lignocaine infusion improves analgesia and reduces opioid requirements after spinal surgery (**N**) (**Level II**).
6. NSAID use for less than 14 days does not increase the risk of nonunion after spinal fusion, except with high-dose ketorolac (**N**) (**Level III-3**).

☑ Acute pain management following spinal surgery is often complicated by preoperative chronic pain and long-term medication use (**N**).

Acute pain following spinal cord injury

1. Alpha-2-delta ligands (gabapentin/pregabalin) are effective in the treatment of neuropathic pain following spinal cord injury (**S**) (**Level I**).
2. Intravenous opioids, ketamine ((**S**) (**Level I**), lignocaine (lidocaine), tramadol and self-hypnosis are effective in the treatment of neuropathic pain following spinal cord injury (**U**) (**Level II**).

☑ Treatment of acute spinal cord injury pain is largely based on evidence from studies of other neuropathic and nociceptive pain syndromes (**U**).

Acute burns injury pain

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during dressings changes (**U**) (**Level I** [Cochrane]).
2. Virtual reality distraction, augmented reality techniques and multimodal distraction methods reduce pain during burns dressings (**S**) (**Level II**).
3. Opioids, particularly via PCA, are effective in burns pain, including procedural pain (**U**) (**Level II**).
4. Pregabalin reduces pain following acute burns injury (**S**) (**Level II**).
5. Sedation and anxiolysis with lorazepam improves procedural pain relief in acute burns injury (**N**) (**Level II**).
6. Regional analgesia reduces donor site pain in selected burns patients (**N**) (**Level II**).
7. Gabapentin reduces pain and opioid consumption following acute burns injury (**U**) (**Level III-3**).
8. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burns dressings (**U**) (**Level IV**).

☑ Acute pain following burns injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related (**U**).

☑ Acute pain following burns injury requires aggressive multimodal and multidisciplinary treatment and may benefit from protocolised management approaches (**S**).

Acute back pain

1. Acute low-back pain is nonspecific in about 95% of cases and serious causes are rare; common examination and investigation findings also occur in asymptomatic controls and may not be the cause of pain (**U**) (**Level I**).
2. Advice to stay active, use of heat-wrap therapy, provision of “activity-focused” printed and verbal information and use of behavioural therapy interventions are all beneficial in acute low-back pain (**U**) (**Level I**).
3. Advice to stay active and to exercise, use of multimodal therapy and use of pulsed electromagnetic therapy are all effective in acute neck pain (**U**) (**Level I**).
4. Soft collars are not effective for acute neck pain (**U**) (**Level I**).

5. Appropriate investigations are indicated in cases of acute low back pain when alerting features ("red flags") of serious conditions are present (**U**) (**Level III-2**).
6. Psychosocial and occupational factors ("yellow flags") appear to be associated with progression from acute to chronic back pain; such factors should be assessed early to facilitate intervention (**U**) (**Level III-2**).

Acute musculoskeletal pain

1. Topical and oral NSAIDs improve acute shoulder pain (**U**) (**Level I**).
2. Subacromial corticosteroid injection relieves acute shoulder pain in the early stages (**U**) (**Level I**).
3. Exercises improve acute shoulder pain in patients with rotator cuff disease (**U**) (**Level I**).
4. Therapeutic ultrasound may improve acute shoulder pain in calcific tendonitis (**U**) (**Level I**).
5. Advice to stay active, and the use of exercises, injection therapy and foot orthoses are effective in acute patellofemoral pain (**U**) (**Level I**).
6. Low-level laser therapy is ineffective in the management of patellofemoral pain (**U**) (**Level I**).

☑ A management plan for acute musculoskeletal pain should comprise the elements of assessment (history and physical examination but ancillary investigations are not generally indicated), management (information, assurance, advice to resume normal activity, pain management) and review to reassess pain and revise management plans (**U**).

☑ Information should be provided to patients in correct but neutral terms with the avoidance of alarming diagnostic labels to overcome inappropriate expectations, fears or mistaken beliefs (**U**).

☑ Regular paracetamol then, if ineffective, NSAIDs may be used for acute musculoskeletal pain (**U**).

☑ Oral opioids, preferably short-acting agents at regular intervals, may be necessary to relieve severe acute musculoskeletal pain; ongoing need for such treatment requires reassessment (**U**).

☑ Adjuvant agents such as anticonvulsants, antidepressants and muscle relaxants are not recommended for the routine treatment of acute musculoskeletal pain (**U**).

Acute medical pain

Acute abdominal pain

1. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).
2. NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**U**) (**Level I** [Cochrane Review]).
3. NSAIDs given for renal colic reduce requirements for rescue analgesia and produce less vomiting compared with opioids, particularly pethidine (meperidine) (**U**) (**Level I** [Cochrane Review]).
4. Alpha blockers as expulsive therapy for ureteral stones reduce the number of pain episodes and analgesic requirements (**N**) (**Level I** [Cochrane Review]).
5. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
6. Antispasmodics and tricyclic antidepressants, but not bulking agents, are effective for the treatment of acute pain in irritable bowel syndrome (**S**) (**Level I** [Cochrane Review]).
7. NSAIDs are effective in primary dysmenorrhoea and superior to paracetamol (**S**) (**Level I** [Cochrane Review]).

8. High-frequency TENS, magnesium, Vitamin B_1, Chinese herbal medicines and possibly acupuncture/acupressure are effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).
9. The smooth muscle relaxant buscopan did not add further analgesic benefit when combined with metamizole (dipyrone) (**N**) (**Level I** [Cochrane Review]), opioids or NSAIDS to treat pain of renal colic (**N**) (**Level II**).
10. NSAIDS are superior to placebo and spasmolytics and as effective as opioids in the treatment of biliary colic, while reducing complications including progression to cholecystitis (**S**) (**Level I** [PRISMA])
11. The perioperative use of rectal indomethacin for endoscopic retrograde cholangiopancreatography (ERCP) reduces the risk of post ERCP pancreatitis (**N**) (**Level I**).
12. Intravenous paracetamol is as effective as intravenous morphine and superior to intramuscular piroxicam for analgesia in renal colic (**N**) (**Level II**).
13. There is no difference between pethidine and morphine for analgesia in renal colic (**U**) (**Level II**).

Herpes zoster

1. Antiviral agents started within 72 hours of onset of the herpes zoster rash accelerate the resolution of acute pain (**U**) (**Level I**) but do not reduce the incidence, severity and duration of postherpetic neuralgia (**S**) (**Level I** [Cochrane]).
2. Immunisation of persons aged 60 years or older with VZV vaccine reduces the incidence of herpes zoster and postherpetic neuralgia (**S**) (**Level I** [Cochrane]).
3. Amitriptyline (used in low doses for 90 days from onset of the herpes zoster rash) reduces the incidence of postherpetic neuralgia (**U**) (**Level II**).
4. Topical aspirin, topical lignocaine patch or controlled-release oxycodone provide analgesia in acute pain due to herpes zoster (**U**) (**Level II**).

☑ Provision of early and appropriate analgesia is an important component of the management of herpes zoster and may have benefits in reducing the incidence of postherpetic neuralgia (**U**).

Acute cardiac pain

1. Morphine is an effective and appropriate analgesic for acute cardiac pain (**U**) (**Level II**).
2. Nitroglycerine is an effective and appropriate agent in the treatment of acute ischaemic chest pain (**U**) (**Level IV**).

☑ The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, nitroglycerine, beta blockers and strategies to improve coronary vascular perfusion (**U**).

☑ The routine use of supplemental oxygen in acute myocardial infarction may not be beneficial (**N**).

Acute pain associated with haematological disorders

1. Parenteral corticosteroids reduce the duration of severe pain, analgesia requirements and length of hospital stay, without major adverse effects, during sickle cell crises (**S**) (**Level I** [Cochrane Review]).
2. There is no evidence that fluid replacement therapy reduces pain associated with sickle cell crises (**U**) (**Level I** [Cochrane Review]).
3. Hydroxyurea decreases the frequency of acute crises, life-threatening complications and transfusion requirements in sickle cell disease (**U**) (**Level I** [Cochrane Review]).
4. Zinc reduces the incidence of painful sickle cell crises (**N**) (**Level I** [Cochrane Review]).

5. Intravenous opioid loading optimises analgesia in the early stages of an acute sickle cell crisis. Effective analgesia may be continued with intravenous opioid therapy, optimally as PCA, or as oral opioids (**S**) (**Level II**).
6. Oxygen supplementation does not decrease pain during a sickle cell crisis (**U**) (**Level II**) but hyperbaric oxygen may be effective (**N**) (**Level III-3**).

☑ Pethidine should be avoided for the treatment of acute pain in sickle cell disease or acute porphyria, with increased seizure risk being a potential problem (**U**).

Acute headache

Tension-type headache

1. Acupuncture is possibly effective in the treatment of tension-type headache (**W**) (**Level I** [Cochrane Review]).
2. Simple analgesics such as paracetamol or NSAIDs, either alone or combined, are effective in the treatment of episodic tension-type headache (**S**) (**Level I** [PRISMA]).
3. Metoclopramide, metamizole and chlorpromazine as parenteral treatments of tension-type headache have high efficacy (**N**) (**Level I** [PRISMA]).
4. The combination of caffeine/aspirin/paracetamol is superior to paracetamol in the treatment of episodic tension-type headache (**Q**) (**Level I**).

Migraine

5. Paracetamol is effective in the treatment of migraine, however less than other analgesics; the efficacy is increased when combined with metoclopramide (**S**) (**Level I** [Cochrane Review]).
6. Aspirin, ibuprofen, diclofenac and dipyrone are effective in the treatment of migraine; soluble preparations of ibuprofen provide a faster onset (**S**) (**Level I** [Cochrane Review]).
7. For sumatriptan, subcutaneous administration achieves the fastest onset of effect and highest efficacy (**N**) (**Level I** [Cochrane Review]).
8. Hyperbaric oxygen therapy is effective in controlling pain in migraine, but no other symptoms and outcomes (**N**) (**Level I** [Cochrane Review]).
9. A significant placebo effect occurs in migraine treatment (**N**) (**Level I** [QUOROM]), which leads to an underestimation of treatment effects of analgesic compounds (**Level II**).
10. All triptans are more effective than placebo in the treatment of severe migraine (**S**) (**Level I**), however 30–40% of patients may not respond (**N**) (**Level I**).
11. Parenteral antiemetics (metoclopramide or droperidol) are effective in the treatment of migraine (**S**) (**Level I**).
12. Triptans and mefenamic acid are effective in treatment of menstruation-related migraine (**N**) (**Level I**).
13. Some opioids are more effective than placebo in the treatment of acute migraine (**N**) (**Level I**), but their use in this setting is associated with significant adverse effects and poor outcomes (**N**) (**Level III-2**).
14. Pethidine is less effective than most other migraine treatments and should not be used (**U**) (**Level I**).
15. Magnesium IV has no analgesic effect compared to placebo in migraine (**N**) (**Level I**).
16. Parenteral prochlorperazine, chlorpromazine or droperidol are effective in the treatment of migraine, especially in the emergency department (**U**) (**Level II**).
17. A "stratified care strategy" is effective in treating migraine (**U**) (**Level II**).

18. Ergotamine derivatives, but not triptans, increase the rate of severe myocardial ischaemic events (**N**) (**Level III-2 SR**).
19. Migraine in pregnancy is a risk factor for gestational hypertension, preeclampsia and cardiovascular complications (**N**) (**Level III-2**).

Cluster headache

20. Parenteral triptans (sumatriptan or zolmitriptan) or high-flow oxygen therapy are effective treatments for cluster headache attacks (**S**) (**Level I** [Cochrane Review]).

Postdural puncture headache

21. There is no evidence that bed rest or fluid supplementation are beneficial in the treatment and prevention of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).
22. Epidural blood patch administration is more effective than conservative treatment or a sham procedure in the treatment of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).
23. Morphine, cosyntropin and aminophylline are successful treatments for postdural puncture headache; dexamethasone is not, with inconclusive data for fentanyl, caffeine and indomethacin (N) (**Level I** [Cochrane Review]).
24. The incidence of postdural puncture headache is reduced by using smaller-gauge spinal or non-cutting bevel needles or by orientating the cutting bevel parallel to the spinal sagittal plane (**S**) (**Level I**).
25. IV theophylline, IV hydrocortisone, gabapentin and pregabalin are effective in the treatment of postdural puncture headache (N) (**Level II**).

☑ Opioids should be used with extreme caution in the treatment of headache; pethidine should not be used (**S**).

☑ Frequent use (>8–10 days/month) of analgesics, triptans and ergot derivatives in the treatment of recurrent acute headache may lead to medication overuse headache (**U**).

Acute pain associated with neurological disorders

1. Various anticonvulsants have an effect in the treatment of neuropathic pain associated with multiple sclerosis (**N**) (**Level I** [PRISMA]).
2. Cannabinoids have a clinically small effect on spasticity caused by multiple sclerosis; the effect on neuropathic pain associated with multiple sclerosis is unclear and may depend on the preparation used (**N**) (**Level I**).
3. With cannabinoid use in multiple sclerosis, serious adverse psychopathological effects occur in nearly 1% of patients (**N**) (**Level I**).

☑ Treatment of acute pain associated with neurological disorders is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain states.

Orofacial pain

Acute dental pain

1. NSAIDs and emergency pulpectomy reduce pain in patients with acute apical periodontitis (**N**) (**Level I**) with insufficient evidence to support analgesic benefit from adding antibiotics (**N**) (**Level I** [Cochrane]).

Dental extraction

2. Paracetamol, nonselective NSAIDs and coxibs provide safe and effective analgesia with minimal adverse effects following dental extraction (**S**) (**Level I** [Cochrane Review]).
3. Nonselective NSAIDs and coxibs provide similar analgesia, which is superior to paracetamol, codeine, combinations of paracetamol/codeine (**N**) (**Level I**) and pethidine/tramadol (**N**) (**Level II**) after dental extraction.

4. Combinations of paracetamol with ibuprofen (**N**) (**Level I** [Cochrane Review]) and other nonselective NSAIDs (**N**) (**Level I**) provide superior analgesia to either drug alone after dental extraction.
5. Tramadol provides equal analgesia to paracetamol/weak opioid and aspirin/weak opioid combinations (**N**) (**Level I** [Cochrane Review]) and tramadol/paracetamol combinations provide superior analgesia to tramadol alone after dental extraction (**N**) (**Level I**).
6. Perioperative corticosteroid administration reduces swelling, but not pain (**U**) (**Level I**), and reduces postoperative nausea (**U**) (**Level II**) following third molar extraction.

Tonsillectomy

7. Paracetamol and NSAIDs are effective analgesics after tonsillectomy (**N**) (**Level I**); paracetamol may be comparable to nsNSAIDs in this setting (**N**) (**Level II**)
8. Nonselective NSAIDs (**U**) (**Level I**), in particular aspirin and ketorolac (**U**) (**Level II**), increase the risk of reoperation for bleeding after tonsillectomy in adults, but not in children (**U**) (**Level I** [Cochrane Review]).
9. Intraoperative dexamethasone administration reduces postoperative pain, nausea and vomiting and time to resumption of oral intake post-tonsillectomy (**S**) (**Level I** [Cochrane Review]), with no increase in adverse effects (**R**) (**Level I** [Cochrane Review]).
10. Peritonsillar infiltration or topical application of local anaesthetics produces a modest reduction in acute post-tonsillectomy pain with topical application and infiltration being equally effective (**U**) (**Level I**).
11. Perioperative antibiotics show no benefit in post-tonsillectomy pain, but increase adverse effects (**N**) (**Level I**).
12. Preoperative gabapentinoids improve analgesia after tonsillectomy (**N**) (**Level II**).
13. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements but was no more effective than equivalent doses administered parenterally (**U**) (**Level II**).

Pharyngitis

14. Corticosteroids (**S**) (**Level I** [Cochrane Review]) and antibiotics (**N**) (**Level I** [Cochrane Review]) improve analgesia and reduce duration of pain in pharyngitis.
15. Paracetamol, NSAIDs (nonselective NSAIDs or coxibs) and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**U**) (**Level I**).
16. Benzydamine spray (**N**) (**Level I)** and other topical analgesics (**N**) (**Level II**) provide analgesia superior to placebo in acute sore throat with minimal adverse effects.
17. Corticosteroids reduce acute pain associated with peritonsillar abscess (following drainage and antibiotics) (**U**) (**Level II**).

Sinusitis

18. Oral corticosteroids have no analgesic effect in sinusitis (**N**) (**Level I** [Cochrane Review]), but intranasal corticosteroids reduce facial pain (**N**) (**Level I**).

Oral mucositis

19. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis; PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
20. Topical treatments (**U**) (**Level I**), including povidone-iodine (**U**) (**Level I**), doxepin mouthwash (**N**) (**Level II**) and morphine (**N**) (**Level II**), provide analgesia in mucositis.
21. There is limited evidence that oral laser light therapy reduces mucositis pain and progression (**U**) (**Level II**).

- ☑ Codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**N**).
- ☑ Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches (**U**).
- ☑ Neuropathic orofacial pain, which is often post-traumatic (iatrogenic), may be exacerbated by repeated dental procedures, incorrect drug therapy or psychosocial factors (**S**).

Acute pain in patients with HIV infection

1. High-concentration capsaicin patches have limited efficacy in treating neuropathic pain in patients with HIV/AIDS **(S)** (**Level I** [Cochrane]).
2. Smoking cannabis is effective in treating neuropathic pain in patients with HIV/AIDS, although potential study bias and legal constraints mean that this is not recommended as routine treatment **(S)** (**Level I** [PRISMA])**.**
3. Lamotrigine is not effective in treating neuropathic pain in patients with HIV/AIDS (**R**) (**Level I** [PRISMA]).
4. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use but also more intense pain (**U**) (**Level III-2**).
5. Pain, and notably neuropathic pain, is common in patients with HIV (**S**) (**Level IV**).

- ☑ HIV/AIDS has become a chronic, manageable condition; in view of limited specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of acute, cancer and chronic pain in the general population (**N**).
- ☑ Interactions between antiretroviral and antibiotic medications and analgesics should be considered in this population (**U**).

Acute cancer pain

1. Transmucosal fentanyl formulations are rapidly effective in treating acute breakthrough pain in cancer patients (**S**) (**Level I** [Cochrane Review]).
2. Radiotherapy and bone-targeting agents (bisphosphonates, denosumab) are effective treatments of acute cancer pain due to bone metastases (**S**) (**Level I** [Cochrane Review]).
3. Neurolytic coeliac plexus block in pancreatic cancer lowers pain intensity and opioid analgesic requirements for at least 8 weeks (**N**) (**Level I** [Cochrane Review]).
4. Patient education about cancer pain is a key factor in optimising pain management (**N**) (**Level I**).
5. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects (**S**) (**Level II**).
6. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity (**U**) (**Level III**).
7. Neuropathic pain or mixed nociceptive-neuropathic pain has an estimated frequency of 40% in patients with cancer (**N**) (**Level IV SR**).

- ☑ Acute pain in patients with cancer often signals disease progression; sudden severe pain in patients with cancer should be recognised as a medical emergency and immediately assessed and treated (**U**).
- ☑ Prompt assessment and fast coordinated management of spinal metastases with suspected spinal cord compression is required to mitigate against neurological deficit (**N**).
- ☑ Cancer patients receiving controlled-release opioids need access to immediate-release opioids for titration of breakthrough pain; selection of breakthrough medication should consider the time course and aetiology of the pain flare (**S**).
- ☑ If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed (**U**).

☑ Transdermal opioids are inappropriate to control acute unstable pain (**N**).

☑ High interindividual variability in opioid conversion rates dictates that all opioid rotations should be individualised and monitored, particularly where higher opioid doses are in use (**N**).

Acute pain management in intensive care

1. Remifentanil provides no advantages over other opioids in ventilated intensive care unit patients (**R**) (**Level I**).
2. Carbamazepine and gabapentin may reduce the pain associated with Guillain-Barre syndrome, based on limited and low-quality evidence (**W**) (**Level I** [Cochrane Review]).
3. Plasma exchange in acute Guillain-Barre syndrome improves outcome including analgesia (**N**) (**Level I** [Cochrane Review]).
4. NSAIDs and paracetamol improve analgesia in selected intensive care unit patients (**N)** (**Level II**).
5. Daily interruptions of sedative infusions reduce duration of ventilation and ICU stay without causing adverse psychological outcomes (**U**) (**Level II**) or increasing the risk of myocardial ischaemia (**U**) (**Level III-1**).
6. The formal assessment and management of pain and agitation in ventilated intensive care unit patients decreases the incidence of pain and the duration of ventilation (**N**) (**Level III-1**).
7. Procedures such as endotracheal tube suctioning are consistently reported as uncomfortable and painful (**N**)(**Level III-2**).

☑ Observation of behavioural and physiological responses permits assessment of pain in unconscious patients (**U**).

☑ Routine monitoring for pain in sedated intensive care patients should be performed, using the Behavioural Pain Scale and the Critical-Care Pain Observation Tool (**N**).

☑ Intensive care unit patients should be provided with appropriate analgesia prior to and during potentially painful procedures (**S**).

☑ Opioids are the recommended first-line analgesic agents in ventilated intensive care patients (**N**).

Acute pain management in emergency departments

1. Appropriate doses of intravenous opioids are effective in treating acute severe pain in the emergency department and ideally should be titrated according to nurse-initiated and patient-driven protocols; there is no preference for a specific opioid (**N**) (**Level I**).

Abdominal pain

2. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).

Migraine (see also Section 8.6.5)

3. NSAIDs, triptans, phenothiazines (prochlorperazine, chlorpromazine) and metoclopramide are effective to treat migraine in the emergency department (**S**) (**Level I**).

Fractured neck of femur

4. Nerve blocks with local anaesthetics reduce pain and analgesia requirements in fractured neck of femur (**N**) (**Level I**).
5. Femoral nerve blocks in combination with intravenous opioids are superior to intravenous opioids alone in the treatment of pain from a fractured neck of femur (**U**) (**Level II**).

Local anaesthesia

6. Buffering of lignocaine with bicarbonate reduces the pain of infiltration, particularly when using lignocaine with adrenaline (**N**) (**Level I** [Cochrane Review]).
7. Topical local anaesthetic agents (including those in liposomal formulations) (**U**) (**Level I**) or topical local anaesthetic-adrenaline agents (**U**) (**Level II**) provide effective analgesia for wound care in the emergency department.

☑ To ensure optimal management of acute pain, emergency departments should adopt systems to ensure adequate assessment of pain, provision of timely, adequate and appropriate analgesia, frequent monitoring and reassessment of pain (**U**).

Prehospital analgesia

1. Intravenous morphine, fentanyl and tramadol are equally effective in the prehospital setting (**N**) (**Level II**).
2. Nitrous oxide is an effective analgesic agent in prehospital situations (**S**) (**Level II**).
3. Methoxyflurane, in low concentrations, is an effective analgesic with rapid onset in the prehospital and hospital setting with good safety data (**S**) (**Level II**).
4. Ketamine is a safe and effective analgesic in the prehospital setting (**S**) (**Level II**).
5. Effective early treatment of trauma pain may reduce the incidence of post-traumatic stress disorder (**N**) (**Level III-3**).
6. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**U**) (**Level IV**).
7. Oral transmucosal fentanyl may be an effective and easy to administer alternative to intravenous morphine for trauma pain in the prehospital setting (**N**) (**Level IV**).

☑ Nonpharmacological measures are effective in providing pain relief and should always be considered and used if practical (**U**).

Discharge medication for acute pain management

1. Short-term opioid therapy may lead to long-term opioid use (**N**) (**Level III-2**).
2. Recent introduction of opioid therapy may increase the risk of falls (**N**) (**Level III-2**).
3. Recent introduction of opioid therapy or recent dose escalation may impair driving (**N**) (**Level III-2**).
4. Many patients who retain unused opioid tablets are willing to share them with others (**N**) (**Level III-2**).
5. The most common source of prescription opioids for nonmedical use is a friend or relative (**N**) (**Level III-3**).

☑ Unused opioids prescribed for postoperative pain are potentially a large reservoir for opioid abuse, misuse and diversion (**N**).

☑ Screening tools used to assess the risk of opioid misuse prior to opioid prescription in chronic pain patients may be used before prescribing discharge opioids (**N**).

☑ A “universal precautions” approach for opioid prescribing should be used in the setting of prescribing discharge medications (**N**).

9. THE PAEDIATRIC PATIENT

Consequences of early pain and injury

1. Pain and injury in early life cause structural changes in cortical and subcortical pathways and are associated with alteration in somatosensory thresholds in later life (**S**) (**Level III-2**).
2. Analgesia may modulate the long-term effects of pain and injury in early life but more information is required to determine the optimal dosing and type of agents to avoid negative impact of the pharmacological intervention itself (**N**) (**Level III-2**).
3. Improving quality of infant pain management delivery in neonatal intensive care (including pharmacological and nonpharmacological interventions) may result in improved neurodevelopmental outcomes (**N**) (**Level III-2**).

Paediatric pain assessment

1. Pain measurement tools are available for children of all ages (**S**) (**Level IV** SR).
2. Paediatric pain measurement tools must be matched to the age and development of the child (**S**) (**Level IV** SR).

☑ Pain assessment and measurement are important components of paediatric pain management (**U**).

☑ Pain measurement tools must be appropriate for the clinical context and be explained and used consistently (**Q**).

Analgesic agents

Paracetamol

1. Paracetamol is effective for moderately severe pain and decreases opioid requirements after major surgery in children (**S**) (**Level I**) (PRISMA).
2. Paracetamol has a similar safety and tolerability profile compared with ibuprofen and placebo if prescribed and administered at recommended doses in children (**N**) (**Level IV SR**).

☑ Safe dosing of paracetamol requires consideration of the age and body weight of the child and the duration of therapy (**U**).

☑ Retrospective epidemiological studies linking paracetamol use to later development of childhood disorders such as asthma are inherently confounded (**N**).

Nonselective NSAIDs

1. Nonselective NSAIDs do not increase the risk of either surgical or nonsurgical intervention for bleeding after tonsillectomy in paediatric patients (**S**) (**Level I** [Cochrane Review]).
2. Nonselective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major paediatric surgery (**S**) (**Level I** [PRISMA]) and postoperative nausea and vomiting (**N**) (**Level I** [QUOROM]).
3. Serious adverse effects after nonselective NSAIDs are rare in children over 6 months of age (**S**) (**Level II**)
4. Short term use of ketorolac does not increase rates of nonunion or reoperation in children undergoing posterior spinal fusion, osteotomy or fracture surgery (**N**) (**Level III-3**).

☑ Aspirin should be avoided in children (**U**).

☑ Combined population pharmacokinetic-pharmacodynamic modelling is required to inform targeted dosing recommendations of analgesics in children (**N**).

Coxibs

☑ The safety profile of coxibs in the setting of allergy or contraindication to nonselective NSAID in adults and children is encouraging (**N**).

Opioids

1. The efficacy of oral codeine in children is unpredictable due to genetic differences in the ability to generate the active metabolite morphine (**S**) (**Level II**), as are adverse effects and serious toxicity (**S**) (**Level IV**).
2. Young and obese children with history of obstructive sleep apnoea syndrome are at higher risk of developing serious opioid-induced ventilatory impairment and death (**N**) (**Level IV**).
3. Safe dosing of opioids requires consideration of the child's age, body weight, comorbidities and ethnicity (**N**) (**Level IV**).

☑ Careful titration of opioids is advised according to the individual child's response (analgesia and adverse effects) (**N**).

☑ Because of its unpredictable effect, codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**N**).

☑ The practice of applying an occlusive dressing to the skin surface of a transdermal opioid delivery system to limit drug delivery is not supported (**N**).

Tramadol

1. Tramadol has similar efficacy to opioids in children of all ages administered by various routes for multiple surgery types (**N**) (**Level II).**

☑ Tramadol shares some adverse effects with the opioid class in children, with similar or reduced rates of nausea and vomiting, sedation and fatigue but less constipation and pruritus (**N**).

☑ Tramadol may cause less ventilatory impairment in adults and children. However, as its active opioid metabolite (M1) is produced by CYP2D6, it may share in part the concerns raised for codeine (and hydrocodone) in patients who are ultrametabolisers, particularly when at risk of opioid-induced ventilatory impairment (**N**).

☑ Tramadol concentrated drops formulation use is potentially harmful in children with possible dosing confusion (drops with millilitres) and resultant overdose (**N**).

Ketamine

1. Low-dose ketamine bolus IV perioperatively is similarly effective to opioids and superior to placebo in reducing early pain scores and analgesic requirements in children (**N**) (**Level I** [PRISMA]).
2. Low-dose ketamine bolus IV perioperatively does not increase the postoperative incidence of nausea and vomiting, sedation, agitation, dreams or hallucinations in children (**N**) (**Level I** [QUOROM]).
3. Peritonsillar infiltration and topical application of ketamine for paediatric tonsillectomy reduces early pain scores and analgesic requirements versus placebo (**N**) (**Level I** [PRISMA]).
4. When added to multimodal analgesia, low-dose intra and postoperative ketamine infusion for minor or moderately invasive paediatric surgery is not opioid sparing with similarly low pain scores vs placebo (**N**) (**Level II**).

☑ High-dose long-term ketamine is neurotoxic in animal models. The neurodevelopmental impact in children of subanaesthetic/analgesic doses of ketamine administered by bolus or postoperative infusion is unclear (**N**).

☑ The benefit of perioperative ketamine in preventing remifentanil-induced hyperalgesia has not been adequately assessed in paediatric surgery (**N**).

Alpha-2-delta ligands (gabapentin/pregabalin)

1. Preoperative oral clonidine reduces postoperative pain scores and analgesic requirement in children compared to placebo or midazolam but not fentanyl **(N) (Level I** [Cochrane Review]).
2. Preoperative oral clonidine reduces postoperative nausea and vomiting in children compared to placebo or midazolam **(N)** (**Level I** [Cochrane Review]).
3. Intraoperative dexmedetomidine reduces postoperative pain scores and need for opioid rescue in children compared to placebo via intravenous (**N**) (**Level I** [PRISMA]) and intranasal route (**N**) (**Level II**).

☑ Alpha-2 adrenergic agonists offer benefits in addition to analgesia in children in the perioperative, intensive care and procedural settings. These benefits include anxiolysis, sedation, behavioural modification, reduction of emergence agitation and prevention or treatment of opioid withdrawal (facilitating opioid weaning) (**N**).

Corticosteroids

1. Dexamethasone reduces pain post tonsillectomy, postoperative vomiting and time to soft diet commencement in children (**S**) (**Level I** [Cochrane Review]).
2. Dexamethasone does not increase the overall risk of bleeding post tonsillectomy but increases the risk of reoperation for bleeding in children (**Q**) (**Level I**).
3. Dexamethasone (given in addition to antibiotics) shortens the time to onset of pain relief in pharyngitis in children (**N**) (**Level I**).

Opioid infusions and PCA

1. In ventilated preterm neonates, routine use of morphine infusions does not affect mortality, duration of ventilation or neurological outcomes (**Q**) (**Level I** [Cochrane Review]), including when followed up as older children (**N**) (**Level III-3**).
2. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**U**) (**Level II**).
3. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).
4. Patient-controlled analgesia (PCA) can provide safe and effective analgesia for children as young as 5 years old (**S**) (**Level III-3**).
5. Intravenous opioids via continuous infusion, nurse-controlled analgesia and parental proxy use of PCA devices can be used effectively in children of all ages (**S**) (**Level III-2**).
6. Nurse-controlled analgesia (**N**) (**Level III-2**) and parental proxy use of PCA devices in children (**N**) (**Level III-3**) may require more rescue interventions (such as naloxone, airway management or intensive care) but this may reflect the younger patient population where this technique is offered.

☑ Initial doses of opioid should be based on the age, weight and clinical status of the child and then titrated against the individual's response (**U**).

☑ Effective PCA prescription in children incorporates a bolus that is adequate for control of movement-related pain, and may include a low-dose background infusion (**W**).

Regional analgesia

1. Topical local anaesthetic does not adequately control pain associated with circumcision in awake neonates (**U**) (**Level I** [Cochrane Review]).
2. Caudal local anaesthetic and dorsal penile nerve block provide perioperative analgesia for circumcision in infants to adolescents (**U**) (**Level I** [Cochrane Review]).

3. Caudal local anaesthetic in addition to general anaesthesia for circumcision does not reduce postoperative nausea and vomiting or the need for early rescue or other analgesia in (infant to adolescent) boys, when compared to parenteral analgesia (**N**) (**Level I** [Cochrane Review]).
4. In acute otitis media, topical local anaesthetic drops are effective in children compared to placebo and equivalent to naturopathic drops (**N**) (**Level I** [Cochrane Review]).
5. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia but not motor block (**N**) (**Level** I [PRISMA]); however concerns regarding neurotoxicity remain.
6. Clonidine improves analgesia in children when added to caudal local anaesthetic blocks (**S**) (**Level I**) [PRISMA] and epidural local anaesthetic infusions (**U**) (**Level II**).
7. In children having scoliosis surgery, the addition of epidural local anaesthetic infusion to IV PCA morphine improves pain scores and patient satisfaction (**N**) (**Level I**) and decreases postoperative nausea (**N**) (**Level II**).
8. Wound infiltration, peripheral nerve blocks, and caudal local anaesthetic provide effective analgesia after day-case paediatric inguinal surgery (**U**) (**Level II**).
9. Epidural infusions of local anaesthetic in children provide similar levels of analgesia compared to systemic opioid infusion (**U**) (**Level II**) and intravenous patient-controlled analgesia (**N**) (**Level III-3 SR**).
10. Epidural opioids alone are less effective than local anaesthetic or combinations of local anaesthetic and opioid in children (**U**) (**Level II**).
11. Intrathecal opioids provide prolonged analgesia after surgery in children and reduce blood loss during paediatric spinal fusion (**U**) (**Level II**).
12. Continuous epidural infusions provide effective postoperative analgesia in children of all ages (**S**) (**Level III-2**).
13. Continuous epidural infusions are safe in children of all ages (**S**) (**Level III-2**) if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**S**) (**Level IV**).
14. Complications of epidural infusions are rare; the rates are slightly higher in neonates and infants versus older children (**N**) (**Level III-2**).
15. Peripheral nerve and neuraxial blocks (as single injections and continuous catheters) are safe and effective analgesic techniques in children (**N**) (**Level IV**).
16. Placement of neuraxial blocks in children under general anaesthesia is not associated with an increased rate of complications (**N**) (**Level IV**).
17. Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery and have a low incidence of serious complications (**S**) (**Level IV**).

Management of procedural pain in children

1. Sweet-tasting solutions (sucrose, glucose and other) reduce pain scores and behavioural response for skin-breaking procedures in neonates (**S**) (**Level I** [Cochrane Review]).
2. Breastfeeding reduces infant heart rate response and crying compared to positioning, holding by mother, placebo, pacifier use, no intervention and/or oral sucrose for skin-breaking procedures in neonates (**S**) (**Level I** [Cochrane Review]).
3. Supplemental breast milk reduces heart rate response and crying when compared to placebo but not when compared to sucrose, glycine, pacifier use, rocking or no intervention for skin-breaking procedures in neonates (**N**) (**Level I** [Cochrane Review]).

4. Sweet-tasting solutions preimmunisation reduce incidence and duration of crying in infants (1–12 months) (**N**) (**Level I** [Cochrane Review]) but not in children older than 12 months (**N**) (**Level II**).
5. Providing physical comfort measures, including kangaroo care (maternal or alternate provider), facilitated tucking (swaddling) or non-nutritive sucking (alone or combined with sweet-tasting solutions) reduces pain experienced by term and preterm neonates having skin-breaking procedures (**N**) (**Level I** [Cochrane Review]).
6. EMLA® is an effective topical anaesthetic for children but amethocaine is superior for reducing needle-insertion pain (**U**) (**Level I** [Cochrane Review]).
7. Topical local anaesthetic application (**S**) (**Level I** [Cochrane Review]), inhalation of nitrous oxide (50%) or the combination of both provides effective and safe analgesia for minor procedures in children (**S**) (**Level I** [PRISMA]).
8. Distraction reduces pain (**Q**) (**Level I** [Cochrane Review]) and hypnosis reduces both pain and distress associated with needle-related procedures in children and adolescents (**S**) (**Level I** [Cochrane Review]).
9. Active and passive music therapy reduces pain and anxiety associated with needle-related procedures in children (**N**) (**Level I**).
10. Combinations of hypnotic and analgesic agents are effective for procedures with moderate pain severity in children (**U**) (**Level II**).
11. Prior application of nonpharmacological physical interventions (cold and vibration) reduced the pain of venipuncture in children (**N**) (**Level II**).
12. Intranasal fentanyl is equivalent to intravenous or intramuscular morphine in reducing pain associated with paediatric fracture presenting to the emergency department (**N**) (**Level II**) and incorporated into a triage protocol achieves earlier onset opioid analgesia compared to intravenous morphine intervention (**N**) (**Level III-2**).
13. In paediatric trauma, prehospital administration of intranasal fentanyl and inhaled subanaesthetic doses of methoxyflurane provides equivalent analgesia to intravenous morphine (**N**) (**Level III-2**).
14. Ketamine is an effective analgesic for children in the prehospital and emergency department settings and is safe and effective for paediatric procedural pain management (**N**) (**Level IV**).

☑ Inadequate monitoring of the child, lack of adequate resuscitation skills and equipment, and the use of multiple medicine combinations has been associated with major adverse outcomes during procedural analgesia and sedation (**U**).

☑ Hypnosis requires teaching by a trained professional but distraction can be readily provided by staff or parents and should be routinely offered in the paediatric setting (**N**).

Acute pain in children with cancer

1. Patient-controlled analgesia and continuous opioid infusions are equally effective in the treatment of pain in mucositis in children but opioid consumption and duration of pain is less with patient-controlled analgesia (**S**) (**Level I** [Cochrane Review]).
2. There is very limited evidence that low-level laser treatment, topical Vitamin E and debridement reduces the severity of the mucositis in children (**N**) (**Level I** [Cochrane Review]).
3. Patient-controlled morphine and hydromorphone are equally effective for the control of pain associated with oral mucositis in children (**U**) (**Level II**).
4. Topical local anaesthetic application for children having central venous port access is effective and analgesia is not further improved by oral analgesics (morphine or paracetamol) (**N**) (**Level II**).

☑ In paediatric cancer pain management, the same therapeutic approaches as in adults are used, although evidence is limited (**N**).

☑ The World Health Organization has removed codeine from the management approach to paediatric cancer pain reducing the number of tiers from three to two: with tier one including nonopioid analgesics and adjuvants and tier two including strong opioids (**N**).

Paediatric migraine

1. In children and adolescents, effective migraine treatments include ibuprofen and intranasal sumatriptan, however there is a significant placebo response rate in this setting (**N**) (**Level I**).
2. Nonpharmacological preventive therapies including relaxation training, biofeedback and cognitive-behavioural therapy reduce the intensity of headache in adolescents for 1 year (**N**) (**Level I**).

☑ Guidelines for the treatment of migraine in children and adolescents recommend environment modification, paracetamol, ibuprofen, naproxen (or other nonselective NSAIDs), dopamine antagonists (if nausea prominent), fluid therapy and intranasal (and oral) triptans. Nonpharmacological interventions should also be considered based on their efficacy as preventive strategies (**N**).

10. OTHER SPECIFIC PATIENT GROUPS

The pregnant patient

Use of analgesics in pregnancy

1. Short-term use of NSAIDs in late pregnancy is associated with a significant increase in the risk of premature closure of the ductus arteriosus (**N**) (**Level I** [Cochrane Review]).
2. No significant impairments for cognitive, psychomotor or observed behavioural outcomes are observed in children after chronic intrauterine opioid exposure (**N**) (**Level III-2 SR**).
3. Use of NSAIDs during pregnancy may be associated with an increased risk of miscarriage, however study results are contradictory (**W**) (**Level III-2**).
4. Epidemiological data show an association between paracetamol use during pregnancy and subsequent development of childhood wheezing and asthma but causation has not been proven (**N**) (**Level III-3 SR**).

☑ For pain management in pregnancy nonpharmacological treatment options should be considered where possible before analgesic medications are used (**U**).

☑ Use of medications for pain in pregnancy should be guided by published recommendations; ongoing analgesic use requires close liaison between the health professional managing the pregnancy and the health professional managing the pain (**U**).

☑ Nonselective NSAIDs and Coxibs should be used with caution in the last trimester of pregnancy and should be avoided after the 32nd week (**U**).

Painful conditions in pregnancy

1. Exercises or acupuncture reduce low-back and pelvic-girdle pain during pregnancy (**N**) (**Level I** [Cochrane Review]).
2. Chiropractic care reduces low-back pain during pregnancy (**N**) (**Level IV SR**).

Neuraxial and regional analgesia

1. Epidural and combined spinal-epidural analgesia provide superior pain relief for labour and childbirth compared with all other analgesic techniques (**S**), however with no difference in maternal satisfaction (**N**) (**Level I** [Cochrane Review]) except in comparison with remifentanil IV PCA (**N**) (**Level II**).

2. Epidural analgesia reduces the risk of fetal acidosis (**N**), increases the duration of the second stage of labour slightly (**Q**) and the rate of instrumental birth (**U**) but does not increase the rate of Caesarean delivery (**U**) or long-term backache (**U**) (**Level I** [Cochrane Review]).
3. Early versus late initiation of epidural analgesia leads to no clinically significant differences in outcome (**N**) (**Level I** [Cochrane Review]).
4. Lower concentrations of local anaesthetics for epidural analgesia in labour result in a shorter duration of second stage of labour, fewer assisted vaginal births, greater ambulation and less urinary retention than higher concentrations (**N**) (**Level I** [Cochrane Review]).
5. In comparison with epidural analgesia, combined spinal-epidural analgesia reduces time to effective analgesia (**U**), does not increase maternal satisfaction (**U**) and increases the incidence of mild pruritus (compared to low-dose epidurals) (**Q**) (**Level I** [Cochrane Review]).
6. Local anaesthetic nerve blocks (in particular paracervical blocks) provide better analgesia than placebo, nonopioids and opioids for labour pain but with an increased rate of adverse effects (**N**) (**Level I** [Cochrane Review]).
7. Patient-controlled epidural analgesia provides effective analgesia for labour (**U**) but optimal settings (**U**) (**Level I**), the need for a background infusion and the utility of programmed intermittent boluses remain unclear (**N**) (**Level I** [PRISMA]).
8. There is no significant difference between use of bupivacaine and ropivacaine for epidural analgesia in labour for any outcome (**U**) (**Level I**).
9. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics, with increased pruritus but no difference in nausea (**U**) (**Level I**).

Systemic analgesia

10. Analgesic concentrations of inhaled volatile anaesthetics provide superior analgesia in labour but more drowsiness, compared to nitrous oxide (**N**) (**Level I** [Cochrane Review]).
11. Nitrous oxide has some analgesic efficacy in labour pain (**S**), increases maternal adverse effects (nausea, vomiting, dizziness) (**N**) but has no adverse effects on the newborn (**S**) (**Level I** [Cochrane Review]); pain relief is comparable to pethidine but inferior to epidural analgesia (**N**) (**Level IV SR**).
12. Use of nonopioid analgesics alone for labour analgesia is not supported by current evidence (**N**) (**Level I** [Cochrane Review]).
13. Parenteral opioids provide moderate analgesic effects in labour pain (**N**), are inferior to epidural analgesia (**N**) and cause increased adverse maternal effects (sedation, nausea, vomiting) (**N**) and adverse short-term effects on the newborn, although long-term effects remain unclear (**W**) (**Level I** [Cochrane Review]).
14. Remifentanil intravenous PCA provides better analgesia in labour compared to parenteral pethidine (**N**) (**Level I**) and probably nitrous oxide (**N**) (**Level II**) but is inferior to epidural analgesia (**N**) (**Level I**).

Complementary and other methods of pain relief in labour

15. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, rate of instrumental and operative birth and dissatisfaction (**S**) (**Level I** [Cochrane Review]).
16. Immersion in water during labour may reduce the requirements for regional and neuraxial analgesia, without any increase of adverse effects on mother or newborn compared to standard care (**N**) (**Level I** [Cochrane Review]).
17. Relaxation by use of instructions and yoga, but not by music or “audioanalgesia”, may reduce labour pain intensity and increases maternal satisfaction compared to standard care (**N**) (**Level I** [Cochrane Review]).

18. Acupuncture and acupressure reduce labour pain, use of pharmacological pain relief, instrumental birth rates and increase satisfaction with pain management compared to standard care or placebo (**S**) (**Level I** [Cochrane Review]).
19. Massage reduces pain during the first stage of labour and improves emotional wellbeing (**N**) (**Level I** [Cochrane Review]).
20. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour, with the exception of reduction of reports of severe pain when applied to acupuncture points (**Q**) (**Level I** [Cochrane Review]).
21. Hypnosis (**R**), biofeedback (**N**), sterile water injections intra or subcutaneously (**N**) and aromatherapy (**N**) have no effect on labour pain or other outcomes (**Level I** [Cochrane Review]).

Pain relief after Caesarean delivery

22. Local anaesthetic wound infiltration, in particular abdominal nerve blocks, reduce opioid consumption following Caesarean delivery (**S**) (**Level I** [Cochrane Review]).
23. Local anaesthetic transversus abdominis plane blocks reduce postoperative opioid requirements and pain scores after Caesarean delivery but only when intrathecal morphine is not used (**N**) (**Level I** [PRISMA]).
24. In relation to controls only and with no direct comparison between the two approaches, local anaesthetic transversus abdominis plane blocks performed by a posterior approach provide longer duration of benefit versus the lateral approach after lower abdominal incision surgery including Caesarean delivery (N) (**Level I** [PRISMA]).
25. Epidural (**N**) (**Level I** [QUOROM]) and intrathecal morphine (**N**) (**Level I**) and patient-controlled epidural analgesia (**N**) (**Level II**) provide effective analgesia after Caesarean delivery but neuraxial morphine increases the rate of pruritus and nausea compared with systemic administration (**N**) (**Level I** [QUOROM]).

☑ Remifentanil IV PCA for relief of labour pain carries a risk of maternal respiratory depression; use is recommended only if there is one-on-one continuous presence of a midwife, continuous oxygen saturation monitoring and continuous cardiotocograph monitoring (as an indirect method of detecting global hypoxaemia) (**N**).

☑ Transversus abdominis plane blocks after Caesarean delivery may result in high plasma concentrations of local anaesthetic and potential toxicity; minimum effective doses should be used (**N**).

Lactation

1. Local anaesthetics, paracetamol and several NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (**S**) (**Level IV**).
2. Morphine, fentanyl, methadone, and short-term oxycodone immediately after giving birth are considered to be safe in the lactating patient and are preferred over pethidine (**S**) (**Level IV**).
3. Repeated dosing of codeine or oxycodone in lactating patients should be avoided if possible and the infant monitored for central nervous system depression (**S**) (**Level IV**).

☑ Prescribing medications during lactation requires consideration of possible transfer into breast milk, uptake by the infant and potential adverse effects for the infant; it should follow available prescribing guidelines (**U**).

Pain in the perineum

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I** [Cochrane Review]).
2. Continuous suturing of all layers compared with interrupted suturing for repair of episiotomy or second-degree tears reduces perineal pain and analgesic use in the postpartum period (**N**) (**Level I** [Cochrane Review]).

3. Paracetamol and NSAIDs are effective in treating perineal pain after childbirth (**S**) (**Level I** [Cochrane Review]).
4. NSAIDs, but not paracetamol, are effective in treating pain from uterine cramping after vaginal birth (**Q**) (**Level I** [Cochrane Review]).
5. There is limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
7. There is insufficient evidence to recommend any specific treatments for nipple pain and breast engorgement (**W**) (**Level I** [Cochrane Review]).

☑ Pain after childbirth requires appropriate treatment as it coincides with new emotional, physical and learning demands and may trigger postnatal depression (**U**).

☑ Management of breast and nipple pain should target the cause (**U**).

The older patient

1. Topical nsNSAIDs for localised pain provide effective analgesia (**S**) (**Level I** [Cochrane Review] with lower plasma concentrations and fewer gastrointestinal adverse effects than oral nsNSAIDs (**S**) (**Level I**); this may improve safety in the elderly.
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).
3. Postoperative cognitive dysfunction is relatively common after surgery and the older patient is particularly at risk (**N**) (**Level III-2 SR**).
4. Experimental pain thresholds to thermal stimuli are modestly increased in older people (**W**) (**Level III-2 SR**).
5. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
6. Common unidimensional self-report measures of pain can be used in the older patient in the acute pain setting; in the clinical setting, the verbal descriptor and numerical rating scales are preferred (**S**) (**Level III-2**).
7. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**U**) (**Level III-2**).
8. The use of nsNSAIDs and coxibs in older people requires caution, although use of opioids may result in more complications (**Q**) (**Level III-2**); paracetamol is the preferred nonopioid analgesic (**S**) (**Level III-2**).
9. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
10. The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany ageing than to the changes in pharmacokinetics (**S**) (**Level IV**).

☑ The assessment of pain and evaluation of pain relief therapies in the older patient may present problems, arising from differences in reporting, cognitive impairment and difficulties in measurement (**U**).

☑ Measures of present pain may be more reliable than past pain, especially in patients with some cognitive impairment (**U**).

☑ The physiological changes associated with ageing are progressive. While the rate of change can vary markedly between individuals and is related to frailty, these changes may decrease the dose (maintenance and/or bolus) of drug required for pain relief and may lead to increased accumulation of active metabolites (**U**).

Culturally responsive care for Culturally and Linguistically Diverse patients

1. Disparities in assessment, analgesic requirements and effective treatment of pain exist across ethnic groups (**N**) (**Level III-3**).

☑ Cultural competence of health professionals supported by cultural competency training improves health outcomes for culturally and linguistically diverse patients (**N**).

☑ If language proficiency poses a communication barrier, an accredited medical interpreter should be included when conducting a pain assessment, to facilitate a positive outcome for the patient (**N**).

☑ Ethnic and cultural background of both health professional and patient can significantly affect the ability to assess and treat acute pain (**U**).

☑ Multilingual printed information and pain measurement scales are useful in managing patients from different cultural or ethnic backgrounds (**U**).

☑ Pain assessment and management should be done on an individual patient basis. Differences between ethnic and cultural groups should not be used to stereotype patients but should only be used to inform of possible cultural preferences (**N**).

Aboriginal and Torres Strait Islander peoples

1. The verbal descriptor scale may be a better choice of pain measurement tool than verbal numerical rating scales in Aboriginal and Torres Strait Islander peoples (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander peoples and may influence the choice of analgesic agent (**U**) (**Level IV**).

☑ Heterogeneity between differing populations of Aboriginal peoples may require tailoring of the service delivered to the population being serviced (**N**).

☑ Pain expression in Aboriginal and Torres Strait Islander peoples may not reflect that which is expected by the health professional's cultural background. This places the onus on the health professional to understand nuances of pain expression and beliefs within such populations (**N**).

Māori peoples and pain

1. Experimental ischaemic pain is tolerated for longer in Māori people than in European New Zealanders (**N**) (**Level III-2**).
2. Māori people report higher levels of pain and/or disability with dental pain, gout and after trauma and joint replacement surgery than European New Zealanders (**N**) (**Level III-2**).

☑ High healthcare inequalities exist regarding access and quality of care (across age ranges, genders and for various medical conditions) between the Māori and Pacific Islander peoples compared with New Zealanders of European origin (**N**).

☑ Māori culture embraces the multidimensional aspects of pain experiences (**N**).

The patient with sleep-disordered breathing including obstructive sleep apnoea

1. Patients with sleep-disordered breathing, including obstructive sleep apnoea, having surgery are at increased risk of adverse cardiac and respiratory effects (**S**) (**Level III-2 SR**), in particular cardiac arrest/shock, atrial fibrillation, aspiration pneumonia, acute respiratory distress syndrome and need for intubation, mechanical and noninvasive ventilation (**N**) (**Level III-2**).
2. Patients with obstructive sleep apnoea have an increased risk of exacerbation of obstructive episodes and hypoxaemia during the postoperative period (**Q**) (**Level III-2**).
3. Morbidly obese patients may be at increased risk of postoperative hypoxaemia, independent of a diagnosis of obstructive sleep apnoea (**S**) (**Level III-2**).

4. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**U**) (**Level III-2**).
5. Increasing severity of obstructive sleep apnoea is associated with increased risk of postoperative respiratory complications (**N**) (**Level III-3**).

☑ The incidence of obstructive sleep apnoea in the surgical patient population is high and the majority (80%) of these patients are undiagnosed (**N**).

☑ Preoperative screening for obstructive sleep apnoea combined with treatment (ideally instituted preoperatively) and increased postoperative observation may decrease postoperative morbidity and mortality; the STOP-Bang questionnaire can be used to identify patients at risk of significant obstructive sleep apnoea (**N**).

☑ Patients with obstructive sleep apnoea may have increased sensitivity to opioids (**N**).

☑ Management strategies that may increase the efficacy and safety of pain relief in patients with obstructive sleep apnoea include multimodal nonsedating opioid-sparing analgesia including regional techniques, continuous positive airway pressure, monitoring and supervision (in a high-dependency area if necessary) and supplemental oxygen (**S**).

☑ Perioperative commencement of continuous positive airway pressure may be beneficial in patients with obstructive sleep apnoea but requires high levels of supervision and poor patient acceptance and postoperative adherence are significant problems (**N**).

The patient with concurrent renal or hepatic disease

☑ Consideration should be given to choice and dose regimen of analgesic agents in patients with hepatic and particularly renal impairment (**U**).

The opioid-tolerant patient

1. Alpha-2 agonists (clonidine and lofexidine) reduce opioid-withdrawal symptoms (**N**) (**Level I** [Cochrane Review]).
2. Remifentanil use leads to opioid-induced hyperalgesia (**N**), which is attenuated by propofol (**N**) (**Level I** [PRISMA]), NMDA-receptor antagonists (**N**) (**Level I**) and pregabalin (**N**) (**Level II**).
3. Gabapentin and pregabalin attenuate opioid-induced hyperalgesia/tolerance and reduce opioid-withdrawal symptoms (**N**) (**Level II**).
4. In opioid-tolerant patients, ketamine improves pain relief after surgery (**S**) (**Level II**) and may reduce opioid requirements (**N**) (**Level II**).
5. Opioid-tolerant patients report higher pain scores (**U**), have slower pain resolution leading to longer hospital stay and increased readmissions (**N**) but have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
6. Opioid-tolerant patients may have significantly higher opioid requirements and interpatient variation in the doses needed than opioid-naïve patients (**N**) (**Level III-2**).

☑ Usual preadmission opioid regimens should be maintained where possible or appropriate substitutions made (**U**).

☑ Liaison with all health care professionals involved in the treatment of the opioid-tolerant patient is important (**U**).

☑ Opioid-tolerant patients are at risk of opioid withdrawal if nonopioid analgesic regimens or tramadol or tapentadol alone are used (**S**).

☑ PCA settings may need to include a background infusion to replace the usual opioid dose and a higher bolus dose (**U**).

☑ Neuraxial opioids can be used effectively in opioid-tolerant patients, although higher doses may be required and these doses may be inadequate to prevent withdrawal (**S**).

☑ Adjuvants are used for their antitolerance, antihyperalgesic, and antiallodynic effects and there is some evidence upon which to base the choice of agent (**S**).

- ☑ In patients with escalating opioid requirements, management considerations are the development of tolerance or opioid-induced hyperalgesia (**N**).
- ☑ Long-term opioid use may increase the risk of sleep-disordered breathing, which requires appropriate assessment, monitoring and management in the perioperative period (**N**).
- ☑ Following short-term opioid dose escalation for acute pain, a "reverse analgesic ladder" approach, using stepwise reduction to the patient's usual opioid regimen is recommended (**N**).

The patient with an addiction

1. Benzodiazepines are effective for alcohol-withdrawal symptoms, in particular reducing seizures (**N**) (**Level I** [Cochrane Review]).
2. Poorly managed acute pain episodes may decrease retention in opioid-maintenance programs (**N**) (**Level III-2**).
3. Methadone- and buprenorphine-maintenance regimens should be continued throughout acute pain episodes wherever possible (**S**) (**Level III-2**).

- ☑ There is no cross-tolerance between alcohol or benzodiazepines or central nervous system stimulants and opioids (**S**).
- ☑ To achieve better analgesic efficacy, daily methadone and buprenorphine maintenance doses should be divided and given 8 to 12 hourly (**N**).
- ☑ Oral naltrexone should be stopped at least 24 hours prior to elective surgery (**U**); naltrexone implants may need surgical removal in cases of severe acute pain and no opioid responsiveness (**N**).
- ☑ Patients who have completed naltrexone therapy should be regarded as opioid naïve; in the immediate post-treatment phase they may be more opioid sensitive (**U**).

1. PHYSIOLOGY AND PSYCHOLOGY OF ACUTE PAIN

1.1 Applied physiology of acute pain

1.1.1 Definition of acute pain

Pain is defined by the IASP as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey 1994; IASP 2014).

Acute pain is defined as "pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to ijury or disease" (Ready 1992 **GL**). Chronic pain "commonly persists beyond the time of healing of an injury and frequently there may not be any clearly identifiable cause".

It has proven clinically useful to differentiate acute and chronic pain but it is important to recognise that classification based on time has limitations if the underlying pathophysiology is not also taken into consideration (Flor 2014 **NR**). Recent advances have increased understanding of mechanisms that cause transitions from acute to chronic pain (pain chronicity). This has led to improvements in clinical management and, in the future, it may be possible to more directly target the pathophysiological processes associated with specific pain syndromes (Flor 2012 **NR**; von Hehn 2012 **NR**; Denk 2014 **NR**).

Section 1.1 focuses on the physiology and pathophysiology of the transmission and modulation of painful stimuli. Psychological factors that affect the experience of pain are outlined in Section 1.2

In each individual, the "pain experience" will be a result of the interaction of biological, psychological, environmental and social factors. An integrated multidisciplinary approach to management, which also considers patient preferences and prior experience, is thus encouraged.

1.1.2 Nociceptive pathways and pain perception

The ability of the somatosensory system to detect noxious and potentially tissue-damaging stimuli (ie nociception) is an important protective feature that involves multiple interacting peripheral and central mechanisms (Woolf 2010 **NR**). In addition to the sensory effects, the perception and experience of pain is multifactorial and will be influenced by genetic, psychological and environmental factors in every individual (Siddall 2004 **NR**; Fields 2009 **NR**).

1.1.2.1 Peripheral nociceptors

The detection of noxious stimuli by peripheral sensory nerve endings (nociceptors) first requires the transduction of noxious stimuli into electrical activity and the conduction of these nociceptive signals in peripheral sensory nerves to the central nervous system (CNS) (Woolf 2007 **NR**; Dubin 2010 **NR**). Nociceptive primary afferents are widely distributed throughout the body (skin, muscle, joints, viscera, meninges) and comprise both medium-diameter lightly myelinated A-delta fibres and small-diameter, slow-conducting unmyelinated C fibres. Distinct classes of nociceptors are activated by noxious stimuli, which include intense pressure, extreme temperatures (>40–45°C or <15 °C) and damaging chemicals. The most prevalent subclass of nociceptor is the C-fibre polymodal type, which responds to mechanical, thermal and chemical stimuli, whereas other subclasses are specialised mechanical, heat or cold nociceptors. Each class shows further heterogeneity determined by the differential expression of a repertoire of transduction molecules (Dubin 2010 **NR**). For example, the transient receptor potential (TRP) channel transient receptor potential vanilloid 1 (TRPV1) transduces noxious temperatures from 39–51°C and generates electrical receptor potentials in a class of polymodal C fibres. Mechanosensitive channels have been difficult to identify with certainty. Some C-fibre nociceptors are referred to as "silent" and become responsive to heat and chemical stimuli in the presence of inflammation (Dubin 2010 **NR**).

In addition to many different TRP family members (Patapoutian 2009 **NR**), nociceptors express other ion channels that include ligand-gated channels such as acid-sensing ion channels (ASICs), as well as the voltage-gated sodium, potassium and calcium channels (Gold 2010 **NR**; Waxman 2014 **NR**). The particular expression of these transducers determines which modalities are detected by each set of nociceptors. Nociceptors in visceral tissue are different to those in somatic tissue. In the viscera, high threshold specific nociceptors are unusual and most mechanosensitive afferents code stimulation in a linear manner, which can reach the noxious range. There is a large proportion of silent nociceptors in viscera, which may become active in settings of inflammation (Robinson 2008 **NR**).

C fibres may also be classified by their relationship to trophic factors. Some C-fibre nociceptors are dependent on nerve growth factor (NGF) and express tyrosine kinase receptor (TrkA), which is a neurotrophin receptor. Most of these nociceptors also express substance P and calcitonin gene-related peptide (CGRP) and are classed as peptidergic. Another class of C fibres are not peptidergic but have glial-derived neurotrophic factor (GDNF) family receptors (GFRa1 and GFRa2) and are thereby targets for GDNF or neurturin. A third group of nociceptors express the purinergic P2X3 receptor; adenosine triphosphate (ATP) acts to stimulate these nociceptors (North 2004 **NR**).

Nociceptor plasticity

Sensitisation is a characteristic of nociceptors. The phenotypes of the nociceptors change in response to nerve injury and inflammation and are not static (Basbaum 2009 **NR**). This dynamic neural plasticity lowers the transduction threshold of nociceptors and contributes to primary hyperalgesia, which is defined as abnormal intensity of pain relative to the stimulus (Sandkuhler 2009 **NR**; Gold 2010 **NR**). Sensitisation is most often produced by chemical signals of tissue damage: such as during infection, inflammation or ischaemia; disruption of cells; degranulation of mast cells; secretions from inflammatory cells; or following induction of enzymes such as cyclooxygenase 2 (COX-2).

A majority of chemical mediators act locally at nociceptor terminals by directly targeting ion channels or indirectly by activating intracellular signalling via calcium-permeable channels (Bourinet 2014 **NR**) or membrane receptors (see Table 1.1). NGFs, immune mediators and other chemicals including proteinases (Russell 2009 **NR**), cytokines such as tumour necrosis factor (TNF) alpha or interleukin B (Schafers 2008 **NR**), and chemokines such as chemokine (C-C motif) ligand 3 (CCL3) (Gold 2010 **NR**; Dawes 2013 **NR**) all have an impact on sensitisation of nociceptors (see Table 1.1).

TRPV1 is an example of a nociceptor transducer that contributes to sensitisation in nociceptor terminals. This is achieved when the thermal and chemical sensitivity of TRPV1 is lowered following direct or indirect modulation by local inflammatory mediators or by noxious environmental chemicals such as capsaicin (which causes the perception of heat and pain elicited by chillies). Neuropeptides (substance P and CGRP) released from the activated peripheral terminals via peripheral antidromic axonal responses cause neurogenic inflammation by promoting vasodilation and plasma extravasation. This promotes recruitment of serum factors and inflammatory cells at the site of injury. Nonsteroidal anti-inflammatory drugs (NSAIDs) modulate peripheral pain by reducing prostaglandin E2 (PGE_2) synthesis from locally induced COX-2. Inflammation also induces changes in protein synthesis in the cell body of neurons in the dorsal root ganglia (DRG) and trigeminal ganglia, and alters the expression and transport of receptors, such as TRPV1 and opioid receptors, to the peripheral nerve terminal (Woolf 2007 **NR**). The latter underlies the peripheral action of opioid agonists in inflamed tissue and could allow nociceptor modulation by immune cells (Stein 2009 **NR**).

Similarly, NGF increases with inflammation, binds to TrkA, which causes phosphorylation of the TRPV1 and facilitates the sodium channels, which both increase nociceptor activity. In addition, NGF-TrkA complex is transported to the DRG, where it impacts on phenotypic changes resulting in changes to receptors and channels (Basbaum 2009 **NR**). NGF regulates relative amounts of neuropeptides and the threshold of nociceptors. The number of receptors for NGF (TrkA) is also determined by the functions of the corresponding DRG cells. Visceral primary afferents have a higher proportion of cells containing TrkA compared to somatic primary afferent neurons

Table 1.1 Examples of primary afferent and dorsal horn pain related receptors and ligands

Ionotropic receptor	Subtype	Ligand
TRP	TRPV1	heat (≥43°C, unsensitised), capsaicin, H^+ (protons)
	TRPV2	heat (≥52°C)
	TRPV3, TRPV4	warm (32–39°C)
	TRPM8	cool (≤26°C)
	TRPA1	environmental irritants (mustard oil, nicotine, formaldehyde, acrolein)
acid sensing	ASIC1-4, TRAAK/TREK	H^+ (protons)
glutamate	NMDA, AMPA Kainate, GlurR1-5, NR1-2	glutamate
purine	P2X1-6	ATP
serotonin	5-HT3	5-HT
nicotinic	nACh (multiple subtypes)	acetylcholine
Metabotropic receptor	**Subtype**	**Ligand**
metabotropic glutamate	$mGluR_{1,2/3,5}$	glutamate
prostanoids	EP_{1-4}	PGE2 (prostaglandins)
	IP	PGI_2 (prostacyclin)
histamine	H_1	HA
serotonin	$5\text{-}HT_{1A}$, $5\text{-}HT_{2A,}$ $5\text{-}HT_4$	5-HT
bradykinin	B_l, B_2	BK
cannabinoid	CB_1, CB_2	anandamide
tachykinin	neurokinin-1 (NK_1)	substance P, neurokinin A
proteinase	PAR_{1-4}	protease
tyrosine kinase receptor	TrkA, p75 neurotrophin	NGF
opioid	mu, delta, kappa, NOP	endorphine, enkephalin, dynorphin

Notes: *Immune mediators including cytokines such as TNF alpha, interleukin B and CCL3 can also act as signalling molecules in nociceptive pathways (*Schafers 2008*).*

5-HT: serotonin; ASIC: acid sensing ion channel; ATP: adenosine triphosphate; BK: bradykinin; NK1: neurokinin-1; P_2X_3: purinergic receptor subtype; PAR: proteinase-activated receptor; PGE_2: prostaglandin E_2; PGI_2: prostacyclin; TRP: transient receptor potential. Others (eg H_1, EP_{14}, TRPV2) are designated subtypes of receptors rather than abbreviations; NOP: Noceptin receptor also known as Orphanin FQ receptor.

Sources: *Russell 2009; Dubin 2010; Gold 2010; Alexander 2011.*

Sodium, potassium, calcium and chloride ion channels contribute to level of activity of nociceptors. Sodium channels are a prerequisite for conduction of neuronal action potentials to the CNS (Cummins 2007 **NR**; Eijkelkamp 2012 **NR**). A rapidly inactivating fast sodium current that is blocked by tetrodotoxin is present in all sensory neurons. This is the principal site of action for local anaesthetics but, as the channel is present in all nerve fibres, conduction in sympathetic and motor neurons may also be blocked. Subtypes of slowly activating and inactivating tetrodotoxin-resistant sodium currents are selectively present on nociceptive fibres. Following injury, changes in sodium-channel kinetics and specific alterations in the expression of sodium channels (upregulation or downregulation) contribute to hyperexcitability that occurs in different pain states. The importance of sodium channels in pain sensitivity is reflected by the impact of mutations in the SCN9A gene encoding the Na(v)1.7 channel. Loss of function results in insensitivity to pain, whereas gain of function mutations produce erythromelalgia and severe pain. These effects are not restricted to sodium channels; functional and expression changes in other classes of calcium, potassium and chloride channels also contribute to nociceptive transmission and processing by nociceptors (Waxman 2014 **NR**).

Medicines that are specific blockers of sodium-channel subtypes or cause state-dependent reductions in sodium-channel activity are becoming available for evaluation in human clinical trials (Eijkelkamp 2012 **NR**). New ion channel targets are also emerging that, as well as regulators of afferent fibre excitability, include a separate class of ion channels that regulate the transfer of the nociceptive signal (synaptic transmission) from primary afferent fibres to the second-order neurons in the spinal cord (Rahman 2013 **NR**; Waxman 2014 **NR**).

1.1.2.2 Nociceptive transmission in the spinal cord

The cell bodies of nociceptive afferents that innervate the trunk, limbs and viscera are found in the DRG, while those innervating the head, oral cavity and neck are in the trigeminal ganglia and project to the brainstem trigeminal nucleus. The central terminals of C and A-delta fibres convey information to nociceptive-specific areas within laminae I and II of the superficial dorsal horn and to wide dynamic range neurons in lamina V, which encode both innocuous and noxious information. By contrast, large myelinated A-beta fibres transmit light touch or innocuous mechanical stimuli to the deeper laminae III and IV (Todd 2010 **NR**).

Primary afferent terminals activate dorsal horn neurons by releasing two major classes of neurotransmitter; glutamate as the primary transmitter and neuropeptides such as substance P, CGRP, galanin and somatostatin as cotransmitters (Sandkuhler 2009 **NR**). Depolarisation of the primary afferent terminal results in glutamate release, which activates postsynaptic ionotropic α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors and rapidly signals information relating to the location and intensity of noxious stimuli. In this “normal mode”, a high-intensity stimulus elicits brief localised pain and the stimulus-response relationship between afferent input and dorsal horn neuron output is predictable and reproducible (Prescott 2014 **NR**).

Summation of repeated C-fibre inputs results in a progressively more depolarised postsynaptic membrane and removal of the magnesium block from the N-methyl-D-aspartate (NMDA) receptor. This is mediated by glutamate acting on ionotropic NMDA receptors and metabotropic glutamate receptors (mGluR), and by substance P acting on neurokinin-1 (NK1) receptors. A progressive increase in action potential output from the dorsal horn cell is seen with each stimulus and this rapid increase in responsiveness during the course of a train of inputs has been termed “wind-up”. Long-term potentiation (LTP) is induced by higher frequency stimuli but the enhanced response outlasts the conditioning stimulus. This mechanism has been implicated in learning and memory in the hippocampus and pain sensitisation in the spinal cord (Sandkuhler 2009 **NR**). Behavioural correlates of these electrophysiological phenomena have been seen in human volunteers as repeated stimuli elicit progressive increases in reported pain (Hansen 2007 **NR**).

Intense and ongoing stimuli further increase the excitability of dorsal horn neurons, leading to central sensitisation (Woolf 2011 **NR**; Baron 2013 **NR**; Woolf 2014 **NR**). Increases in intracellular calcium due to influx through the NMDA receptor and release from intracellular stores activate a number of intracellular kinase cascades. Subsequent alterations in ion channel and/or receptor activity and trafficking of additional receptors to the membrane increase the efficacy of synaptic transmission. As a result of the increased excitability of central nociceptive neurons, their threshold for activation is reduced. In this situation, pain can occur in response to low-intensity previously nonpainful stimuli (ie allodynia) and sensitivity spreads beyond the area of tissue injury (ie secondary hyperalgesia) (Sandkuhler 2009 **NR**). Wind-up, LTP and secondary hyperalgesia may all contribute to central sensitisation and may share some of the same cellular mechanisms but are independent phenomena.

The intracellular changes associated with sensitisation may also activate a number of transcription factors both in DRG and dorsal horn neurons, with resultant changes in gene and protein expression (Ji 2009 **NR**; Simonetti 2013 **NR**). Unique patterns of either upregulation or downregulation of neuropeptides, G-protein coupled receptors, growth factors and their receptors, and many other signalling molecules occur in the spinal cord and DRG in inflammatory, neuropathic and cancer pain. Further elucidation of changes specific to different pain states may allow more accurate targeting of therapy in the future.

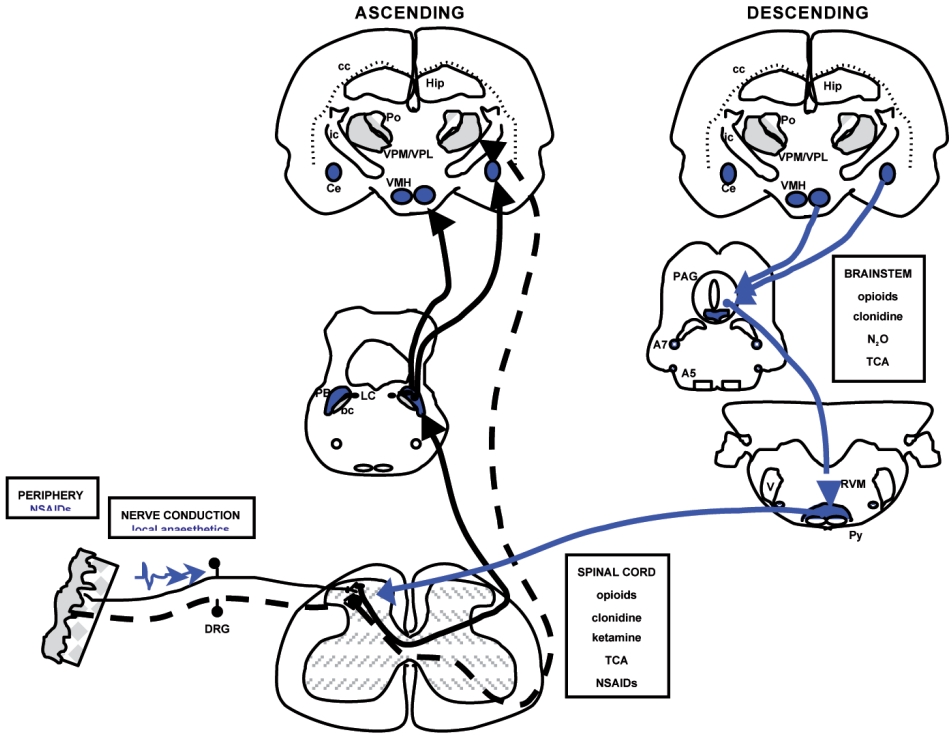
In addition to activity in neurons, central neuroinflammation involving surrounding glial and immune cells can also modulate synaptic transmission. This glial activation is a likely contributor to development of chronic pain states but is also relevant to acute pain and opioid treatment as opioids have been shown to activate peripheral glia, which may reduce their analgesic efficacy (Ji 2013 **NR**). Cannabinoids have been shown to inhibit glial inflammatory responses via cannabinoid type 2 (CB_2) receptors (Burstein 2009 **NR**).

1.1.2.3 Central projections of nociceptive pathways

Different qualities of the overall pain experience are subserved by five major ascending spinal cord projection pathways; the spinothalamic, spinoreticular, spinomesencephalic, cervicothalamic and spinohypothalamic pathways (Wang 2013b **NR**). The spinothalamic pathway ascends from primary afferent terminals in laminae I and II, via connections in lamina V of the dorsal horn, to the thalamus and then to the somatosensory cortex (Craig 2003 **NR**). This pathway provides information on the sensory-discriminative aspects of pain (ie the site and type of painful stimulus). The spinoreticular and spinomesencephalic (spinoparabrachial) tracts project to the medulla and midbrain and are important for integrating nociceptive information with arousal, homeostatic and autonomic responses as well as projecting to central areas mediating the emotional or affective component of pain (Price 2000 **NR**; Craig 2009 **NR**; Kobayashi 2012 **NR**). Many of the second-order projection neurons in these pathways are superficial dorsal horn lamina I neurons that express the NK1 receptor and are stimulated by peptidergic C-fibre afferents (Todd 2010 **NR**). Other connections include those to cortical areas involved in the affective and motivational components of pain (eg anterior cingulate cortex, insular and prefrontal cortex), projections back to the periaqueductal grey (PAG) region of the midbrain and rostroventromedial medulla (RVM), which are crucial for fight or flight responses and stress-induced analgesia, and projections to the reticular formation that are important for the regulation of descending pathways to the spinal cord.

Descending projections from the medullary dorsal reticular nucleus (DRt) are important in facilitating the diffuse noxious inhibitory control (DNIC) (see Figure 1.1) (Tracey 2007 **NR**; Tracey 2008 **NR**; Ossipov 2010 **NR**).

Figure 1.1 The main ascending and descending spinal nociceptive pathways



Notes: *(a) There are two primary ascending nociceptive pathways. The spinoparabrachial pathway (black) originates from the superficial dorsal horn and influences areas of the brain concerned with affect. The spinothalamic pathway (stippled black) originates from deeper dorsal horn (lamina V) after receiving input from the superficial dorsal horn and predominantly distributes nociceptive information to areas of the cortex concerned with discrimination. The ascending projections target thalamus DRt (dorsal reticular nucleus), RVM and PAG. Rostral projections connect to cortex and amygdala. The lateral capsular amygdala (CcA=Nociceptive Amygdala) receives input from spinal cord and brain stem. The cortex and thalamus also project to the amygdala. The CcA sends output to cortex and thalamus in which cognitive and conscious aspects of pain perception occur.*

(b) The descending pathway highlighted originates from the amygdala and hypothalamus and terminates in the PAG and communicates with RVM. Neurons project from here to the lower brainstem and control many of the antinociceptive and autonomic responses that follow noxious stimulation. Other pathways are to Locus Coeruleus, which sends descending noradrenergic inhibitory projections to spinal cord. Antinociceptive and pronociceptive projections from RVM modulate positively or negatively the nociceptive input. Other less prominent pathways are not illustrated.

The sites of action of some commonly utilised analgesics are included.

Legend: *A: adrenergic nucleus; bc: brachium conjunctivum; cc: corpus callosum; Ce: central nucleus of the amygdala; DRG: dorsal root ganglion; Hip: hippocampus; ic: internal capsule; LC: locus coeruleus; PAG: periaqueductal grey; PB: parabrachial area; Po: posterior group of thalamic nuclei; Py: pyramidal tract; RVM: rostroventromedial medulla; V: ventricle; VMH: ventral medial nucleus of the hypothalamus; VPL: ventral posterolateral nucleus of the thalamus; VPM: ventral posteromedial nucleus of the thalamus*

Source: *Modified from* Hunt 2001.

1.1.2.4 Descending modulatory pathways

The brain has a remarkable capacity to modulate pain according to the competing demands of physiological, psychological and social factors. The neural contributors to this modulation are complex and only partly elucidated. Best understood is a descending pain-modulatory circuit that projects to the spinal cord and changes the experience of pain by directly or indirectly modulating (inhibiting or facilitating) nociceptive traffic (Ossipov 2010 **NR**). Descending pathways contribute to the modulation of nociceptive transmission in the spinal cord via presynaptic actions on primary afferent fibres, postsynaptic actions on projection neurons or via effects on interneurons within the dorsal horn. Sources include direct corticofugal and indirect (via modulatory structures such as the PAG) pathways from the cortex and from the hypothalamus, which is important for coordinating autonomic and sensory information. The RVM receives afferent input from brainstem regions (PAG, parabrachial nucleus and nucleus tractus solitarius) as well as direct ascending afferent input from the superficial dorsal horn and is an important site for integration of descending input to the spinal cord (Ossipov 2010 **NR**). The relative balance between descending inhibition and facilitation varies with the type and intensity of the stimulus and also with time following injury (Vanegas 2004 **NR**; Tracey 2007 **NR**; Heinricher 2009 **NR)**. Serotonergic and noradrenergic pathways in the dorsolateral funiculus (DLF) contribute to descending inhibitory effects and serotonergic pathways have been implicated in facilitatory effects (Ossipov 2010 **NR**).

Inhibitory modulation occurs within the dorsal horn and can be mediated by non-nociceptive peripheral inputs, local inhibitory gamma-amino butyric acid (GABA) and glycine interneurones, descending bulbospinal projections and higher-order brain function (eg distraction, cognitive input). These inhibitory mechanisms are activated endogenously through neurotransmitters such as endorphins, enkephalins, noradrenaline (norepinephrine), to reduce the excitatory responses to persistent C-fibre activity. Serotonin has been implicated as both pronociceptive and inhibitory (Bardin 2011 **NR**).

Similar mechanisms are the basis of many exogenous analgesic agents (Bonin 2013 **NR**). Thus, analgesia may be achieved by either enhancing inhibition (eg opioids, clonidine, antidepressants) or by reducing excitatory transmission (eg local anaesthetics, ketamine) (Sandkuhler 2009 **NR**; Ossipov 2010 **NR**).

A feature of sensory processing is that not all of the signals received from receptors are perceived. The limited processing capacity of the brain is optimised by prioritising behaviourally relevant signals while suppressing less important signals. Advances in human functional brain imaging have provided new evidence of how pain perception is shaped by other sensory modalities and attentional or emotional processing by the cerebral cortex and basal forebrain. The engagement of attention, expectation and reappraisal mechanisms provides for complex cognitive modulation of pain. This is the basis of placebo-induced analgesia and for using psychological interventions to target endogenous pain modulation (Bushnell 2013 **NR**; Wiech 2013 **NR**; Flor 2014 **NR**).

1.1.3 Physiological and pathological pain

The clinical definition of acute pain as pain experienced for <2, 3 or 6 mth does not explicitly identify underlying pathophysiology. A more useful perspective for psychobiological models is the functional classification proposed by Woolf and colleagues (Costigan 2009 **NR**; Woolf 2010 **NR**). This addresses the heterogeneity of pain by identifying “nociceptive” and “inflammatory” classes of physiological or adaptive pain, together with “neuropathic” and “CNS dysfunctional” classes of pathological or maladapative pain.

In this scheme, nociceptive and inflammatory pain are physiological functions of the nociceptive division of the somatosensory nervous system, which monitors the physical state of the body. It has been understood from the earliest investigations of Sherrington and later landmark studies of Wall and Melzack that this system does not simply locate and measure the intensity of painful sensory stimulation; it also encodes innate aversive reinforcing signals that drive motivational, emotional and cognitive processing in the brain (as described below). In humans and other animals these systems support escape and defensive behaviours that

minimise potential lethal tissue damage, as well as coping behaviours that manage recovery from such damage and avoidance behaviours that use learning signals to minimise the risk of such damage in the future. This broad functionality can be shown to engage most of the major functional brain subdivisions. Their basic physiological importance is shown by the unavoidable tissue damage suffered in humans with rare genetic mutations that render them insensitive to pain (Waxman 2014 **NR**).

Neuropathic pain has been recently redefined as "pain caused by a lesion or disease in the somatosensory nervous system" (Jensen 2011). The estimated prevalence of neuropathic pain is much higher than commonly thought and in the range of 7–10% of the population (van Hecke 2014 **NR**). Although commonly regarded as a cause of chronic symptoms, neuropathic pain can also present acutely following trauma and surgery. The incidence has been conservatively estimated as 3% of acute pain service (APS) patients (Hayes 2002 **Level IV**). Similarly, acute medical conditions may present with neuropathic pain (Gray 2008 **NR**) as discussed further in Chapter 8. Nerve injury and associated alterations in afferent input or hyperexcitability associated with central pain (eg caused by stroke, spinal cord injury [SCI], multiple sclerosis) can induce structural and functional changes at multiple points in nociceptive pathways with complex long-term psychobiological consequences (Baron 2013 **NR**).

CNS dysfunctional pain syndromes such as migraine, fibromyalgia and chronic pelvic pain show chronicity that often cannot be reliably linked to clinical pathophysiology in the somatosensory system (Woolf 2010 **NR**). There is ongoing debate about the most suitable terminology for these states, which have been differentiated from neuropathic pain by the recent change in definition; an agreement on the best term or a precise definition by the IASP Taxonomy subgroup has not been reached. Terms other than CNS dysfunctional pain include "dysfunctional pain"; "maldynia" "nociplastic" or "neuroplastic" also refer to these conditions (Mayer 2009 **NR**; Dickinson 2010 **NR**).

When viewed from this perspective, acute pain will most commonly be linked to nociceptive and inflammatory pain but also less common neuropathic pain. It is clear, however, that the clinical definition will also capture early stages of chronicity that could lead to neuropathic and dysfunctional pain in some patients. It is important to recognise that it is currently not possible to identify in advance specific patients who will undergo this transition. The probability of chronic pain developing is subject to the influences of genetic and physiological factors and how these interact with the accumulated psychological and social experiences of pain (von Hehn 2012 **NR**; Denk 2014 **NR**). How these combine will determine how individuals experience pain and is also highly likely to determine their underlying resilience in coping with this experience (Bushnell 2013 **NR**; Elman 2013 **NR**) (see Sections 1.4 and 1.5).

1.2 Psychological aspects of acute pain

Pain is an individual, multifactorial experience influenced, among other things, by culture, previous pain experience, beliefs, expectations, mood and ability to cope. Pain may be an indicator of tissue damage but may also be experienced in the absence of an identifiable cause, especially when it becomes chronic. The degree of pain and disability experienced in relation to similar physical injury varies; similarly there is individual variation in response to methods to alleviate pain (Flor 2012 **NR**).

The IASP's definition of pain (Merskey 1994) emphasises that pain is not a directly observable or measurable phenomenon but rather a subjective experience that has a variable relationship with actual tissue damage. Factors that might contribute to the individual's pain experience include somatic (physical) and psychological factors as well as contextual factors, such as situational and cultural considerations. Pain expression, which may include facial expressions, body posture, language, vocalisations and avoidance behaviour, partially represents the complexity of the psychological experience but is not equivalent to it (Kunz 2004 **NR**; Vervoort 2009 **Level IV**). Engel's enunciation (Engel 1997 **NR**) of a biopsychosocial model of illness has provided a framework for considering pain phenomena.

Biopsychosocial models of pain (Turk 1995 **NR**) are based on the proposal that the psychobehavioral process is mediated via neurobiological processes, which are inextricably

enmeshed with the neurobiology of pain. Thereby biological factors can influence physiological changes and psychological factors are reflected in the appraisal and perception of internal physiological phenomena. These appraisals and behavioural responses are, in turn, influenced by social or environmental factors, such as reinforcement contingencies (Flor 2002 **NR**). At the same time, the model also proposes that psychological and social factors can influence biological factors, such as hormone production, activity in the autonomic nervous system and physical deconditioning. Experimental evidence supports these propositions (Flor 2012 **NR**). Other concepts and models of pain that challenge traditional reductionist, mind-body or biomedical paradigms have also been promulgated (Quintner 2008 **NR**).

1.2.1 Psychological factors

Psychological factors that influence the experience of pain include the processes of attention, other cognitive processes (eg learning, thinking styles, beliefs, mood), behavioural responses and interactions with the person's environment.

Psychological factors that contribute to the experience and impact of pain (acute or chronic) can be amenable to change and thus influence outcomes for the individual (Nicholas 2011 **NR**).

1.2.1.1 Attention

In relation to pain, attention is viewed as an active process and the primary mechanism by which nociception accesses awareness and disrupts current activity (Eccleston 1999 **NR**; Legrain 2012 **NR**). The degree to which pain may interrupt attention depends on factors such as the intensity of pain, its novelty, unpredictability, degree of awareness of bodily information, threat value, catastrophic thinking, presence of emotional arousal, environmental demands (such as task difficulty) and emotional significance.

Concepts like somatosensory amplification and hypervigilance have been used to describe the selective attention of patients towards pain to the detriment of more functional activities. These processes have been characterised as attentional bias (ie the preferential allocation of attention to information that is related to pain) and this has been extensively studied in relation to acute, chronic and experimentally induced pain. There is no evidence for an attentional bias towards pain-related words and pictures for acute pain (standard paired difference: d=0.049), procedural pain (d=0.142) and experimental pain (d=0.069) (Crombez 2013 **Level IV SR**, 50 studies, n=2,035). However, when attentional bias towards signals of impending experimental pain in healthy volunteers was investigated, an attentional bias of medium effect size (d=0.676) was found. These experimental studies may not be completely representative of clinical acute pain (eg postsurgical pain). The role of attentional mechanisms in pain experience and impact is not uniform and terms like "hypervigilance" should not be used loosely as other processes, particularly emotional ones (eg sense of threat), are likely to be involved as well as attention.

1.2.1.2 Learning processes

The role of learning processes has primarily been studied in laboratory settings with experimentally induced pain. A number of studies using healthy subjects have demonstrated that reports of pain (eg pain severity ratings) can be conditioned by their consequences and this effect can be reflected in measures of associated skin conductance responses, facial activity and cortical responses (Flor 2002 **NR**; Jolliffe 2004, **Level III-2**). Taken together, these studies provide support for the thesis that the experience of pain is not solely due to noxious input but that environmental reinforcement contingencies can also influence this experience (see also Section 1.3).

Learning processes have also been implicated in the development and maintenance of chronic pain (Flor 2012 **NR**) but that topic is beyond the focus of these guidelines.

1.2.1.3 Beliefs and thought processes

Empirical evidence supports a role for "fear of pain" contributing to the development of avoidance responses following pain and injury, which ultimately lead to disability in many people with persisting pain (Leeuw 2007 **NR**). From this perspective, negative appraisals of

internal and external stimuli (eg catastrophising), negative affectivity and anxiety sensitivity can contribute to the development of pain-related fear and, in turn, lead to escape and avoidance behaviours, as well as hypervigilance to internal and external illness information, muscular reactivity, and physical disuse and behavioural changes.

Studies with a range of samples have confirmed that thinking styles that are overly negative, ruminative and helpless (eg catastrophic thinking) are frequently associated with more severe acute pain and associated distress, as well as persistent pain.

In patients who underwent anterior cruciate ligament repair, those with high Pain Catastrophising Scale (PCS) scores assessed prior to surgery reported more pain immediately after surgery and when walking at 24 h compared with those with low scores; however there was no difference in analgesic consumption (Pavlin 2005 **Level IV**). After breast surgery, catastrophising was associated with increased pain intensity and analgesic use (Jacobsen 1996 **Level IV**) and after abdominal surgery (Granot 2005 **Level IV**) and Caesarean delivery with higher pain scores (Strulov 2007 **Level IV**). Preoperative PCS scores also predicted pain after knee arthroplasty in the postoperative period (Roth 2007 **Level IV**). After a wide range of surgical procedures (n=1,490), the most important predictors of pain severity up to 5 d following surgery were surgical fear and pain catastrophising (beside preoperative pain and expected pain) (Sommer 2010 **Level IV**). In a clinical sample of aged patients, attentional avoidance of emotionally aversive stimuli prior to surgery predicted acute postoperative pain, measured by the consumption of opioids via patient-controlled analgesia (PCA) (Lautenbacher 2011 **Level IV**). This measure was a better predictor of postoperative pain than depression, anxiety and pain catastrophising.

A significant association between anxiety or pain catastrophising and the subsequent development of chronic postsurgical pain (CPSP) was reported in 16 of 29 studies (Theunissen 2012 **Level III-2 SR**, 29 studies, n=6,628). Following total knee joint replacement, catastrophising is the strongest predictor of chronic pain (Lewis 2015 **Level IV SR**, 32 studies, n=29,993). Patients with acute and subacute back pain with high levels of catastrophising complained of more pain and disability at 6 mth and more disability at 1 y than those with low levels (Wertli 2014a **Level III-2 SR**, 16 studies, n unspecified) (see also Section 1.4).

High fear avoidance beliefs in patients with back pain of <6 mth duration are associated with poor outcomes, which may be improved by treatment approaches aimed at fear avoidance (Wertli 2014b **Level I** [PRISMA], 17 RCTs, n unspecified). Early postoperative fear of movement also predicted pain, disability and physical health 6 mth after spinal surgery for degenerative conditions (Archer 2014 **Level III-2**, n=141).

1.2.1.4 Depression and anxiety

Anxiety and depression have repeatedly been found to contribute to the experience and impact of both acute and chronic pain.

There is a consistent association between chronic postsurgical pain and depression as well as psychological vulnerability and stress (Hinrichs-Rocker 2009 **Level IV SR**, 50 studies, n≈25,000). Similarly, there is a strong relationship between depression and persistent knee pain (with higher levels of depression being positively related to higher levels of knee pain) but not with anxiety and poor mental health in general (Phyomaung 2014 **Level IV SR**, 16 studies, n=15,113).

Anxiety is one of the most significant predictive factors (in addition to pre-existing pain, age and type of surgery) for the severity of postoperative pain (Ip 2009 **Level IV SR**, 48 studies, n=23,037). Psychological distress (besides type of surgery and age) is the most significant predictor of postoperative analgesic consumption, not gender as is commonly believed.

Among other factors, preoperative anxiety predicted pain intensity 48 h after hysterectomy for benign conditions (Pinto 2012 **Level IV**). Subsequent multivariable analysis revealed that

pain catastrophising acted as a full mediator between presurgical anxiety and postsurgical pain intensity. In the late phase after leg injury, anxiety has the only significant relationship to pain (Castillo 2013 **Level IV**). Anxiety predicted pain over all time periods (3–6 mth SRW 0.11, p=0.012; 6–12 mth SRW 0.14, p=0.0065; 12–24 mth SRW 0.18, p<0.0001).

In opioid-tolerant patients, the anxiety and autonomic arousal associated with withdrawal (Tetrault 2008 **NR**) may also have an impact on acute pain experience and report (see Section 10.7 for further details).

1.2.1.5 Conclusions

The accumulating evidence that a range of psychological factors can contribute to the experience and impact of acute pain, as well as the development and impact of persisting or chronic pain, has potentially important implications for pain management in the acute pain setting. In particular, it means that the presence of these psychological factors, especially anxiety, catastrophising and depression, should be considered in these settings and, if identified, should be targeted by treatment. The results of research evaluating psychological interventions for these factors are considered elsewhere in this document (see Section 7.1).

Importantly, the literature reviewed here also demonstrates that these psychological contributors to higher pain levels and interference in daily activities are not universal and there is considerable variability between individuals. This highlights the importance of assessing their presence in the first instance.

1.2.2 Patient-controlled analgesia

A number of studies have looked specifically at the relationship between pain relief and psychological factors in patients using PCA in the postoperative period.

In general, anxiety seems to be the most important psychological variable that affects PCA use. Preoperative anxiety correlates with increased postoperative pain intensity, the number of PCA demands made by the patient (often "unsuccessful" presses during the lockout interval), degree of dissatisfaction with PCA and lower self-reports of quality of analgesia (Jamison 1993 **Level IV**; Perry 1994 **Level IV**; Thomas 1995 **Level III-1**; Brandner 2002 **Level IV**; Ozalp 2003 **Level IV**; Hsu 2005 **Level IV**; De Cosmo 2008 **Level IV**). Another study designed to look at predictors of PCA demands made during the lockout interval also found that anxiety and negative affect positively predicted unsuccessful PCA demands and postoperative pain, as did preoperative intrusive thoughts and avoidant behaviours about the impending surgery (Katz 2008a **Level IV**).

Evidence regarding PCA opioid consumption and psychological variables is however contradictory, with some studies showing no change (Gil 1990 **Level IV**; Gil 1992 **Level IV**; Jamison 1993 **Level IV**) and others showing an increase in analgesia demands (Ozalp 2003 **Level IV**; De Cosmo 2008 **Level IV**; Katz 2008a **Level IV**).

In a study looking at the effect of a number of psychological factors on both pain and PCA-morphine use in the immediate postoperative period, and on pain 4 wk after surgery, preoperative self-distraction and coping positively predicted postoperative pain levels and morphine consumption; emotional support and religious-based coping positively predicted PCA-morphine consumption; and preoperative distress, behavioural disengagement, emotional support, and religious-based coping also positively predicted pain levels 4 wk after surgery (Cohen 2005 **Level IV**).

There was no relationship between locus of control and postoperative pain intensity, satisfaction with PCA or PCA dose-demand ratio (Brandner 2002 **Level IV**). Preoperative depression was associated with increased pain intensity, opioid requirements, PCA demands and degree of dissatisfaction (Ozalp 2003 **Level IV**; Hsu 2005 **Level IV**).

Key messages

1. High fear avoidance beliefs in patients with back pain of less than 6 months duration are associated with poor outcomes, which may be improved by treatment approaches aimed at fear avoidance (**N**) (**Level I** [PRISMA]).
2. There is significant association between anxiety, pain catastrophising (**N**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**N**) (**Level IV SR)** and the subsequent development of chronic postsurgical pain.
3. There is a significant association between high levels of catastrophising in acute and subacute back pain and pain and disability at later points of time (**N**) (**Level III-2 SR**).
4. Preoperative anxiety (**S**) (**Level IV SR**), catastrophising (**S**) (**Level IV SR**) and depression (**U**) (**Level IV**) are associated with higher postoperative pain intensity.
5. Preoperative anxiety and depression are associated with an increased number of PCA demands and dissatisfaction with PCA (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope **(U).**

1.3 Placebo and nocebo effects in acute pain

The study of placebo effects is directly relevant to the field of pain management, as it provides further understanding of the mind–brain interaction in the modulation of pain and is a core element of routine clinical management (Finniss 2010 **NR**).

The term "placebo", originally defined as an inert substance having therapeutic response, has been used in the medical literature for over 200 y. Only in the last 50 y, however, has interest grown in the effect seen after placebo administration. The first major systematic review of the topic showed a placebo effect for many interventions but particularly for those interventions aimed at analgesia (Beecher 1955 **Level I**, 15 RCTs, n=1,082). The early studies included in this systematic review of placebo effects were mainly studies of placebo vs active medicine or intervention alone without a control no-treatment group (nonplacebo group).

Placebo effects are psychobiological effects that are attributable to the psychosocial context (or treatment ritual) surrounding the patient. Importantly, these genuine effects must be distinguished from other causes of improvement following administration of a placebo, such as spontaneous remission, regression to the mean and the natural history of acute pain (Price 2008 **NR**). Defining placebo and placebo effects has been difficult, primarily due to the traditional definition, which uses the word "inert", therefore theoretically rendering it as being unable to have any power to elicit an effect (Moerman 2002 **NR**). Recent reconceptualisations of placebo effects have emphasised several key points which are highly relevant to modern pain management practice (Finniss 2010 **NR**; Miller 2008 **NR**).

- The key aspect of placebo administration is the act of simulating a treatment context or ritual, regardless of the content of the placebo.
- Routine clinical care occurs in a rich therapeutic context and, on this basis, placebo effects exist in everyday practice even though no placebo is given. The overall outcome of a treatment is related to both the treatment itself and the context in which it is given (the component attributable to placebo effects).

The term "nocebo" has been used to express the opposite (negative) response following placebo administration, particularly in relation to development of adverse effects from interventions or, in the case of painful stimuli, with an increased pain response expressed. Nocebo studies in pain show moderate to large nocebo effects of high variability (Petersen 2014 **Level I** [PRISMA], 10 RCTs, n=619). The results are similar to those seen for placebo effects; combinations of verbal suggestions and conditioning (see below) are more effective than

verbal suggestions alone. The authors suggest that these results demonstrate "the importance of minimising nocebo effects in clinical practice".

1.3.1 Mechanisms

The study of placebo mechanisms has traditionally been divided into psychological and neurobiological categories, although it is the interplay between the two that is the key to the topic area.

1.3.1.1 Psychological mechanisms

There are many psychological mechanisms of placebo effects proposed, including expectation, conditioning, learning, reward and anxiety reduction (Price 2008 **NR**).

Expectancy

Expectancy has been one of the most studied psychological mechanisms and relates to patient expectations of a future response. Expectancy can result in increased pain response to nociceptive stimuli as well as a placebo response to an analgesic intervention (Atlas 2012 **NR**). It has been associated with placebo effects in studies, where verbal cue ranges from a simple instruction "this is a powerful painkiller" (Price 1999 **Level II**, n=40, JS 4) to the use of conditioning protocols to maximise expectancy (Voudouris 1989 **Level II**, n=20, JS 4; Voudouris 1990 **Level III-1**). Furthermore, a "graded" effect can be seen in studies with variable levels of expectancy (such as the classic "double-blind" instruction, which carries a 50% uncertainty) to more certain information about treatment expectations "the drug I will give you is a powerful painkiller" (Pollo 2001 **Level II**, n=38, JS 3; Vase 2003 **Level II**, n=13, JS 4; Verne 2003 **Level II**, n=10, JS 4).

Treatment expectations are also involved in studies of the open-hidden paradigm (Finniss 2010 **NR**). Giving a treatment "hidden", without the patient's knowledge (eg by a computerised pump behind a curtain) and comparing the effects when the same treatment is given "open" (in the usual therapeutic context with a health professional present) has shown that open administration of a range of analgesics is, by far, more effective than hidden administration. This approach permits measurement of the placebo effect as "the difference in effect between the open and hidden administration". An example of such a trial compared the efficacy of a remifentanil infusion (0.8 ng/mL effect site concentration) on experimental pain in volunteers under three conditions (Bingel 2011 **Level III-3 EH**):

- without expectation of analgesia (hidden administration);
- with expectancy of a positive analgesic effect (open administration by a clinician); and
- with negative expectancy of analgesia (claimed discontinuation of analgesic infusion while infusion continued).

The pain relief achieved by hidden administration of remifentanil was more than doubled by the open administration and completely negated by the claimed discontinuation of the infusion. Functional MRI (fMRI) showed that, during positive expectancy, activity in the endogenous pain modulatory system was increased, while negative expectancy increased activity in the hippocampus.

These findings and the results of other groups suggest that RCTs comparing an analgesic with a placebo may underestimate the efficacy of the analgesic (Lund 2014 **Level II EH**, n=48 [cross over], JS 5). The hypothesis that placebo effect and drug effect is additive, upon which calculation of efficacy is based, is most likely flawed. This is particularly true when the placebo response is large.

In conclusion, expectancy is a powerful determinant of placebo response, with only minor changes in the way information is delivered to the patient having the ability to significantly alter expectancy and the magnitude of the placebo effects.

Classical conditioning

Classical conditioning is a learning phenomenon whereby repeated associations between a neutral stimulus and an active treatment (unconditioned stimulus) can result in the ability of the neutral stimulus itself being able to elicit an effect similar to that of the unconditioned stimulus (Finniss 2010 **NR**). Typically, an opioid analgesic is given on repeated occasions and then replaced with a placebo-treatment simulation. These phenomena have been demonstrated in animals (Pacheco-Lopez 2006 **BS**) and in humans (Voudouris 1989 **Level II EH**, n=20, JS 4; Voudouris 1990 **Level III-1 EH**). In a similar way, treatment history can influence the efficacy of a subsequent treatment (Kessner 2014 **Level III-2 EH**). In an experimental setting, induced negative experience with a first treatment resulted in reduced response to a second analgesic treatment; the size of the effect was modulated by psychological trait variables such as anxiety, depression and locus of control. There is growing evidence that social or observational learning may also be a determinant of placebo effects (Colloca 2006 **Level III-1 EH**). For example, placebo effects were larger in subjects who had higher empathy after witnessing another volunteer in pain (Colloca 2009 **Level II EH**, n=48, JS 2).

1.3.1.2 Neurobiological mechanisms

Studies into placebo analgesia have provided a substantial component of the knowledge about placebo mechanisms, although it is now known that there are multiple placebo effects that operate across many different medical conditions (Benedetti 2008 **NR**).

At a biochemical level, pioneering studies have shown that placebo effects in acute pain are either completely or in part mediated by endogenous opioids, by virtue of their reversibility with naloxone (Benedetti 1995 **Level II EH**, n=47, JS 3; Levine 1978 **Level II EH**, n=93, JS 3). The role of cholecystokinin (CCK) was demonstrated through the potentiation of placebo effects using a CCK antagonist (proglumide) (Benedetti 1995 **Level II EH**, n=93, JS 3). Interestingly, CCK has also been shown to be responsible for nocebo effects and this suggests that anxiety and panic mechanisms (also associated with CCK release) may be activated (Benedetti 2007 **NR**).

Using both conditioning and expectancy manipulations with the administration of an opioid analgesic, the resulting placebo effect was mediated by endogenous opioids (Amanzio 1999 **Level II EH**, n=229, JS 3). In contrast, in patients who received a nonopioid analgesic during conditioning, the placebo effect was not reversed by naloxone. These findings are a powerful demonstration that there is not one placebo effect but many. Recently, one mechanism for this nonopioid-mediated placebo analgesia was found to be the endogenous cannabinoid system (cannabinoid type 1 [CB_1] receptor) (Benedetti 2011 **Level III-1 EH**).

The neuroanatomy of placebo analgesic effects has been partially unravelled. A positive emission tomogram (PET) study demonstrated similar brain changes to placebo as seen with opioid administration (Petrovic 2002 **Level III-2 EH**). Further PET and fMRI studies have supported the involvement of key regions of the brain associated with opioid analgesia (Zubieta 2005 **Level III-3 EH**), including subcortical (Bingel 2006 **Level III-2 EH**) and spinal cord mechanisms (Eippert 2009 **Level III-1 EH**). Taken together, these studies show growing neurobiological evidence of placebo-induced brain and spinal cord modulation of pain, although much more research is needed in this area.

A meta-analysis of 25 neuroimaging studies identified that placebo analgesia and expectancy-based pain modulation resulted in reductions of activity in brain regions involved in pain processing (eg the dorsal anterior cingulate, thalamus and insula) (Atlas 2014 **Level IV SR EH**). Other regions with reduced activity were the amygdala and the striatum; as these are related to affect and valuation, placebo effects involve these components too. In addition, regions such as the prefrontal cortex, the midbrain surrounding the PAG and rostral anterior cingulate showed increased activity with expectations for pain reduction.

1.3.1.3 Clinical findings

Contemporary meta-analyses include studies that also have a control nonplacebo/nocebo group. One of these reveals a relatively small size of placebo effect for all clinical conditions (60 assessed) (Hrobjartsson 2010 **Level I** [Cochrane], 234 RCTs, n unspecified). The

majority of studies measured continuous outcomes (158 RCTs, n=10,525) but the results are also consistent in those assessing binary outcomes (44 RCTs, n=6,041). In the studies with continuous outcomes, there is an effect of placebo treatment (SMD -0.23; 95%CI -0.28 to 0.17) (158 RCTs, n=10,525), which is larger for patient-reported (SMD -0.26; 95%CI -0.32 to 0.19) (109 RCTs, n=8,000) than for observer-reported outcomes (SMD -0.13; 95%CI -0.24 to 0.02) (49 RCTs, n=2,513). Overall, larger placebo effects are seen with physical placebo interventions (eg acupuncture), patient-involved outcomes, smaller trials and trials that did not inform patients about the possible placebo intervention.

Importantly, trials aimed at studying placebo effects (rather than assessing responses in placebo-control groups) demonstrate larger placebo effects, particularly in the case of analgesia (Vase 2002 **Level I**, 37 RCTs, n=2,298). Effect sizes can be five times higher in these studies than in analysis of placebo effects on control groups, demonstrating an important difference when understanding placebo effects in clinical trials (where instructions are uncertain and the context does not replicate routine clinical care) (Vase 2009 **Level I** [QUORUM], 24 RCTs, n=602). Consistently positive but highly variable placebo responses are obvious in studies involving analgesia specifically (pooled SMD -0.28; 95%CI -0.36 to -0.19) (60 RCTs [continuous outcome, pain], n=4,154) with a wide range of response in the individual trials from around SMD -1.0 to 0.5. This variability is also seen in targeted studies on placebo (Vase 2009 **Level I** [QUORUM], 24 RCTs, n=602).

1.3.1.4 Clinical implications

The clinical implications of placebo effects are widespread and there is much more research needed to understand how placebo effects operate and how they can be manipulated in clinical practice. However, the notion that placebo effects (and therefore mechanisms) may be a component of routine pain management practice is highly important (Finniss 2009 **NR**; Klinger 2014 **NR**). If one can study how psychosocial factors alter the patient's nociception and the experience of pain (by running experiments in which placebos are given), this has direct implications for clinical care where, even though no placebo is given, placebo effects are present.

In recent times, the ethical debate has shifted somewhat as the concept of placebo is better understood. It is widely accepted that placebos should not be administered in a deceptive manner (Brody 1982 **NR**; Finniss 2010 **NR**). However, there are not the same ethical problems associated with harnessing the placebo effects that coexist with routine "active" treatments, as the outcome of a treatment is attributable to both the treatment itself and the specific context in which it was given (the placebo component).

It is suggested that, in a therapeutic interaction, the placebo effect can be clinically utilised by enhancing expectations and using learning components (Klinger 2014 **NR**). Practical examples of this are listed below.

To enhance expectations:

- emphasise positive effects of medicines;
- avoid stressing adverse effects;
- explain effects and mechanisms of action of medicines;
- interact personally with the patient;
- do not rely only on written handouts; and
- avoid unrealistic expectations.

To enhance learning components:

- administer analgesics in an open manner;
- connect the administration to positive internal states and external conditions;
- combine analgesics with other pain-relieving approaches, preferably with time-contingent administration of analgesics; and
- reinforce positive and minimise negative experiences.

Key messages

1. Placebo effects for all clinical conditions are small but consistently positive. They are more prominent, although highly variable, in studies of pain (**N**) (**Level I** [Cochrane Review]).
2. Nocebo effects in studies of pain are of moderate to large size and of high variability (**N**) (**Level I** [PRISMA]).
3. Trials aimed at studying placebo effects demonstrate larger placebo effects than those assessing responses in placebo-control groups (**N**) (**Level I** [QUOROM]).
4. Analgesic placebo effects are based upon multiple neurobiological mechanisms, including involvement of endogenous opioid, cholecystokinin (**N**) (**Level II**) and endogenous cannabinoid systems (**N**) (**Level III-1**).
5. Analgesic placebo effects are based upon multiple psychological determinants including expectancy, classical conditioning and social and observational learning (**N**) (**Level II**).
6. Placebo and nocebo effects have significant influence on the efficacy of analgesics (**N**) (**Level II**)

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Placebo effects are the consequence of the psychosocial context (or treatment ritual) on the patient's mind, brain and body (**N**).

☑ Placebo effects occur in routine clinical care even when no placebo is given. The outcome of a treatment is attributable to both the treatment itself and the contextual (or placebo) component (**N**).

☑ Nocebo effects occur in routine clinical care and are seen as an increased pain response to a painful stimulus or the development of adverse effects not caused by, or separate from, the intervention (**N**).

☑ Ethical harnessing of placebo and minimisation of nocebo effects will improve response to clinical management interventions (**N**).

1.4 Progression of acute to chronic pain

Chronic pain is common in the community and leads to significant personal and economic cost (Breivik 2006 **Level IV**). Episodes of acute pain may result in chronic pain with subsequent impact on quality of life, employment and mental health (Lavand'homme 2011 **NR**; McGreevy 2011 **NR**; Steyaert 2012 **NR**). The prediction and prevention of transition to chronic pain may therefore convey significant health and economic benefits.

Chronic pain is common after surgery (see Table 1.2) and often has an identifiable neuropathic component (Kehlet 2006 **NR**; Macrae 2008 **NR**; Wylde 2011 **Level IV**; Chan 2011 **Level II**, n=423, JS 5). Other well-characterised acute pain events may also lead to chronic pain, such as post-traumatic pain (see below and Section 8.1), acute back pain (see Section 8.4) and herpes zoster (see Section 8.6.2).

This section will focus primarily on CPSP, although the underlying mechanisms and risk factors are also relevant to the nonsurgical conditions mentioned above.

1.4.1 Epidemiology of chronic postsurgical pain

There is a high prevalence of CPSP and chronic pain following trauma; 22.5% of 5,130 patients attending chronic pain clinics in North Britain cited surgery as a cause for their pain and 18.7% felt that trauma was the primary cause (Crombie 1998 **Level IV**). A Norwegian population-based study (n=2,043) found 40.4% prevalence of pain in the anatomical region of surgery 3 mth–3 y later (Johansen 2012 **Level IV**). In 18.3% (n=373), the pain was moderate to severe. The prevalence of moderate to severe pain was reduced to 10.5% by excluding all respondents

with the same pain before surgery and to 6.2% by excluding all respondents with any pain before surgery. Factors associated with CPSP were sensory abnormalities in the area of surgery (hyperaesthesia [OR 6.27; 95%CI 4.43 to 8.86] or hypoaesthesia [OR 2.68; 95%CI 1.05 to 3.50]) and psychological distress (OR 1.69; 95%CI 1.22 to 2.36).

The incidence of CPSP varies with the type of operation and it is particularly prevalent where nerve trauma is inevitable (eg amputation) or where the surgical field is richly innervated (eg chest wall) (see Table 1.2) (Kehlet 2006 **NR**; Macrae 2008 **NR**; Wylde 2011 **Level IV**). In a prospective cross-sectional study at a university-affiliated hospital and level 1 trauma centre, 14.8% of patients described CPSP, in particular those after trauma and major orthopaedic surgery (Simanski 2014 **Level IV**, n=3,020). A similar study, focussing on neuropathic CPSP only following two procedure types, identified an incidence of 3.2% for laparoscopic herniorrhaphy vs 37.1% for breast cancer surgery at 6 mth after surgery (Duale 2014 **Level IV**). Among children experiencing major general or orthopaedic surgery, 22% reported moderate to severe CPSP 1 y after surgery. However, most had minimal functional disability (Page 2013b **Level IV**). Overall, these data support the high incidence of CPSP and the frequent linkage of CPSP to nerve injury.

Table 1.2 Incidence of chronic pain after surgery

Type of operation	Incidence of chronic pain (%)	Estimated incidence of chronic severe pain [>5 out of 10/10] (%)
Amputation	30–85	5–10
Thoracotomy	5–65	10
Mastectomy	11–57	5–10
Inguinal hernia	5–63	2–4
Coronary bypass	30–50	5–10
Caesarean delivery	6–55	4
Hip arthroplasty	27	6
Knee arthroplasty	44	15
Cholecystectomy	3–50	Not estimated
Vasectomy	0–37	Not estimated
Dental surgery	5–13	Not estimated

Sources: Adapted from Kehlet 2006, Macrae 2008, Wylde 2011.

1.4.2 Characteristics of chronic postsurgical pain

CPSP is defined as pain developing and persisting beyond the time expected for the normal healing process (ie at least 2 mth) (Macrae 2008 **NR)**. Other causes of ongoing pain (eg infection, malignancy etc) need to be excluded, as well as pain continuing from a pre-existing cause. Refinements to this definition have been suggested, including a change in duration to at least 3 mth to more closely match other studies of chronic pain (Werner 2014 **NR**). Chronic postsurgical and posttraumatic pain will be defined in the new version of the International Classification of Diseases (ICD-11) as pain that develops after a surgical procedure or a tissue injury (involving any trauma, including burns) and persists at least 3 months after surgery or tissue trauma; this is a definition of exclusion, as all other causes of pain (infection, recurring malignancy) as well as pain from a preexisting pain problem need to be excluded (Treede 2015).

Importantly, efforts are now being made to standardise outcome measures to characterise CPSP in future RCTs and epidemiological studies (Wylde 2014 **Level IV**; VanDenKerkhof 2013 **GL**). CPSP may persist as a continuum from acute postsurgical pain or it may occur following a pain-free interval. CPSP may occur in the skin or deep tissues of the region of surgery, it may be referred to characteristic areas due to viscerosomatic convergence or be related to the course of a nerve injured by surgery.

A significant proportion of patients with CPSP demonstrate sensory abnormalities, suggesting that CPSP frequently has a neuropathic component (Aasvang 2008 **Level IV**; Johansen 2012 **Level IV**). However, sensory abnormalities may exist in pain-free postoperative patients. Following video-assisted thoracotomy, sensory changes suggestive of nerve injury were demonstrated in most patients but there was no difference in sensory abnormalities or measures of central sensitisation between patients with and without CPSP (Wildgaard 2012 **Level IV**). Similarly, changes in sensory thresholds (warmth detection and heat pain) were demonstrated in most pain-free patients following open inguinal herniorrhaphy (Aasvang 2010b **Level IV**). This suggests that, although nerve injury is frequently associated with CPSP, such injury does not inevitably lead to chronic pain. It should be recognised however that numbness might still be distressing to some patients.

The intensity and character of CPSP is variable. The descriptors often relate to neuropathic pain (shooting, burning, tingling) (VanDenKerkhof 2013 **Level IV**) but somatic pain characteristics (aching, tender, stabbing, squeezing) are also reported (Chan 2011 **Level III-1**), especially associated with joint arthroplasty (Wylde 2011 **Level IV**). From 1–15% of patients describe the CPSP as severe (Kehlet 2006 **NR**). The impact of the pain varies from mild discomfort to having a significant impact on quality of life. Such an impact is similar to the impact of any form of chronic pain and along with psychological distress may include the need for strong analgesic medications, regular medical attendances, inability to undertake certain activities and limitation in return to work (Chan 2011 **Level III-1**; Steyaert 2012 **NR**).

1.4.3 Predictive factors for chronic postsurgical pain

Demographic factors such as younger age for adults and female gender influence the frequency of CPSP, as do psychological factors such as anxiety, depression, catastrophising, fear of surgery and hypervigilance (Hinrichs-Rocker 2009 **Level IV SR**, 50 studies, n≈25,000; Theunissen 2012 **Level IV SR**, 29 studies, n=6,628). Very young age may be a protective factor as hernia repair in children <3 mth of age did not lead to chronic pain in adulthood (Aasvang 2007 **Level IV**). In children aged 8–18 y, "parent pain catastrophising" was the main risk factor for the development of CPSP (Page 2013a **Level IV**). The significance of each risk factor varies with the operation but pre-existing psychological factors (high state anxiety and pain magnification as a component of catastrophising) increased the risk across two types of surgery (total knee joint replacement and breast cancer surgery) (n=189) (Masselin-Dubois 2013 **Level III-2**).

The intensity of acute postsurgical pain is a consistent predictor of CPSP (Althaus 2012 **Level IV**; Chan 2011 **Level II**, n=640, JS 5). This has been shown following a wide range of procedures including breast surgery (Bruce 2014 **Level IV**), thoracic surgery (Katz 1996 **Level IV**; Yarnitsky 2008 **Level IV**), gynaecological surgery (VanDenKerkhof 2012 **Level IV**), Caesarean delivery (Nikolajsen 2004 **Level IV**), lower limb amputation (Hanley 2007 **Level IV**), hip arthroplasty (Nikolajsen 2006 **Level IV**) and inguinal herniotomy (Aasvang 2010a **Level IV**). After thoracic surgery, higher acute pain intensity postoperatively predicted the incidence of CPSP (OR 1.80; 95%CI 1.28 to 2.77), nearly doubling the chance of developing chronic pain for each point increase on a 10-point numerical rating scale (NRS) (Yarnitsky 2008 **Level IV**). Sensitisation and "wind-up" of nociceptive pathways within the CNS is thought to play a significant role in the establishment and maintenance of chronic pain following an intense nociceptive stimulus. Nociceptive processes occurring in the periphery, including nerve injury, are also implicated in the transition from acute to chronic pain (Baron 2013 **NR**).

Preoperative chronic pain is a universal risk factor (Aasvang 2010a **Level IV**; Wylde 2011 **Level IV**; Johansen 2014 **Level IV**; VanDenKerkhof 2012 **Level IV**). This is likely due to the increase in sensitivity of the nociceptive system found in patients with chronic pain. This may partly explain the relatively high rates of CPSP following hip and knee arthroplasty (25 and 44% respectively) (Wylde 2011 **Level IV**). Taking preoperative opioids increased the risk of CPSP after gynecological surgery (RR 2.0; 95%CI 1.2 to 3.3) (VanDenKerkhof 2012 **Level IV**).

Presurgical sensitivity to painful stimuli, identified using some form of quantitative sensory testing, variably accounts for 5–54% of the variance in acute postoperative pain and can predict risk for CPSP (Werner 2010 **Level I** [QUOROM], 15 RCTs, n=962). The relative efficacy of the endogenous descending inhibitory system determined by assessing DNIC partly predicted

patients who developed CPSP after thoracotomy (OR 0.52; 95%CI 0.33 to 0.77) (Yarnitsky 2008 **Level IV**). Widespread pressure pain sensitivity was correlated with worse functional outcome following knee arthroplasty (Wylde 2013 **Level IV**). Sensitivity to noxious heat and mechanical stimuli did not correlate with CPSP in an unselected surgical population, whereas cold sensitivity correlated both with CPSP and comorbid chronic pain conditions (Johansen 2014 **Level IV**). Prior to herniotomy, high pain scores from a 47°C temperature probe were predictive of postherniotomy pain (OR 1.34; 95%CI 1.15 to 1.57) (Aasvang 2010a **Level IV**).

It is also likely that genetic and epigenetic factors influence both the sensitivity of individuals to analgesics and their risk of CPSP (Buchheit 2012 **NR**; Mauck 2014 **NR**). For example, different haplotypes of the gene for the enzyme catechol-O-methyltransferase (COMT), involved in the modulation of pain responses, were associated not only with differences in experimental pain sensitivity but also with the development of chronic temporomandibular joint disorder (TMD) (Nackley 2007 **Level IV**). However, opioid receptor mu-1 (OPRM1) genotype, but not COMT genotype, was associated with the development of CPSP after abdominal surgery (Kolesnikov 2013 **Level IV**). (See also Section 1.7.)

Attempts have been made to generate predictive models of CPSP but these do not yet have sufficient sensitivity and specificity to prove clinically useful (Althaus 2012 **NR**). However, a screening tool has been developed for breast cancer surgery using the factors of preoperative chronic pain, four or more previous operations, preoperative pain in the area to be operated upon, high body mass index (BMI), previous smoking and older age (Sipila 2012 **Level IV**).

Table 1.3 Risk factors for chronic postsurgical pain

Preoperative factors	Pain, moderate to severe, lasting >1 mth
	Repeat surgery
	Psychological vulnerability (eg catastrophising)
	Preoperative anxiety
	Female gender
	Younger age (adults)
	Workers' compensation
	Genetic predisposition
	Inefficient diffuse noxious inhibitory control
Intraoperative factors	Surgical approach with risk of nerve damage
	Avoidance of nitrous oxide anaesthesia
Postoperative factors	Pain (acute, moderate to severe)
	Radiation therapy to area
	Neurotoxic chemotherapy
	Depression
	Psychological vulnerability
	Neuroticism
	Anxiety

Sources: Adapted from Kehlet 2006; Macrae 2008; Hinrichs-Rocker 2009; Wylde 2011; Johansen 2014.

1.4.4 Mechanisms for the progression from acute to chronic pain

Central and peripheral sensitisation are the most likely underlying factors in the development of CPSP (Lavand'homme 2011 **NR**). There is limited trial data to infer mechanisms and therefore most evidence relating to likely mechanisms is based on laboratory or epidemiological data. Initiation of these processes is most likely in a situation where an individual is "primed" (eg by pre-existing pain) or susceptible (eg inefficient DNIC, psychological state or genetic predisposition) (Lavand'homme 2011 **NR**). The imposition of an intense surgical stimulus induces both central and peripheral changes (Baron 2013 **NR**). Maintenance of these intense

nociceptive inputs by poorly controlled postoperative pain, peripheral nerve damage (D'Mello 2008 **NR**) and complications (eg wound infection) then lead on to a chronic pain state. It is proposed that these all lead to neuroplastic processes such as peripheral and central sensitisation. Such processes include inflammation at the site of tissue damage as well as ectopic discharges after nerve injury and lead to a barrage of afferent input that produces changes in the peripheral nerves, spinal cord, higher central pain pathways, somatosensory cortex and the sympathetic nervous system (see Section 1.1). Evidence for sensitisation includes the presence of larger area of secondary hyperalgesia at 48 h (88 vs 33 cm^2; p=0.001) in patients having iliac crest bone harvesting who developed CPSP with higher neuropathic pain scores on the Doleur Neuropathique 4 (DN4) questionnaire (4.3 vs 2.3; p=0.001) (Martinez 2012 **Level IV**). Similarly, following abdominal surgery, patients with analgesic regimens resulting in smaller areas of wound hyperalgesia (indicating less sensitisation) had a lower incidence of CPSP (Lavand'homme 2005 **Level II**, n=85, JS 5). Punctuate hyperalgesia around a surgical incision could be shown in a large area, suggesting central sensitisation, which was suppressed by intravenous (IV) ketamine injection (Stubhaug 1997 **Level II**, n=20, JS 5).

The relative degree of ongoing inflammation or intraoperative nerve injury resulting in peripheral and central sensitisation may explain the variation in risk and, to an extent, the characteristics of CPSP for different operations (Simanski 2014 **Level IV**).

Psychological factors (depression, psychological vulnerability and stress) are important in the development of CPSP (Hinrichs-Rocker 2009 **Level IV SR**, 50 RCTs, n≈25,000) and cortical processing of nociceptive information and descending inhibitory and excitatory pathways provides a plausible mechanism for some of these effects.

1.4.5 Prevention of chronic postsurgical pain

Effective prevention of CPSP is limited by an incomplete understanding of the mechanisms that generate it. However, a strategy felt most likely to be effective involves a proactive approach to acute pain management and its resolution, an understanding of individual endogenous pain modulatory processes, and fostering the patient's engagement with optimising their psychological functioning.

Interventions evaluated thus far are divided into four broad groups and include regional and neuraxial analgesia, pharmacotherapy, surgery and multidisciplinary nonpharmacological interventions. Analgesic strategies for which the clinical efficacy outlasts the pharmacological activity are described as "preventive analgesia" (defined as analgesia that persists more than 5.5 half-lives of the medicine) and most likely rely on reducing peripheral and central sensitisation (Katz 2011 **NR**) (see Section 1.5).

1.4.5.1 Regional or neuraxial analgesia

A meta-analysis on the prevention of CPSP by regional anaesthesia found benefits for two procedure types; thoracotomy and breast cancer surgery (Andreae 2013 **Level I** [Cochrane], 23 RCTs, n unspecified). Following thoracotomy (3 RCTs, n=250), epidural anaesthesia reduces the incidence of CPSP at 6 mth compared to systemic analgesia or cryoanalgesia (number-needed-to-treat [NNT] 4) (OR 0.33; 95%CI 0.20 to 0.56). For breast cancer surgery (2 RCTs, n=89), paravertebral block (PVB) reduced CPSP at 6 mth compared with systemic analgesia (NNT 5) (OR 0.37; 95%CI 0.14 to 0.94). These findings are supported by another systematic review (overlapping by 7 RCTs), which also identified that three of four RCTs investigating timing of regional anaesthesia in thoracic surgery found that initiating blocks prior to surgery was associated with lower rates of CPSP (Humble 2014 **Level I**, 32 RCTs, n unspecified).

For many procedures, studies investigating the effect of regional anaesthesia and analgesia on chronic pain outcomes are limited in number and have differing designs, which prevents meta-analysis. In patients undergoing open colonic resection, continuous perioperative epidural analgesia led to a lower risk of developing chronic pain up to 1 y after surgery compared with IV analgesia (Lavand'homme 2005 **Level II**, n=85, JS 5). In a case-control study, epidural anaesthesia reduced chronic pain at 6 mth after surgery (OR 0.19; 95% CI 0.05 to 0.76) (Bouman 2014 **Level III-2**). Spinal anaesthesia in comparison to general anaesthesia reduced the risk of CPSP after Caesarean delivery (Nikolajsen 2004 **Level III-2**) and hysterectomy (OR 0.42;

95%CI 0.21 to 0.85) (Brandsborg 2007 **Level III-2**). The latter study found no difference in risk between abdominal and vaginal hysterectomy.

A systematic review on phantom limb pain prophylaxis showed that perioperative (pre, intra and postoperative) epidural analgesia reduced the incidence of severe phantom limb pain 12 mth after surgery (NNT 5.8) (Gehling 2003 **Level III-2 SR**, 9 studies, n=836). The use of epidural analgesia to prevent the development of phantom pain or CPSP following limb amputation may be a useful component of multimodal therapy in patients with severe preoperative pain (Karanikolas 2011 **Level II**, n=65, JS 5).

An infusion of ropivacaine into the site of iliac crest bone graft harvest resulted in significantly less pain in the iliac crest during movement at 3 mth (Blumenthal 2005 **Level II**, n= 36, JS 5). Local anaesthetic wound infiltration reduced the proportion of patients with chronic pain and neuropathic pain 2 mth following intracranial tumour resection (Batoz 2009 **Level II**, n=52, JS 3).

Lignocaine IV has preventive effects on acute postoperative pain (Barreveld 2013 **Level I**, 89 RCTs, n unspecified) (see Section 1.5) and reduced CPSP following breast cancer surgery at 3 mth compared to placebo (2/17 vs 9/19; p=0.03) (Grigoras 2012 **Level II**, n=36, JS 5).

1.4.5.2 Pharmacotherapy

Ketamine is commonly used to treat both acute and chronic pain. When used as a preventive analgesic, perioperative ketamine compared to placebo significantly reduces CPSP at 3 mth (5 RCTs, n unspecified) but only when administered for >24 h (OR 0.37, 95%CI 0.14 to 0.98) (Chaparro 2013 **Level I** [Cochrane], 14 RCTs [ketamine], n=1,388). At 6 mth (10 RCTs, n=516), perioperative ketamine reduces CPSP (OR 0.63; 95%CI 0.47 to 0.83), which remains significant when infused for <24 h (OR 0.45; 95%CI 0.26 to 0.78). These effects were predominantly in abdominal surgery. Another meta-analysis (overlapping by 11 RCTs) found a benefit of perioperative IV ketamine vs placebo in reducing the incidence of CPSP at 3 mth (NNT 12) (RR 0.74; 95%CI 0.60 to 0.93), 6 mth (NNT 14) (RR 0.70; 95%CI 0.50 to 0.98) but not at 12 mth postoperatively (McNicol 2014 **Level I**, 14 RCTs [IV route], n=1,586); such beneficial effects were not found with epidural administration of ketamine (3 RCTs, n=302).

Two parallel meta-analyses (overlapping by 10 RCTs) investigated the use of perioperative gabapentin or pregabalin in reducing CPSP across a diverse range of procedures. One concluded that both gabapentin (6 RCTs, n=356) (OR 0.52; 95%CI 0.27 to 0.98) and pregabalin (2 RCTs, n=285) (OR 0.09; 95%CI 0.02 to 0.79) are effective in reducing the incidence of chronic pain at 3–6 mth after surgery, but that dose and duration of treatment are not yet clear (Clarke 2012 **Level I** [PRISMA], 11 RCTs, n=930). This study also identified a high likelihood of positive publication bias. In response to correspondence (Chelly 2013), the authors reanalysed their pregabalin data including three unpublished trials from the USA government trial registry (www.clinicaltrials.gov). This reanalysis no longer found an effect from pregabalin in preventing CPSP at 3 mth (OR 0.73; 95%CI 0.28 to 1.89; p=0.51)) (Clarke 2013 **Level I**, 5 RCTs, n=875).

The second meta-analysis concluded there is overall no significant effect from gabapentin or pregabalin on CPSP, although analysis of any wound site pain at 3 mth identified an effect for pregabalin (OR 0.70; 95%CI 0.51 to 0.95) (4 RCTs, n=439), which was substantially influenced by a strong outcome in the only positive (cardiac surgery) study, but no effect was identified for gabapentin (OR 0.99, 95%CI 0.80 to 1.21) (5 RCTs [2 overlapping], n=280) (Chaparro 2013 **Level I** [Cochrane], 15 RCTs [gabapentin and pregabalin], n=1,300); there was a large degree of heterogeneity among the pregabalin studies (I^2=43%). These results reflect significant uncertainty in this area, due to the small size of most included studies, the variability in existing study design, doses used, duration of treatment and measured outcomes, and positive publication bias.

Following mastectomy, 10 d treatment with venlafaxine (37.5 mg/d) commencing preoperatively was associated with significantly lower burning and stabbing pain after 6 mth (Amr 2010 **Level II**, n=150, JS 3).

The intraoperative use of nitrous oxide (N_2O) reduced the risk of CPSP in an Asian subset of a large multicentre RCT at a median of 4.5 y following the initial (mostly abdominal) surgery

(OR 0.48; 95%CI 0.33 to 0.93) (Chan 2011 **Level II**, n=423, JS 5); factors increasing risk included severity of acute postoperative pain, wound length, wound infection and anxiety.

1.4.5.3 Modification of surgical approach

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of CPSP (from 21–6%) in one RCT (Malekpour 2008 **Level II**, n=100, JS 4) and in another study (Smeds 2010 **Level III-2**), while an earlier nonrandomised multicentre prospective study (n=973) found this increased CPSP risk (Alfieri 2006 **Level III-2**). Intraoperative nerve identification of the iliohypogastric, ilioinguinal and genitofemoral nerves did not reduce the risk of development of sensory loss or postherniotomy pain syndrome compared with nonidentification (Bischoff 2012 **Level III-3**, n=244). International guidelines for the reduction in CPSP following inguinal herniorraphy have been developed, recommending preservation of all three nerves (Alfieri 2011 **GL**).

Sparing of the intercostobrachial nerve during mastectomy with axillary dissection reduces the likelihood of a patient having hyposensitivity but not hypersensitivity (Warrier 2014 **Level I** [PRISMA], 3 RCTs, n=309).

Cryoanalgesia of the intercostal (IC) nerves at the time of thoracotomy results in no improvement in acute pain and an increase in chronic pain in comparison to IV PCA or epidural analgesia or in conjunction with epidural analgesia (Humble 2014 **Level I**, 6 RCTs, n=186).

1.4.5.4 Multidisciplinary approaches

The impact of psychological interventions such as preoperative pain management programs prior to surgery is being assessed but no clear evidence yet exists for their efficacy in reducing rates of CPSP (Wylde 2014 **Level IV**).

See also the following Section 1.5 for more examples of the use of pre-emptive and preventive analgesic interventions in attempts to reduce the risk of chronic pain after surgery and Sections 8.1.5 to 8.1.6 for more details on prevention of phantom pain after limb amputation and other postoperative pain syndromes.

Key messages

1. Perioperative ketamine reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
2. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review]).
3. Following breast cancer surgery, paravertebral block reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
4. Sparing of the intercostobrachial nerve during mastectomy does not decrease chest wall hypersensitivity (**N**) (**Level I** [PRISMA]).
5. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain but an increase in chronic pain (**S**) (**Level I**).
6. There is significant association between anxiety, pain catastrophising (**N**) (**Level III-2 SR**), depression, psychological vulnerability and stress (**N**) (**Level IV SR**) and the subsequent development of chronic postsurgical pain.
7. Other risk factors that predispose to the development of chronic postsurgical pain include the severity of presurgical chronic pain and postsurgical acute pain and intraoperative nerve injury (**S**) (**Level IV SR**).
8. Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean delivery (**U**) (**Level III-2**).
9. Chronic postsurgical pain is common and may lead to significant disability (**S**) (**Level IV**).
10. Chronic postsurgical pain often has a neuropathic component (**S**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Although pregabalin and gabapentin may have an effect in preventing chronic postsurgical pain, considerable uncertainty exists regarding efficacy with contradictory meta-analyses of few, usually small studies with a large degree of heterogeneity (**N**).

1.5 Pre-emptive and preventive analgesia

The understanding of pre-emptive analgesia has evolved since the term was first coined in early 1988 (Wall 1988 **NR**). In laboratory studies, administration of an analgesic prior to an acute nociceptive stimulus more effectively minimised dorsal horn changes associated with central sensitisation than the same analgesic given after the pain state was established (see Section 1.1) (Woolf 1983 **BS**). This led to the hypothesis that pain relief prior to surgery may enhance postoperative pain management; that is, "pre-emptive preoperative analgesia" (Wall 1988 **NR**). However, individual clinical studies have reported conflicting outcomes when comparing "preincisional" with "postincisional" interventions. In part this relates to variability in definitions, deficiencies in clinical trial design and differences in the outcomes available to laboratory and clinical investigators (Kissin 1994 **NR**; Katz 2002 **NR**).

Central and peripheral sensitisation affects both the intensity of acute pain and the persistence of pain well into the postoperative period and beyond (see also Section 1.4). This is complex and relates not only to skin incision but also to the extent of intraoperative tissue and nerve injury, postoperative inflammation and the nervous system's response. The research focus has shifted from the "timing" of a single analgesic intervention to the concept of modifying sensitisation and thus having a longer-term impact on pain relief. This is termed "preventive" analgesia (Kissin 1994 **NR**) rather than pre-emptive analgesia. The differences between these two terms relate to the timing and outcomes being described, because both aim to minimise sensitisation. "Pre-emptive" analgesia, as described above, relates to the timing of administration of the analgesic intervention prior to the insult and is measured in terms of pain intensity or related outcomes. "Preventive" analgesia is the persistence of analgesic treatment efficacy beyond its expected duration (see Table 1.4). This had been defined as analgesia that persists for >5.5 half-lives of a medicine, to ensure complete washout of any direct pharmacological effect (Katz 2011 **NR**). A useful summary of medicines and their criterion value of 5.5 half-lives has been published (Katz 2008b **NR**). In clinical practice, preventive analgesia appears to be the most relevant and, of pharmacological options, holds the most hope for minimising chronic pain after surgery or trauma because it decreases central sensitisation and "wind-up". An important consideration to maximise the benefit of any analgesic strategy is that the active intervention should be continued for as long as the sensitising stimulus persists (ie well into the postoperative period) (Dahl 2004 **NR**; Pogatzki-Zahn 2006 **NR**). However from a "preventive" perspective, the critical aspect is that the effect of the intervention is sufficient to modify sensitisation and hence longer-term outcomes; the timing and duration for specific interventions still require clarification.

Table 1.4 Definitions of pre-emptive and preventive analgesia

Pre-emptive analgesia	Preoperative treatment is more effective than the identical treatment administered after incision or during surgery. The key clarification point is the timing of administration "pre" insult/surgery. A treatment given pre-emptively can also be preventive if it satisfies the below definition.
Preventive analgesia	Postoperative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment or no treatment with the effect observed at a point in time beyond the expected duration of action of the intervention (eg 5.5 half-lives of the medicine). The intervention may or may not be initiated before surgery.

Sources: Moiniche 2002; Katz 2002; Katz 2011

1.5.1 Pre-emptive analgesia

The benefits of pre-emptive analgesia have been questioned (Dahl 2004 **NR**; Moiniche 2002 **Level I**, 80 RCTs, n=3,761; Katz 2008b **Level I**, 27 RCTs, n unspecified). However one meta-analysis provided support for pre-emptive analgesia (Ong 2005 **Level I**, 66 RCTs, n=3,261). The efficacy of different pre-emptive analgesic interventions (epidural analgesia, local anaesthetic wound infiltration, systemic NMDA antagonists, systemic opioids and systemic NSAIDs) was analysed in relation to different analgesic outcomes (pain intensity scores, supplemental analgesic consumption, time to first analgesic). The effect size is most marked for epidural analgesia, with improvements found in all outcomes (13 RCTs, n=653) (overall effect size 0.38; 95%CI 0.28 to 0.47). Pre-emptive effects of local anaesthetic wound infiltration and NSAID administration were also suggested but reanalysis is required as one of the positive studies for each of these treatments has subsequently been withdrawn (White 2011 **NR**). As a result of this withdrawal, evidence supporting the pre-emptive effects of nonselective NSAIDS (nsNSAIDs) and COX-2 inhibitors is equivocal (White 2009 **NR**). Reductions in analgesic consumption ranged from 44–58%, which the authors regarded as clinically significant, but associated changes in adverse effects were not analysed. Pain score results were equivocal for systemic NMDA antagonists (7 RCTs, n=418) (ES 0.00; 95%CI -0.19 to 0.20) and there was no clear evidence for a pre-emptive effect of opioids (7 RCTs, n=324) (ES -0.24; 95%CI -0.46 to -0.01).

Following thoracotomy, pre-emptive thoracic epidural analgesia (local anaesthetic +/– opioid prior to surgery) reduces the severity of acute pain on coughing for up to 48 h, with a marginal effect on pain at rest compared with the same therapy initiated postoperatively (Bong 2005 **Level I**, 6 RCTs, n=458). Acute pain intensity was a predictor of chronic pain at 6 mth in two studies but there was no statistically significant difference in the incidence of chronic pain between the pre-emptive epidural (39.6%) vs control epidural (48.6%) groups.

The variability in clinical trial design coupled with the complexity of clinical pain management means that, with the exception of epidural analgesia, benefits remain unclear regarding pre-emptive analgesia in a clinical setting.

1.5.2 Preventive analgesia

A systematic review analysed dichotomous trial outcomes (overall positive or negative outcomes) (Katz 2008b **Level I**, 39 RCTs, n unspecified) and identified overall beneficial acute preventive effects following the use of a range of different medicines (28 positive trials, 11 negative trials; p=0.03). Again results of this meta-analysis might be affected by the subsequent withdrawal of some of the studies included (White 2011 **NR**). The methodology was unable to identify specific therapeutic techniques that may be of benefit.

The use of non-neuraxial (perineural or systemic) local anaesthetics demonstrates a preventive analgesic effect in the perioperative period whether given pre or postincision but there is insufficient evidence at this stage to identify a longer-term benefit in reducing the incidence of CPSP (Barreveld 2013 **Level I**, 89 RCTs, n unspecified).

Activation of the NMDA receptor plays an important role in central sensitisation and many studies have focussed on the ability of NMDA-receptor antagonists to produce pre-emptive or preventive analgesic effects. A medicine which, when used perioperatively, reduces CPSP has by definition a preventive analgesic effect (see Section 1.4). The preventive effects of perioperative ketamine, dextromethorphan and magnesium on CPSP are described in Sections 1.4 and 4.6. Analgesic benefit is seen in the acute postoperative period with ketamine following a range of doses, timings and procedures (Laskowski 2011 **Level I** [PRISMA], 70 RCTS, n=4,701) (see also Section 4.6.1). However, in the immediate postoperative period, it is difficult to separate persistence of direct pharmacological effects from preventive actions, as many studies continued treatment for over 24 h.

The alpha-2-delta ligands, gabapentin and pregabalin, reduce opioid requirements and improve analgesia when given perioperatively (Tiippana 2007 **Level I** [QUOROM], 21 RCTs, n=1,711; Zhang 2011 **Level I** [QUOROM], 11 RCTs, n=899) (see also Section 4.8). However, even though some of these studies used only single-dose therapy, the range of doses, duration of follow-up and long half-life of gabapentin (6–7 h) means that an early preventive benefit is difficult

to discern from a direct pharmacological effect. Longer-term preventive effects on CPSP are discussed in Section 1.4.

In a study of multimodal epidural analgesia (local anaesthetic, opioid, ketamine and clonidine) in four groups of patients having colonic resection, a clear preventive effect on the development of residual pain up to 1 y after surgery was demonstrated with continuous perioperative epidural analgesia (Lavand'homme 2005 **Level II**, n=85, JS 5). Residual pain at 1 y was lowest in patients who received intraoperative vs postoperative epidural analgesia.

Key messages

1. The timing of a single analgesic intervention (preincisional rather than postincisional), defined as pre-emptive analgesia, has a significant effect on postoperative pain relief as seen with epidural analgesia (**U**) (**Level I**).
2. There is evidence that some analgesic interventions have an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the medicine, defined as preventive analgesia (**S**) (**Level I**).
3. NMDA-receptor antagonists (ketamine) show preventive analgesic effects (**S**) (**Level I**).
4. Local anaesthetic administration, either perineural or systemic, shows preventive analgesic effects (**S**) (**Level I**)

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ In clinical trials assessing acute postoperative pain for many systemic medicines, the range of doses administered, the variable durations of follow-up and variable half-lives following infusion or repeated dosing means that "early" preventive effects, although possible, are difficult to discern from persistence of direct pharmacological effects (**N**).

1.6 Adverse physiological and psychological effects of acute pain

1.6.1 Acute pain and the injury response

Acute pain, and its associated injury and treatment, triggers a complex haemodynamic, metabolic, neurohumoral, immune as well as somatosensory response (see Figure 1.2).

Clinically, acute pain is commonly associated with actual tissue damage. This tissue damage may be due to trauma or surgery. It is difficult to separate the complex array of potential individual or interacting triggers associated with pain from other aspects of the stress response observed clinically (see Figure 1.2). However, some data have been obtained with experimental pain in the absence of injury. For example, electrical stimulation of the abdominal wall results in a painful experience (visual analogue scale [VAS] 8/10) and an associated hormonal/metabolic response, which includes increased levels of cortisol, catecholamines and glucagon, and a decrease in insulin sensitivity (Greisen 2001 **EH**). A systematic review of the effect of experimental pain on the autonomic nervous system, assessed by heart rate variability, determined that experimental pain increases baroreflex activity and decreases parasympathetic activity (Koenig 2013 **Level IV EH SR**, 20 studies, n unspecified).

Although acute pain is only one of the important triggers of the "injury response" (see Figure 1.2), as the magnitude and duration of the response is related to the magnitude and duration of the nociceptive stimulus, effective pharmacological pain relief may have a significant impact on this response (Moselli 2011 **Level II**, n=35, JS 3), although this may be variable (Liu 2008 **NR**; Carli 2008 **NR**; Fant 2013 **Level II**, n=26, JS 3). Beyond pharmacological interventions, mere distraction of attention away from the pain protects against experimental pain-induced changes in heart-rate variability (Koenig 2013 **Level IV EH SR**, 20 studies, n unspecified).

The release of proinflammatory cytokines and other substances as a result of pain and trauma associated with surgery or injury may contribute to multiple physiological responses that

hamper the recovery of a patient. Limiting these effects by analgesic techniques may affect some surgical outcomes. A group of patients having abdominal surgery were randomised to receive intraoperative epidural analgesia or IV opioid analgesia, with both groups receiving postoperative epidural analgesia (Moselli 2011 **Level II**, n=35, JS 3). In the intraoperative epidural group, inflammatory markers were lower up to 24 h postoperatively and minor complications were reduced in number (39 vs 76%, p=0.024), although there was no difference in major complications or length of hospital stay. Postoperative ileus is attenuated in patients receiving lignocaine infusions compared to saline in patients undergoing colonic surgery (Vigneault 2011 **Level I** [PRISMA], 29 RCTs, n=1,754; Sun 2012 **Level I** [PRISMA], 21 RCTs, n=1,108). Analgesic and bowel motility benefits of lignocaine were more marked when administered via the thoracic epidural route than by IV infusion (Kuo 2006 **Level II**, n=60, JS 5); however, both lignocaine groups were associated with reduced opioid consumption compared with saline. The postoperative decreases in proinflammatory cytokines, such as interleukin-6 (IL-6), IL-8 and IL-1RA (a competitive inhibitor of IL-1β), were associated with more rapid return of bowel function following abdominal surgery.

In addition to the stress responses to surgery and analgesia, aberrant firing during acute pain creates a state of altered cell function in nociceptive pathways. This may not be perceived as pain by higher brain centres (eg under general anaesthesia) nor acknowledged consciously by the individual. Cellular adaptations to acute nociceptive inputs in primary and secondary fibres are well established to drive peripheral and central sensitisation (Kuner 2010 **NR**; Woolf 2011 **NR**; von Hehn 2012 **NR**; Baron 2013 **NR**). Critically, these result in multiple changes to gene transcription and protein translation (see also Section 1.1).

Figure 1.2 The injury response

Triggers and predisposing factors	Mediators	Injury response
Surgical trauma or injury	Neural	Pain experience, primary and secondary hyperalgesia (peripheral and central sensitisation)
Preoperative pain	Immune factors	Inflammation
	Proteins and other molecules: • growth factors • ecosanoids • nitric oxide • others	Haemodynamic
Psychological factors	Endocrine	Catabolism
Social and environmental factors	Metabolic	Physical deconditioning
Genetic factors		Psychological effects
Anaesthesia and analgesia, other medications		Other adaptations systemic

Source: Modified from NHMRC 1999.

1.6.2 Adverse physiological effects

Clinically significant injury responses that are often associated with nociceptive stimuli trigger diffuse physiological responses such as stress and inflammation, which leads to hyperalgesia, hyperglycaemia, protein catabolism, increased free fatty acid levels (lipolysis) and changes in water and electrolyte flux (Carli 2008 **NR**; Liu 2008 **NR**). In addition, increased sympathetic activity has diverse effects on the cardiovascular, gastrointestinal and respiratory systems and on coagulation, endocrine, immune and psychological function (Cardinale 2011 **NR**; Blackburn 2011 **NR**; Prabhakar 2014 **NR**).

Table 1.5 Metabolic immunologcal and endocrine responses to injury

Endocrine	↑ Catabolic hormones	↑ ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons,
	↓ Anabolic hormones	↓ Insulin, testosterone
Immune	Mitochondrial initiation	Alarmins (DAMP molecules)
	Proinflammatory followed by compensatory response	IL-1, TNFα, IL-6, IL-4, IL-8, IL-10
		Chemokines
Metabolic		
Carbohydrate	Hyperglycaemia, glucose intolerance, insulin resistance	↑ Glycogenolysis, gluconeogenesis (cortisol, glucagon, growth hormone, adrenaline, free fatty acids)
		↓ Insulin secretion/activation
Protein	Muscle protein catabolism, ↑ synthesis of acute phase proteins	↑ Cortisol, adrenaline, glucagons, IL-1, IL6, TNF
Lipid	↑ Lipolysis and oxidation	↑ Catecholamines, cortisol, glucagon, growth hormone
Water and electrolyte flux	Retention of water and sodium, ↑ excretion of potassium and ↓ functional ECF with shifts to ICF	↑ Catecholamine, aldosterone, ADH, cortisol, angiotensin II, prostaglandins and other factors

Note: *ACTH: adrenocorticotrophic hormone; ADH: antidiuretic hormone; DAMP: damage-associated molecular pattern; ECF: extracellular fluid; ICF: intracellular fluid; IL: interleukin; TNF: tumour necrosis factor.*

Source: *Modified from NHMRC 1999.*

1.6.3 Pain and analgesia: effects on injury-induced organ dysfunction

Pain from injury activates a range of adverse physiological effects (Cardinale 2011 **NR**; Blackburn 2011 **NR**; Prabhakar 2014 **NR**). Increased sympathetic efferent nerve activity increases heart rate, contractility and blood pressure. As sympathetic activation increases myocardial oxygen demand and reduces myocardial oxygen supply, the risk of cardiac ischaemia, particularly in patients with pre-existing cardiac disease, is increased. Enhanced sympathetic activity can also reduce gastrointestinal motility and contribute to ileus. Severe pain after upper abdominal and thoracic surgery contributes to an inability to cough and a reduction in functional residual capacity, resulting in atelectasis and ventilation-perfusion abnormalities, hypoxaemia and an increased incidence of pulmonary complications. The injury response also contributes to a suppression of cellular and humoral immune function and a hypercoagulable state following surgery, both of which can contribute to postoperative complications. Alterations to glucose metabolism and accelerated protein breakdown also contribute to the injury response. These factors need to be considered when evaluating analgesic interventions. Patients at greatest risk of adverse outcomes from unrelieved acute pain include very young or elderly patients, those with concurrent medical illnesses and those undergoing major surgery (Liu 2008 **NR**). Analgesic technique may reduce adverse physiological impact and improve surgical outcomes. Often a multimodal approach to anaesthesia, pain management and the surgical stress

response is undertaken making it difficult to separate individual factors involved in outcome. The influence of epidural anaesthesia and analgesia on outcome has been evaluated (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044) (see also Section 5.6).

There is also limited evidence that stress and opioid analgesia in some circumstances may inhibit immune function, promoting tumour growth or metastasis. Regional anaesthetic and analgesic techniques might have a beneficial effect on rates of cancer recurrence after tumour resection but overall study results are still unclear (Colvin 2012 **NR**; Meserve 2014 **NR**).

Key messages

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**S**) (**Level I** [PRISMA]).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Acute pain and injury of various types are inevitably interrelated and, if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (**U**).

1.6.4 Adverse psychological effects

Psychological changes associated with acute pain have received less attention than those associated with chronic pain, however they are no less important. Sustained acute nociceptive input, as occurs after surgery, trauma or burns, can also have a major influence on psychological function, which may in turn alter pain perception. Failure to relieve acute pain may result in increasing anxiety, inability to sleep, demoralisation, a feeling of helplessness, loss of control, inability to think and interact with others; in the most extreme situations, where patients can no longer communicate, effectively they have lost their autonomy (Cousins 2004 **NR**). Psychological and environmental responses in the acute phase may be major determinants of progression to persistent pain (Young Casey 2008 **NR**; Williamson 2009 **Level III-2**; Jenewein 2009 **Level III-2**).

In acute pain, attention has been focussed on postoperative cognitive dysfunction (POCD). Although the aetiology of POCD is unknown, factors probably include dysregulation of cerebral neurotransmitters, patient factors (age, comorbidities, preoperative cognitive function and general health) (Newman 2007 **Level IV SR**; Monk 2008 **Level III-3**), surgical procedures (eg coronary artery bypass) and perioperative pharmacological therapy (Flacker 1999 **NR**). Elderly patients have an increased incidence of POCD and are more likely to have prolonged symptoms (see Section 10.2.2). Neurotransmitters involved may include acetylcholine and serotonin and inflammatory mediators (eg cytokines) may contribute, especially in the elderly (Caza 2008 **NR**). POCD after cardiac surgery may also be due in part to cerebral microembolism, global cerebral hypoperfusion, cerebral temperature perturbations, cerebral oedema, and possible blood-brain barrier dysfunction (Flacker 1999 **NR**; Gao 2005 **NR**).

1.7 Genetics and acute pain

An increasing number of genetic variants modulating nociception, susceptibility to pain conditions, as well as response to pharmacotherapy are being discovered.

Pharmacogenomics deals with the influence of variations in the human genome on response to medicines in patients. By correlating gene alterations with a medicine's efficacy or toxicity, it is possible to gain a better understanding of the causes of interpatient variability in response to a specific medicine and so to develop a rational means to optimise pharmacological therapy with respect to the patient's genotype and ensure maximum efficacy with minimal adverse effects. For example, genetic factors regulating opioid pharmacokinetics (metabolising enzymes, transporters) and pharmacodynamics (receptors and signal transduction elements) contribute to the large interpatient variability in postoperative opioid requirements (Trescot

2014 **NR**). Information from genotyping may help in selecting the analgesic medicine and the dosing regimen for an individual patient (Lotsch 2006 **NR**; Allegri 2010 **NR**).

Although there is increasing information from studies, often small numbers of subjects are involved and therefore translation into clinical practice is still limited (Stamer 2007b **NR**; Trescot 2014 **NR**). Nevertheless, some preliminary estimates for dose adaptations are possible (Lotsch 2006 **NR**; Allegri 2010 **NR**). However, genetic factors must be considered within the context of the multiple interacting physiological, psychological, cultural, ethnic and environmental factors that influence individual responses to pain and analgesia (Searle 2009 **NR**; Kim 2009 **NR**; Sadhasivam 2014 **NR**).

1.7.1 Single gene pain disorders

A number of rare pain-related conditions have been identified though family linkage mapping, which are due to single gene mutations (Mendelian gene).

Recognised hereditary syndromes associated with reduced pain sensation include the following.

- Channelopathy-associated insensitivity to pain (CAIP) is caused by variants in the *SCN9A* gene, which codes for the alpha-subunit of the voltage-gated sodium channel $Na_v1.7$. $Na_v1.7$ is located in peripheral neurones and plays an important role in action potential production in these cells. Mutations result in loss of $Na_v1.7$ function and affected individuals are unable to feel physical pain (Bennett 2014 **NR**). Patients with a single-nucleotide polymorphism (SNP) in *SCN9A* (3312T) had lower postoperative pain sensitivity after pancreatectomy, lower PCA requirements and a lower likelihood of developing inadequate analgesia than those carrying the 3312 G allele (OR 0.10; 95%CI 0.01 to 0.76) (Duan 2013 **Level III-2**).
- Hereditary sensory and autonomic neuropathy (HSAN) I–V syndromes are associated with a range of genetic abnormalities and produce varying patterns of sensory and autonomic dysfunction and peripheral neuropathy (*NTRK1* gene) (Mogil 2012 **NR**; Auer-Grumbach 2013 **NR**). These syndromes present as various combinations of loss or reduced sensitivity to pain accompanied by other autonomic and sensory deficits. HSAN type IV is also known as congenital insensitivity to pain with anhydrosis (CIPA).

Recognised hereditary syndromes associated with increased pain sensation include (Mogil 2012 **NR**):

- erythromelalgia and paroxysmal extreme pain disorder, also known as familial rectal disorder, both of which are due to different mutations of sodium channel $Na_v1.7$ (*SCN9A*) (Dabby 2012 **NR**);
- familial hemiplegic migraine;
- hereditary neuralgic amyotrophy; and
- hereditary pancreatitis (Rebours 2012 **NR**).

1.7.2 Genetic influences on sensitivity to pain

Apart from these rare Mendelian inherited conditions, "pain sensitivity" variability is thought to vary up to 50% in the general population due to genetic differences with environmental influences responsible for the remainder of variability (Norbury 2007 **Level IV**). Twin studies have helped identify inheritable traits for development of back pain, postherpetic neuralgia, fibromyalgia and other common painful conditions (Mogil 2012 **NR**).

While several hundred genes have been identified as associated with pain expression in mice, they are not necessarily relevant to humans (LaCroix-Fralish 2011 **BS**). Evidence for a genetic association with more common pain conditions has come from association studies, which require large cohorts (Mogil 2012 **NR**). Studies often suffer from low sample sizes and the restricted number of potential genotype variants studied. Many findings of an association of a particular gene allele with pain sensitivity have not been replicated in subsequent studies, so caution is needed in this area.

Many genetic variants have been associated with pain sensitivity (Crist 2014 **NR**); the most commonly studied genes include:

- mu opioid receptor (*OPRM1*);
- catechol-O-methyltransferase (*COMT*);
- guanosine triphosphate cyclohydrolase 1;
- transient receptor potential (*TRPV1*); and
- melanocortin-1 receptor (*MC1R*)

Other gene variants that have been associated with alteration to pain sensitivity in acute pain states include *ADRB2, HTR2A, IL1RN, KCNJ6, MAOA* and *MAOB* (Mogil 2012 **NR**).

1.7.2.1 OPRM1

A variant of the gene encoding the mu opioid receptor OPRM1, A118G SNP was targeted as a very promising candidate for modulation of analgesia and has been the most studied variant (Crist 2014 **NR**).

Overall findings on the effects of this SNP remain contradictory (Crist 2014 **NR**). In a random-effects meta-analysis in the postoperative setting, *OPRM1* 118G-allele carriers have higher mean opioid requirements than *OPRM1* 118AA homozygotes (SMD -0.18; p=0.003) (Hwang 2014 **Level III-2 SR**, 18 studies, n=4,607). These findings were robust in a subgroup analysis of Asian patients, whose frequency of the G variant is about 40% compared to about 15% for Caucasians (SMD -0.21; p=0.001), morphine users (SMD -0.29; p<0.001) and patients after bowel surgery (SMD -0.20; p=0.008). A preceding systematic review found a similar but smaller effect (SMD 0.096; 95%CI 0.025 to 0.167) of *OPRM1* 118G with increased opioid requirements in the perioperative and postoperative period (Walter 2013 **Level III-2 SR**, 14 studies, n=3,346); there was no significant association of *OPRM1* 118G with opioid requirements, when using the random-effects environment (Cohen's d=0.044; 95%CI -0.113 to 0.202; p=0.58). For epidural analgesia using fentanyl during labour however, G-allele (AG+GG) carriers of the *OPRM1* 118 polymorphism required lower (not higher) fentanyl doses to achieve adequate pain relief compared with those with the AA homozygote (SMD=-0.24; 95%CI -0.44 to -0.03; p=0.022) (Song 2013 **Level III-2 SR**, 6 studies, n=838). *OPRM1* 304A/G polymorphism did not influence the duration of effect or the requirement for breakthrough analgesia after intrathecal (IT) opioid administration for labour pain (Wong 2010 **Level III-2**). There was also no effect of A118G mu-opioid receptor polymorphism on duration of analgesia found in a subsequent study but patients of Hispanic/African origin had increased duration of analgesia and pruritus vs Jewish/Arabic patients in labour (Ginosar 2013 **Level III-2**).

OPRM1 A118G seems to modulate effects of opioids given in experimental pain; in the clinical setting it has limited impact in Caucasians, which is not clinically relevant, but it explains increased opioid requirements in Asians. Studies that assessed different haplotypes of the *OPRM1* and combinations of genetic variants, eg *OPRM1* and COMT, found greater predictability suggesting more complexity (Reyes-Gibby 2007 **Level III-2**; Mura 2013 **NR**). Overall *OPRM1* 118 polymorphisms maybe too complex to be used as a predictive tool for individual opioid dosing (Mogil 2012 **NR**).

1.7.2.2 COMT

COMT metabolises noradrenaline, adrenaline, and dopamine and has been implicated in the modulation of pain. COMT inhibition or low activity via genetic polymorphisms may lead to increased pain sensitivity via beta-adrenergic receptor-dependent mechanisms (Nackley 2007 **NR**). Haplotypes with high COMT activity are associated with low pain sensitivity to mechanical and thermal stimuli (Diatchenko 2005 **NR**). The Val158Met polymorphism influences the activity of the COMT enzyme with the Met158 allele associated with low COMT activity and increased pain sensitivity (Vuilleumier 2012 **NR**), leading to greater morphine requirements post surgery in adults (Dai 2010 **Level IV**) and children (Sadhasivam 2014 **Level IV**).

A large study undertaken to address influence of *COMT* polymorphism on postoperative pain in a homogenous ethnic sample of 1,000 women having breast surgery showed no association with any *COMT* polymorphism and postoperative oxycodone requirements (Kambur 2013 **Level III-2**). Furthermore the most studied *COMT* mutation, Val158Met, showed no association with pain levels in these patients but two previously unstudied mutations did. Combinations of several genetic mutations act together to determine pain sensitivity associated with COMT (Smith 2014 **Level III-2**). Similarly genetic association studies using *COMT* variants have also revealed conflicting results (Belfer 2011 **NR**).

1.7.2.3 TRPA1

Emerging evidence suggests that genetic variations of the TRPA1 receptor may be responsible for some of the genetically determined individual differences in pain sensitivity (Bell 2014 **Level III-2**).

There is considerable complexity associated with genetic mutations influencing pain sensitivity and much to be unravelled before clear evidenced-based conclusions can be drawn.

1.7.3 Drug metabolism

Drug-metabolising enzymes represent a major target for identifying associations between an individual's genetic profile and drug response (pharmacogenetics) (Stamer 2007c **NR**; Trescot 2014 **NR**). The polymorphic cytochrome P450 enzymes metabolise most medicines and show interindividual variability in their catalytic activity. There are 57 enzymes in this family of which 8 are clinically relevant to drug metabolism: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/3A5, all of which have different and often overlapping activity. Medicines can be substrates, inhibitors or inducers of metabolism of analgesic medications.

CYP2D6, CYP2C19, and CYP2C9 are highly polymorphic and they are involved in approximately 40% of CYP-mediated drug metabolism. Of these, CYP2D6 is the most relevant to analgesic medications. Those who have the genetic variant resulting in poor metabolism by CYP2D6 are likely to have more severe postoperative pain than those who have other variants (Yang 2012 **Level III-2**).

The *CYP2D6* gene is of clinical interest as it influences the metabolism of many medications including codeine, tramadol, oxycodone, hydrocodone, dextromethorphan, amitriptyline, nortriptyline, duloxetine, metoclopramide and venlafaxine. Specifically, CYP2D6 metabolises codeine, dihydrocodeine, hydrocodone, oxycodone and tramadol to their more potent hydroxyl metabolites, which have a higher affinity for the mu receptor (Somogyi 2007 **NR**). For additional detail related to individual opioids see Section 4.1.2.

Over 100 allelic variants of *CYP2D6* have been identified, resulting in wide variability in function. Individuals carrying two wild type alleles display normal enzyme activity and are known as extensive metabolisers; intermediate metabolisers are heterozygotes with one reduced function and one nonfunctional allele; poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Zhou 2009a **NR**; Zhou 2009b **NR**; Vuilleumier 2012 **NR**; Crews 2014 **NR**). Ultrarapid metabolisers have multiple copies of the wildtype *CYP2D6* alleles (Stamer 2007b **NR**; Vuilleumier 2012 **NR**; Crews 2014 **NR**).

In Caucasian populations, 8–10% of people are poor metabolisers and 3–5% are ultrarapid metabolisers (Stamer 2007b **NR**; Vuilleumier 2012 **NR**; Crews 2014 **NR**). There are large interethnic differences in the frequencies of the variant alleles. For example, the proportion of ultrarapid metabolisers is higher (up to 29%) in Middle Eastern and Northern African populations and lower (0.5%) in Asian populations (Stamer 2007c **NR**). The proportion of poor metabolisers is lower in Asian and African American populations (Holmquist 2009 **NR**; Yee 2013 **Level IV**).

Other genetic factors indirectly affecting the metabolism or effect of analgesics are liver cell transporter proteins: organic cation transporter (OCT1) (Fukuda 2013 **Level III-2**); ABCC3 (Venkatasubramanian 2014 **Level III-2**) and ATP-binding cassette subfamily member B1 (also known as multidrug resistance protein [MDR]1 or p-glycoprotein) (Sadhasivam 2015 **Level III-2**).

The latter affects efflux transport of morphine at the blood-brain barrier and thereby cerebral pharmacokinetics.

Further considerations are the differential risk with genetic differences and varying prevalence of racial/ethnic phenotypes (Anderson 2014 **NR**) and consequent variability in sensitivity to adverse effects (Fukuda 2013 **Level IV;** Jimenez 2012 **Level III-3**).

1.7.3.1 Codeine

In children and adults receiving codeine for postoperative pain, very low or undetectable levels of plasma morphine have been noted in those with poor metaboliser or intermediate metaboliser genotypes but with variable impact on analgesia (Persson 1995 **Level IV**; Poulsen 1998 **Level IV**; Williams 2002 **Level II**, n=96, JS 3).

CYP2D6 genotypes predicting ultrarapid metabolism resulted in about 50% higher plasma morphine and its glucuronides concentrations following oral codeine compared with the extensive metaboliser (Kirchheiner 2007 **Level IV**). Both the impaired renal clearance of these metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in reports of respiratory depression due to codeine (Stamer 2007b **Level IV**; Kelly 2012 **Level IV**; Friedrichsdorf 2013 **Level IV**). (See also Sections 4.1.1, 8.6.7 and 9.4.4.)

1.7.3.2 Tramadol

O-demethylation of tramadol by CYP2D6 produces the active metabolite (+)-O demethyltramadol (M1), which has an affinity for mu-opioid receptors that is approximately 200 times more than the parent drug (Shipton 2000 **NR**). Poor metabolisers have significantly lower plasma concentrations of M1 compared with both homozygous and heterozygous extensive metabolisers (Stamer 2003 **Level III-3**; Fliegert 2005 **Level II**, n=26, JS 2) and experience less analgesia (**Level IV**; Stamer 2003 **Level III-3**; Stamer 2007a **Level III-3**). As with codeine, impaired renal clearance of metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in cases of respiratory depression after tramadol (Desmeules 1996 **Level II**, n=10, JS 3**;** Stamer 2008 **CR**) (see also Section 4.1.1).

1.7.3.3 Methadone

Genetic polymorphisms in genes coding for methadone-metabolising enzymes, transporter proteins (p-glycoprotein) and mu-opioid receptors may explain part of the observed interindividual variation in the pharmacokinetics and pharmacodynamics of methadone; blood concentrations may vary up to 20-fold for a given dose (Li 2008 **NR**; Somogyi 2014 **NR**).

Methadone is metabolised primarily by the cytochrome P450 3A4 and 2B6 (Kapur 2011 **NR**). Differing effects for isomers of methadone have also been reported; genetic variability in *CYP2B6* influenced (S)-methadone (less active isomer) and, to a lesser extent, (R)-methadone (more active isomer) plasma concentrations (Somogyi 2014 **NR**). In addition, genetic polymorphisms in *CYP2C19* gene (responsible for a minor role in methadone metabolism) have effects on methadone-maintenance dosing, R methadone/methadone ratio and cardiotoxicity of methadone (prolonged QT interval) (Wang 2013a **NR**) (see also Section 4.1.1).

1.7.3.4 Oxycodone

The O-demethylated metabolite oxymorphone has up to 40-fold higher affinity for the mu receptor and eight-fold higher potency than oxycodone and represents about 11% of its overall metabolism (Crews 2014 **NR**). Oxycodone is metabolised primarily to noroxycodone by CYP3A (≈80%) and by CYP2D6 to oxymorphone (Lalovic 2006 **EH**). Oxymorphone may contribute significantly to the overall analgesic effect of oxycodone in experimental pain (Samer 2010 **EH**); noroxycodone, the major metabolite, is only a weak mu-receptor agonist (Coluzzi 2005 **NR**; Lalovic 2006 **EH**).

The dependence of oxymorphone concentrations on CYP2D6 activity and its high potency explains why oxycodone's pharmacodynamics and pharmacokinetics are dependent on CYP2D6 polymorphism (Soderberg Lofdal 2013 **NR**), at least in experimental pain (Samer 2010 **EH**).

However, in acute postoperative pain, *CYP2D6* genotype had either no influence on oxycodone requirements (Zwisler 2010 **Level III-2**) or a small difference in dosage that was not gene-dose related (Stamer 2013 **Level III-2**). Overall, the data on the association of CYP2D6 pheno/genotype and oxycodone response in acute pain are unconvincing (Crews 2014 **NR**) (see also Section 4.1.1).

1.7.3.5 NSAIDs

Wide variability in gene expression and functional polymorphisms in the COX-2 gene (*PTGS2*) may explain part of the interindividual variations in acute pain and the analgesic efficacy of nsNSAIDs and coxibs; this may be useful to predict patient risk and benefit from medicines based on individual genetic variations (Somogyi 2007 **NR**; Lee 2006 **Level III-2**).

NSAIDs such as ibuprofen, diclofenac and celecoxib are metabolised by CYP2C9 (Rollason 2014 **NR**). Between 1 and 3% of Caucasians are poor metabolisers. Homozygous carriers of the *CYP2C9*3* allele may accumulate celecoxib and ibuprofen in blood and tissues and be at risk of increased adverse effects (Kirchheiner 2002 **Level IV**; Kirchheiner 2003 **Level III-3**; Stamer 2007b **NR**; Rollason 2014 **NR**) but this is unlikely to affect acute pain response.

Key messages

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine, oxycodone and tramadol (**Q**) (**Level II**).
2. The mu opioid receptor OPRM1 polymorphism is unlikely to be clinically relevant as a single gene mutation in Caucasian populations and is more likely to be of clinical relevance in Asian populations (**N**) (**Level III-2** SR).
3. CYP2D6 ultrarapid metabolisers are at increased risk of codeine and tramadol toxicity (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Genetic polymorphisms contribute to the wide interindividual variability in plasma concentrations of a given dose of methadone (**U**).

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2. ASSESSMENT AND MEASUREMENT OF PAIN AND PAIN TREATMENT

Reliable and accurate assessment of acute pain is necessary to ensure safe and effective pain management. The assessment and measurement of pain are fundamental to the process of assisting in the diagnosis of the cause of a patient's pain, selecting an appropriate analgesic therapy and evaluating then modifying that therapy according to the individual patient's response. Pain should be assessed within a biopsychosocial model that recognises that physiological, psychological and environmental factors influence the overall pain experience. Likewise, the decision regarding the appropriate intervention to make following assessment needs to be made with regard to a number of factors, including recent therapy, potential risks and side effects, any management plan for the particular patient and the patient's own preferences. A given pain 'rating' should not automatically trigger a specific intervention without such considerations being undertaken (van Dijk 2012a **Level IV**; van Dijk 2012b **Level IV**).

2.1 Assessment

The assessment of acute pain should include a thorough general medical history and physical examination, a specific "pain history" (see Table 2.1) and an evaluation of associated functional impairment (see Section 2.3). In acute pain management, assessment must be undertaken at appropriate frequent intervals. At these times, evaluation of pain intensity, functional impact and adverse effects of treatment must be undertaken and recorded using tools and scales that are consistent, valid and reliable (Scott 2008 **NR**). In addition, pain assessment must lead to changes in management and re-evaluation of the patient to ensure improvements in the quality of care (Gordon 2005 **GL**).

Although not always possible in an acute setting, a complete pain history provides important diagnostic information that may help distinguish different underlying pain states such as nociceptive (somatic and visceral) or neuropathic pain (Victor 2008 **Level III-2**). Somatic pain may be described as sharp, hot or stinging, is generally well localised and is associated with local and surrounding tenderness. By contrast, visceral pain may be described as dull, cramping or colicky, is often poorly localised and may be associated with tenderness locally or in the area of referred pain, or with symptoms such as nausea, sweating and cardiovascular changes (Scott 2008 **NR**).

While nociceptive pain typically predominates in the acute pain setting, neuropathic pain may also be present (Guastella 2011 **Level IV**) (see also Section 1.3). Features in the pain history that may suggest a diagnosis of neuropathic pain include (Gray 2008 **NR**; Dworkin 2007 **Level III-2**; Haanpaa 2011 **GL**):

- clinical circumstances associated with a high risk of nerve injury (eg thoracic or chest wall procedures, amputations or hernia repairs);
- pain descriptors such as burning, shooting and stabbing;
- the paroxysmal or spontaneous nature of the pain which may have no clear precipitating factors;
- the presence of dysaesthesias (spontaneous or evoked unpleasant abnormal sensations), hyperalgesia (increased response to a normally painful stimulus), allodynia (pain due to a stimulus that does not normally evoke pain such as light touch) or areas of hypoaesthesia; and
- regional autonomic features (changes in colour, temperature and sweating) and phantom phenomena.

The recent IASP definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011). Symptoms consistent with neuropathic pain may occur without nerve injury and the terms "neuroplastic" or "nociplastic" pain are under discussion for these conditions (Haanpaa 2011 **GL**). To determine if pain is neuropathic, further quantitative sensory testing (QST) may be needed (Haanpaa 2011 **GL**; Garcia-Larrea 2012 **NR**).

It is useful to draw the distinction between the different types of pain because the likely duration of the pain and the response to analgesic strategies may vary. The concept of "mechanism-based pain diagnosis" has been promoted (Woolf 2001 **NR**) and although the correlation between symptoms, mechanisms and response to therapy is not fully defined, specific therapy targeted at, for example, neuropathic pain, may be of benefit (Gray 2008 **NR**)

Table 2.1 Fundamentals of a pain history

1	**Site of pain**		
	a	primary location: description ± body map diagram	
	b	radiation	
2	**Circumstances associated with pain onset**		
	including details of trauma or surgical procedures		
3	**Character of pain**		
	a	sensory descriptors eg sharp, throbbing, aching (Victor 2008)	
	b	McGill Pain Questionnaire: includes sensory and affective descriptors (Melzack 1987)	
	c	neuropathic pain characteristics (eg NPQ; DN4; LANSS; PainDETECT; ID Pain)	
4	**Intensity of pain**		
	a	at rest	
	b	on movement	
	c	temporal factors	i duration
			ii current pain, during last week, highest level
			iii continuous or intermittent
	d	aggravating or relieving factors	
5	**Associated symptoms (eg nausea)**		
6	**Effect of pain on activities and sleep**		
7	**Treatment**		
	a	current and previous medications — dose, frequency of use, efficacy, adverse effects	
	b	other treatment eg transcutaneous electrical nerve stimulation	
	c	health professionals consulted	
8	**Relevant medical history**		
	a	prior or coexisting pain conditions and treatment outcomes	
	b	prior or coexisting medical conditions	
9	**Factors influencing the patient's symptomatic treatment**		
	a	belief concerning the causes of pain	
	b	knowledge, expectations and preferences for pain management	
	c	expectations of outcome of pain treatment	
	d	reduction in pain required for patient satisfaction or to resume "reasonable activities"	
	e	typical coping response for stress or pain, including presence of anxiety or psychiatric disorders (eg depression or psychosis)	
	f	family expectations and beliefs about pain, stress and postoperative course	

Notes: *NPQ=Neuropathic Pain Questionnaire; DN4=Douleur Neuropathique en 4*; LANSS=*Leeds Assessment of Neuropathic Symptoms and Signs.*

2.2 Measurement

The definition of pain underlies the complexity of its measurement. Pain is an individual and subjective experience modulated by physiological, psychological and environmental factors such as previous events, culture, prognosis, coping strategies, fear and anxiety. Therefore, most measures of pain are based on self-report. These measures lead to sensitive and consistent results if done properly (Moore 2003 **NR**). Self-report measures may be influenced by mood, sleep disturbance and medications (Scott 2008 **NR**).

In some instances it may not be possible to obtain reliable self-reports of pain; eg patients with impaired consciousness or cognitive impairment, young children (see Section 9.3), elderly patients (see Section 10.2) or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety. In these circumstances other methods of pain assessment will be needed.

There are no objective measures of "pain" but associated factors such as hyperalgesia (eg mechanical withdrawal threshold), the stress response (eg plasma cortisol concentrations), behavioural responses (eg facial expression), functional impairment (eg coughing, ambulation) or physiological responses (eg changes in heart rate) may provide additional information. Analgesic requirements (eg patient-controlled opioid doses delivered) are commonly used as *post hoc* measures of pain experienced (Moore 2003 **NR**).

Recording pain intensity as "the fifth vital sign" aims to increase awareness and utilisation of pain assessment (JCAHO 2001 **GL**) and may lead to improved acute pain management (Gould 1992 **Level III-3**). Regular and repeated measurements of pain should be made to assess ongoing adequacy of analgesic therapy. An appropriate frequency of reassessment will be determined by the duration and severity of the pain, patient needs and response, and the type of medicine or intervention (Gordon 2005 **GL**). Such measurements should incorporate different components of pain. For example, in the postoperative patient this should include assessments of static (rest) and dynamic (on sitting, coughing or moving the affected part) pain. Whereas static measures may relate to the patient's ability to sleep, dynamic measures can provide a simple test for mechanical hyperalgesia and determine whether analgesia is adequate for recovery of function (Breivik 2008 **NR**).

Uncontrolled pain should always trigger a reassessment of the diagnosis and consideration of alternatives such as developing surgical or other complications, or the presence of neuropathic pain. Review by an APS or other specialist group should be considered.

2.2.1 Unidimensional measures of pain

A number of scales are available that measure either pain intensity or the degree of pain relief following an intervention. Pain relief scales, although less commonly used, have some advantage when comparing the response to different treatments as all patients start with the same baseline "relief" score (zero), whereas they may have differing levels of baseline pain intensity (Moore 2003 **NR**; Breivik 2008 **NR**).

2.2.1.1 Categorical scales

Categorical scales use words to describe the magnitude of pain or the degree of pain relief (Moore 2003 **NR**). The verbal descriptor scale (VDS) is the most common example (eg using terms such as none, mild, moderate, severe and excruciating or agonising) typically using four or five graded descriptors.

These terms can then be converted to numeric scores (eg 0, 2, 5, 8, 10) for charting and easy comparison over time. There is a good correlation between descriptive verbal categories and visual analogue scales (VAS) (Banos 1989 **Level III-2**) but the VDS is a less sensitive measure of pain treatment outcome than the VAS (Jensen 2002 **Level IV**). Pain "relief" may also be graded as none, mild, moderate or complete using a VDS.

Categorical scales have the advantage of being quick and simple and may be useful in the elderly or visually impaired patient and in some children. However, the limited number of choices in categorical compared with numerical scales may make it more difficult to detect

differences between treatments (Breivik 2000 **Level III-2**). Other limitations include personal, cultural or linguistic differences in interpretation of the specific words chosen as descriptors both between patients and between patients and their clinicians.

2.2.1.2 Numerical rating scales

Numerical rating scales have both written and verbal forms. Patients rate their pain intensity on the scale of zero to ten where zero represents "no pain" and ten represents "worst pain imaginable". The Verbal NRS (VNRS) is typically administered using a phrase such as: "On a scale of zero to ten, with zero being no pain at all and ten being the worst pain you could imagine, where would you rate the pain you are experiencing right now?". It is important that scales are consistent, and it is recommended that the "no pain" point be represented as zero rather than one (Scott 2008 **NR**). Pain relief may be measured in the reverse direction with zero representing "no relief" to ten representing "complete relief". A visual form of the 11-point NRS with tick marks on a line or boxes with numbers may also be used (Breivik 2008 **NR**). Although NRS are widely used, some patients have difficulty representing their pain in numerical terms and are better suited to a categorical scale. A value of four or more is often used as a threshold to guide clinical intervention (Hartrick 2003 **Level IV**).

Visual analogue scales consist of a 100 mm horizontal line with verbal anchors at both ends and no tick marks. The patient is asked to mark the line and the "score" is the distance in millimetres from the left side of the scale to the mark. VAS are the most commonly used scales for rating pain intensity in research, with the words "no pain" at the left end and "worst pain imaginable" at the right. Pictorial versions also exist. VAS can also be used to measure other aspects of the pain experience (eg affective components, patient satisfaction, adverse effects).

Assessment of pain immediately after surgery can be more difficult and lead to greater interpatient variability in pain scores because of transient anaesthetic-related cognitive impairment and decreases in visual acuity. A "pain meter" (PAULA), which used five coloured emoticon faces on the front of a ruler and corresponding VAS scores on the back and allowed patients to move a slider to mark the pain they were experiencing, resulted in less variance than pain scores obtained from a standard VAS (Machata 2009 **Level III-2**).

VAS ratings ≥70 mm are indicative of "severe pain" (Aubrun 2003 **Level IV**; Jensen 2003 **Level IV**) and 0–5 mm "no pain", 5–44 mm "mild pain" and 45–69 "moderate pain" (Aubrun 2003 **Level IV**). A reduction in pain intensity by 30–35% has been rated as clinically meaningful by patients with postoperative pain (Cepeda 2003 **Level IV**; Jensen 2003 **Level IV**), acute pain in the emergency department (ED) (Lee 2003 **Level IV**), breakthrough cancer pain (Farrar 2000 **Level IV**) and chronic pain (Farrar 2001 **Level IV**).

These scales have the advantage of being simple and quick to use, allow for a wide choice of ratings and avoid imprecise descriptive terms (Scott 2008 **NR**). However, the scales require concentration and coordination, need physical devices, are unsuitable for children aged <5 y and may be unsuitable in up to 26% of adult patients (Cook 1999 **NR**).

The VAS has been shown to be a linear scale for patients with postoperative pain of mild to moderate intensity (Myles 1999 **Level IV**) and severe pain (Myles 2005 **Level IV**). Therefore, results are equally distributed across the scale, such that the difference in pain between each successive increment is equal.

Verbal numerical rating scales are often preferred because they are simpler to administer, give consistent results and correlate well with the VAS (Hjermstad 2011 **Level IV SR**, 54 studies, n unspecified). Recall of pain intensity using the VNRS over the previous 24 h was a reasonable indicator of average pain experienced by the patient during that time (Jensen 2008 **Level III-2**).

2.2.2 Functional impact of acute pain

Analgesia should be titrated to achieve both decreased pain intensity and the ability to undertake appropriate functional activity (Breivik 2008 **NR**). This will enable analgesia to optimise recovery. Most tools for measuring the functional impact of pain are based on

chronic pain assessment and therefore are not routinely applicable to the acute pain environment.

Measurement of pain intensity scores on movement or with coughing is a useful guide, however, this reflects the subjective pain experience and not the capacity to undertake the specific activity. The Functional Activity Scale (FAS) score is a simple three-level ranked categorical score designed to be applied at the point of care (Scott 2008 **NR**). Its fundamental purpose is to assess whether the patient can undertake appropriate activity at their current level of pain control and to act as a trigger for intervention should this not be the case. The patient is asked to perform the activity or is taken through the activity in the case of structured physiotherapy (joint mobilisation) or nurse-assisted care (eg ambulation, turned in bed). The ability to complete the activity is then assessed using the FAS as:

A — no limitation	the patient is able to undertake the activity without limitation due to pain (pain intensity score is typically zero to three);
B — mild limitation	the patient is able to undertake the activity but experiences moderate to severe pain (pain intensity score is typically four to ten); and
C — significant limitation	the patient is unable to complete the activity due to pain, or pain treatment-related adverse effects, independent of pain intensity scores.

This score is then used to track effectiveness of analgesia on function and trigger interventions if required. Disadvantages of the FAS score are that it has not been independently validated and clinical staff need to be educated in its application.

2.2.3 Multidimensional measures of pain

Rather than assessing only pain intensity, multidimensional tools provide further information about the characteristics of the pain and its impact on the individual. Examples include the Brief Pain Inventory, which assesses pain intensity and associated disability (Daut 1983 **Level IV**) and the McGill Pain Questionnaire (MPQ), which assesses the sensory, affective and evaluative dimensions of pain (Melzack 1987 **NR**). The MPQ also exists in a 15-item short-form (SF-MPQ), which is well validated and has a VAS item for pain intensity and a VRS for rating the overall pain experience.

Neuropathic pain is not easily identified using unidimensional tools such as the VAS (Haanpaa 2011 **GL**). Specific scales have been developed that identify (and/or quantify) descriptive factors specific for neuropathic pain (Bouhassira 2004 **Level IV**; Cruccu 2004 **Level IV**; Bouhassira 2005 **Level III-2**; Freynhagen 2006 **NR**; Dworkin 2007 **Level III-2**) and may also include sensory examination (Cruccu 2004 **Level IV**; Bouhassira 2005 **Level III-2**) and allow evaluation of response to treatment (Bouhassira 2004 **Level IV**).

Useful screening tools for identifying neuropathic pain include:

- the Neuropathic Pain Questionnaire (NPQ) comprises twelve items and can be self-reported — a three-item short-form also exists (Krause 2003 **Level III-2**; Backonja 2003 **NR**);
- the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) has five symptom items and two clinical assessment items — a subjective-only form also exists (Bennett 2001 **Level III-3**);
- the Douleur Neuropathique en 4 (DN4) has ten items — seven symptomatic and three from clinical examination (Bouhassira 2005 **Level III-3**);
- the Pain DETECT has nine self-reported items that do not require a clinical examination and gives a likelihood scoring for neuropathic pain (Freynhagen 2006 **NR**);
- the ID Pain has six self-reported items (Portenoy 2006 **Level IV**).

These scales have similar specificity and sensitivity (except for the ID Pain, which has lower values here than the others), have mostly been validated and are often available in validated translations in many languages (Haanpaa 2011 **GL**).

Global scales are designed to measure the effectiveness of overall treatment (see Section 2.3.1). They are more suited to outcome evaluation at the end of treatment than to modifying treatment in the acute stage (Moore 2003 **NR**). Questions such as "How effective do you think the treatment was?" recognise that unimodal measures of pain intensity cannot adequately represent all aspects of pain perception.

Satisfaction is often used as a global indicator of outcome; however, patients may report high levels of satisfaction even if they have moderate to severe acute pain (Svensson 2001 **Level IV**). Satisfaction may also be influenced by preoperative expectations of pain, effectiveness of pain relief, the patient–provider relationship (eg communication by medical and nursing staff), interference with function due to pain and number of opioid-related adverse effects (Svensson 2001 **Level IV**; Carlson 2003 **Level IV**; Jensen 2004 **Level IV**). Although complete absence of pain is not required for patients to report high levels of satisfaction, moderate pain (VAS >50, scale 0–100) has been associated with dissatisfaction (Jensen 2005 **Level III-2**).

2.2.4 Patients with special needs

Validated tools are available for measuring pain in neonates, infants and children but must be both age and developmentally appropriate (see Section 9.3). These include behavioural assessments, pictorial scales (eg faces) and response to treatment. Adult patients who have difficulty communicating their pain (eg patients with cognitive impairment or who are critically unwell in the ED or intensive care unit [ICU]) require special attention as do patients whose language or cultural background differs significantly from that of their health care team. Communication aids and behavioural scales such as the modified Faces, Legs, Activity, Cry and Consolability (FLACC) scale (Erdek 2004 **Level III-3**) can be particularly useful in these situations (see Section 10.2.3).

NRS are considered the best tool for measurement of pain intensity for adult ICU patients. If they are not feasible then the Behavioural Pain Scale (BPS) or Critical-Care Pain Observation Tool (CPOT) should be used (Chanques 2010; Barr 2013; Gelinas 2013). The CPOT has been validated in neurosurgical patients (Echegaray-Benites 2014 **Level III-3**) and in different countries (Li 2014 **Level III-3**; Rijkenberg 2015 **Level III-3**). The CPOT appears to be more specific for pain than the BPS (Rijkenberg 2015 **Level III-3**).

Key messages

1. Regular assessment of pain leads to improved acute pain management (**U**) (**Level III-3**).
2. There is good correlation between the visual analogue and verbal numerical rating scales (**S**) (**Level IV SR**).
3. Appropriate assessments (including screening tools) are required to determine the presence of neuropathic pain (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Self-reporting of pain should be used whenever appropriate as pain is by definition a subjective experience (**U**).
- ☑ The pain measurement tool chosen should be appropriate to the individual patient and the clinical context (eg intensive care, ward, community). Developmental, cognitive, emotional, language and cultural factors should be considered (**S**).
- ☑ Scoring should incorporate different components of pain including the functional capacity of the patient. In the postoperative patient this should include static (rest) and dynamic (eg pain on sitting, coughing) pain (**U**).
- ☑ Uncontrolled or unexpected pain requires a reassessment of the diagnosis and consideration of alternative causes for the pain (eg new surgical/ medical diagnosis, neuropathic pain) (**U**).

2.3 Outcome measures in acute pain management

What follows is a brief guide to some of the outcome measures used particularly in the acute pain literature. A comprehensive review is beyond the scope of this document and more detail may be found elsewhere (Breivik 2008 **NR**). Concerns have been raised regarding trial design limitations resulting in type II errors (failure to identify a difference when one really exists) and recommendations have been made for the design of chronic pain RCTs that include patient numbers, study site and outcome measurements to reduce this problem (Dworkin 2012 **GL**). Similar issues are of relevance to studies in acute pain interventions.

2.3.1 Outcome measures

2.3.1.1 Pain

The aim of many clinical trials is to determine whether a medicine or intervention provides adequate pain relief for the majority of participants or is equivalent or noninferior to an existing accepted treatment. This can be achieved by repeated single measures at fixed time points, which may encompass only a proportion of the total illness. When comparison is made with a placebo, a statistically significant result can be achieved with a relatively small number of patients (eg n=40) (Collins 2001 **Level I**, 11 SRs [151 RCTs], n unspecified). The primary outcome is chosen by the researcher and may not be of direct importance to the individual patient, particularly if it relates to only a proportion of the total time he/she was in pain. It is also important to consider that statistically significant differences in pain scores may not reflect clinically significant differences, although these are harder to define (see above).

Data derived from categorical and VAS of pain intensity or relief produce a range of summary outcomes that can be used to assess (Moore 2003 **NR**):

- the degree of analgesic effect:
  - difference between the baseline and post-intervention score of pain intensity or pain relief (summed pain intensity difference [SPID]);
  - the area under the time-analgesic effect curve for a given time (total pain relief [TOTPAR]);
  - dose of rescue analgesic consumption required in a given time period (eg PCA use);
- the time to analgesic effect:
  - the time to onset of analgesic effect;
  - time to maximum reduction in pain intensity or to peak relief;
- the duration of effect:
  - time for pain to return to at least 50% of baseline;
  - time for pain intensity to return to baseline or for pain relief to fall to zero; and
  - time to remedication/rescue analgesia.

A widely used method of describing the effectiveness of an analgesic intervention is the NNT. In this setting it is commonly defined as the number of patients that need to be treated to achieve at least 50% pain relief (eg at least 50% maximum TOTPAR) in one patient compared with a placebo over a 4–6 h treatment period (Moore 2003 **NR**). Analysis at other cut-off points (30–70% max TOTPAR) has shown the same relative efficacy of different treatments (McQuay 2003 **NR**).

The validity of this approach as a true method of comparison may be questioned as there is no standardisation of the acute pain model or patient and only single doses of the analgesic agents are used. However, it may sometimes be reasonable to extrapolate estimates of analgesic efficacy from one pain model to another (Barden 2004 **Level I**, 160 RCTs, n=14,410).

The use of supplemental analgesic consumption as an outcome measure has been questioned in situations where pain scores are not similar (McQuay 2008 **Level I**, 18 RCTs, n=1,217).

2.3.1.2 Physical functioning

Measures of physical functioning quantify many aspects of a patient's life including their ability to sleep, eat, think, deep breathe, cough, mobilise, perform activities of self-care and daily living, undertake their usual vocation and to enjoy leisure activities and sport (Williams 1999 **NR**). In acute pain, this may be measured by pain intensity scores with movement or other functional activity scores (see above).

Global or multidimensional measures of function attempt to combine various abilities or disabilities to derive a summary measure. Scales that employ a large number of items might be comprehensive but risk patient exhaustion or error, while scales with fewer items might be patient friendly but risk becoming insensitive to state or change (Williams 1999 **NR**). These scales have been used in some studies of acute spinal pain and cancer-related pain:

- *disability scales* — generic scales include Short Form 36 of Medical Outcomes Study (SF-36), the Sickness Impact Profile (SIP) and Roland & Morris Short SIP (Williams 1999 **NR**); and
- *quality of life (QOL) measures* — these measures are not widely used in pain studies other than for cancer-related pain (Higginson 1997 **NR**).

Disease-specific measures quantify the impact of a specific pain problem on function and can be used to track changes after an intervention (eg ability to cough after thoracotomy, ability to lift a baby after Caesarean delivery) (Garratt 2001 **Level IV**). Generic measures facilitate comparisons among the functional limitations of different conditions and treatments and may have advantages for audit of an APS that includes patients with a range of conditions (Patrick 1989 **NR**).

2.3.1.3 Emotional functioning

Acute pain is an unpleasant sensory and emotional experience. The unpleasantness of the experience and its meaning for the individual may have short-term (anxiety, depression, irritability) and long-term (lost confidence or self-efficacy or post-traumatic stress disorder) consequences for the individual's emotional functioning.

2.3.1.4 Adverse effects

In trials of efficacy, adverse effects are usually considered to be of secondary importance and inadequate reporting has been found in as many as half of randomised trials reviewed (Edwards 1999 **Level I**, 52 RCTs, n unspecified; Ioannidis 2001 **Level I**, 192 RCTs, n=130,074). If adverse effects are sufficiently common (eg nausea with opioids) they may be quantifiable in trials of efficacy and specifically measured using dichotomous (present or absent), categorical (none, mild, moderate, severe) or interval (analogue or Likert) scales. Analogous to NNTs, the number-needed-to-harm (NNH) may be used to describe the incidence of adverse effects.

Most efficacy trials will have inadequate power to detect rare adverse effects and therefore they are also absent from systematic reviews. Large clinical trials specifically designed to detect adverse effects are required (eg the Vioxx Gastrointestinal Outcomes Research [VIGOR] study investigated gastrointestinal toxicity of NSAIDs) (Bombardier 2000 **Level II**, n=8,076, JS 5). Case reports and postmarketing epidemiological research and surveillance (eg the Australian Adverse Drug Reactions Advisory Committee) remain important for detection of delayed effects occurring after the initial trial period. More recently, results from comprehensive large prospective audits and database reviews have provided a sufficiently reliable denominator for incidence and risk-factor evaluation in rare but serious adverse effects in acute pain management (Cameron 2007 **Level IV**; Wijeysundera 2008b **Level IV**; Wijeysundera 2008a **NR**).

Besides the adverse effects attributed to acute pain management interventions, another area of interest is whether the adverse effects of trauma and surgery might be prevented by effective acute pain management. Outcomes such as mortality, morbidity due to derangements of the cardiovascular, respiratory, gastrointestinal and coagulation systems and progression to chronic pain have also been reported (see Chapter 1).

Key message

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Multiple outcome measures are required to adequately capture the complexity of the pain experience and how it may be modified by pain management interventions (**U**).

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3. PROVISION OF SAFE AND EFFECTIVE ACUTE PAIN MANAGEMENT

The safe and effective management of acute pain requires the appropriate education of medical, nursing and allied health staff and patients, and attention to the organisational aspects involved in the delivery of pain relief. These include appropriate guidelines for prescription of medicines, monitoring of patients and recognition and treatment of any adverse effects of pain relief and, in some situations, the provision of an APS. It is recognised that the need for and complexity of these requirements will vary according to the setting in which acute pain relief is delivered (eg hospital, general practice).

Successful acute pain management also requires close liaison with all personnel involved in the care of the patient including anaesthetists, pain specialists, surgeons, physicians, palliative care clinicians, general practitioners, specialists in addiction medicine, nurses, physiotherapists and psychologists.

Patient participation (ie including patients in the decision-making team, taking into account their values, concerns and expectations) is required if each patient is to get the best treatment. Patients should be provided with accurate up-to-date information, including benefits, risks and likely outcomes of treatment. They should also have access to other evidence-informed information that explains current treatment recommendations in addition to having access to treatment consistent with evidenced-based recommendations (Duckett 2009 **NR**).

3.1 Education

3.1.1 Patients

Patients and their carers who learn about assessment of pain as well as risks and adverse effects of treatment and who are informed that they should communicate both effectiveness (or otherwise) of treatment and onset of any adverse effects, will be well placed to have some control over the quality of their pain relief, regardless of the technique used. Information on treatment options, goals, likely benefits and probability of success should be available; this advice is found in most published recommendations and guidelines. Despite this, many patients still feel uninformed about pain, particularly in the perioperative period (Counsell 2008 **NR**; Macintyre 2015 **NR**). A national survey of patients who were undergoing total hip replacement revealed that 70% did not believe they had been given adequate information about their procedure (including pain relief) and those who had higher levels of education perceived a larger deficit (Johansson Stark 2014 **Level IV**). Depression was a predictor of higher perceived knowledge gaps. A survey of health professionals acknowledged that perioperative pain management knowledge and other aspects of colonic surgery were deficient in patients undergoing the procedure (Sjostedt 2011 **Level IV**).

3.1.1.1 General principles

A systematic review of systematic reviews (using the AMSTAR tool) pertaining to methods of patient education in general concludes that the teaching strategies that increased patient knowledge, decreased anxiety and improved patient satisfaction were those using computer technology, audio and videotapes, written materials and demonstrations (Friedman 2011 **Level IV SR**, 23 systematic reviews and meta-analyses, n unspecified). While only one systematic review addressed pain management, the more general results are relevant to this topic. Educational strategies were better when combined, structured, culturally appropriate and patient-specific, rather than generic and *ad hoc*. Verbal teaching and discussions were found to be the least effective strategies. Web-based teaching improved patient knowledge, anxiety, and satisfaction, as did audiotapes, videotapes, written materials and lectures, all of which were more effective than verbal teaching and discussions. Demonstrations had the highest effect of any of the teaching strategies evaluated. Multiple teaching strategies are better than single ones, with one systematic review finding that 67% of patients who received patient education using several different strategies had better outcomes than those who

received routine care. Structured teaching has been shown to be much more effective than unstructured *ad hoc* teaching.

Patient education prior to surgery has been studied most extensively in relationship to joint replacement and cardiac surgery. Many factors are critical to the effectiveness of information giving, including timing and amount of information given in relationship to the type of patient receiving the information, as well as the needs of the patient (Oshodi 2007a **NR**).

While some studies show promising results, a series of systematic reviews (with overlap of included studies) has not found good evidence to support preoperative education influencing pain levels and hospital stay, although knowledge may improve. Procedural information (often combined with behavioural instructions, like exercises or body positions) was found to be effective in reducing pain reports in only three of seven RCTs and in reducing pain medications in seven of twelve RCTs (Johnston 1993 **Level I**, 38 RCTs, n=1,734). A subsequent systematic review assessed education of patients undergoing cardiac surgery (40%) and arthroplasty patients (15%) but also ophthalmological surgery patients (12%) and other minor or ambulatory procedures (Johansson 2004 **Level III-3 SR**, 32 studies, n=2,723). Overall, it concludes that there may be beneficial effects although these are difficult to prove and better-designed studies are needed. A further systematic review of all experimental and quasiexperimental studies published between 1951 and 2005 examined the impact of patient education on pain, anxiety and recovery (Oshodi 2007b **Level III-2 SR**, 12 studies, n unspecified). The reviewed studies all compared some form of education against routine information or standard education but none compared education with no education. As outcome measures varied considerably, the studies were individually analysed. While some studies failed to show a significant difference in outcome measures between the experimental and control groups, all except one reported one or more statistically significant outcome effects. The review concludes that preoperative education is indeed effective in some aspects but its influence on outcome measures may not have been large enough in some studies to produce statistically significant effects. Subsequent studies published between 2004 and 2010 have undergone systematic review (Ronco 2012 **Level III-2 SR**, 12 RCTs and 7 studies, n=3,944). Interventions were based on verbal education, written/visual education or both but the content of interventions varied widely. Frequent outcomes evaluated were anxiety, knowledge, pain and length of stay. Only three studies specifically targeted pain education. Objective knowledge (what a patient retains from education) was the only positive outcome influenced by education.

A systematic review of studies of postoperative education (conducted between 1986 and 2007) aimed at improvement in self-knowledge and symptom experience (including pain) for the purpose of evaluating the best type and amount of postoperative education (Fredericks 2010 **Level III-3 SR**, 58 studies, n=5,271). All types of surgery were included with 46% assessing cardiac surgery, 26% general surgery, 4% abdominal/ colorectal surgery and 5% hip and knee surgery. Individualised education with the patient having input into their educational requirements, use of combined media for delivery, provision of one-on-one education and multiple sessions are associated with improvement in educational and/or health outcomes. Individuals <50 y and those with higher educational level showed the highest benefit.

Patient or carer education may take a number of forms; the most common methods are the use of booklets or short videos and one-on-one specialist education. There is some evidence that written information is better than verbal and the former resulted in more satisfaction, lower pain scores and lower analgesic use after gynaecological cancer surgery (Angioli 2014 **Level II**, n=190, JS 2). Similarly, knowledge was lower in those given verbal (nonstandardised) information (which included pain management information) at the time of seeing the anaesthetist prior to surgery compared with those given written information before they attended the interview (Binhas 2008 **Level III-2**). Patients receiving verbal vs verbal plus written information prior to joint replacement surgery favoured the combination, which allowed them to refresh their memory (Andersson 2015 **Level III-1**).

3.1.1.2 Effects in specific postoperative settings

PCA use

Structured vs brief patient education prior to PCA use resulted in improved patient knowledge of PCA (Yankova 2008 **Level III-1 SR**, 5 RCTs and 1 study, n=592). None of the randomised studies demonstrated that structured education about PCA improved postoperative pain scores.

Arthroplasty

After total hip and knee joint replacement, there appears no benefit to adding preoperative education to usual care; there were only small trends towards reduction in pain and anxiety (McDonald 2014 **Level I** [Cochrane], 18 RCTs, n=1,463). This is confirmed by a slightly earlier systematic review of the same group of patients (overlap 10 RCTs) (Louw 2013 **Level III-1 SR**, 12 RCTs and 1 study, n=1,021); it concluded that preoperative education centered on a biomedical model of anatomy and pathoanatomy as well as procedural information has limited effect in reducing postoperative pain after total hip arthroplasty and total knee arthroplasty surgeries. Preoperative educational sessions that aim to increase patient knowledge of pain science may be more effective in managing postoperative pain.

Cardiac surgery

A systematic review finds no effect of preoperative education interventions on pain levels or other outcome measures in patients after coronary artery bypass graft (CABG) surgery (Guo 2015 **Level I**, 2 RCTs [pain], n=762).

Other types of surgery

After cosmetic day-surgery procedures, preoperative education reduced postoperative opioid requirements and pain intensity and duration (Sugai 2013 **Level II**, n=135, JS 2). Preoperative written and verbal education (two sessions by the same surgeon) on the adverse and negative effects of opioids resulted in 90% of the treatment group declining an opioid prescription (vs 100% filling their opioid prescription in the control group).

Patients undergoing modified radical mastectomy, who had received a specific 20-min education about their analgesia management and medications, reported less pain and mobilised earlier than those who had not received the education (Sayin 2012 **Level III-1**).

Patients receiving neuroscience education, via a conversation with physical therapist for 30 min plus a neuroscience booklet, prior to spinal surgery for radicular pain (decompressive laminectomy) had the same pain levels and function at 12 mth following surgery compared to those in a control group that received routine care (Louw 2014 **Level II**, n=67, JS 3). However, those in experimental group utilised 45% less healthcare expenditure at 12 mth and felt better prepared for surgery.

3.1.1.3 Effects in other acute pain settings

The effect of patient education has also been studied in patients with acute nonsurgical pain.

A systematic review of pain education strategies for neck pain was unable to find good evidence for benefit of patient education apart from one RCT (n=348) showing that an educational video of advice about being active was more beneficial in the medium term (Gross 2012 **Level I** [Cochrane], 15 RCTs, n unspecified). However, after acute whiplash injury specifically (overlap 2 RCTs) short educational interventions reduce pain and disability and enhance recovery and mobility (Meeus 2012 **Level I** [PRISMA], 10 RCTs, n unspecified).

For acute back pain there is high-quality evidence of no effectiveness of education for pain, function, work issues and healthcare use, low-quality evidence of no effectiveness for self-rated overall improvement, satisfaction and pain beliefs and lack of evidence in terms of QoL (Ramond-Roquin 2014 **Level III-1 SR**, 12 RCTs and 1 study, n unspecified). However, another meta-analysis (overlap of 5 studies) shows that targeted education by primary care physicians is an important strategy in the management of acute back pain (Traeger 2015 **Level III-1 SR**, 14 studies, n=4,872). This meta-analysis included only trials assessing measures of reassurance, which was defined as changes in psychological factors such as fear, worry, anxiety, catastrophisation

and healthcare utilisation. Reassurance is increased by education interventions in the short and long term, reduces healthcare utilisation (NNT 17 to reduce one back pain-related primary-care visit) and is more effective when provided by a physician than by other health professionals (physiotherapist, nurse).

In cancer-pain patients, educational interventions improved knowledge and attitude (WMD 0.52/5; 95%CI 0.04 to 1.0) and reduced average pain intensity (WMD -1.1/10; 95%CI 1.8 to 0.41) and worst pain intensity (WMD -0.78/10; 95%CI 1.21 to 0.35) (Bennett 2009 **Level III-1 SR**, 19 RCTs and 2 studies, n=3,501).

Antenatal teaching about postnatal nipple pain and trauma resulted in reduced nipple pain and improved breastfeeding (Duffy 1997 **Level II**, n=70, JS 3).

Patients using triptans for migraine management who recalled having received education about the medication when they commenced care with a headache service had better knowledge of their medications (Baron 2014 **Level IV**).

3.1.1.4 Web-based education for acute pain management

The internet is being increasingly used for pain education; there are however few published studies that have evaluated interventions for patients with acute pain. A systematic review of internet-based pain education included only two RCTs that evaluated educational websites with information on acute postoperative pain (Bender 2011 **Level I**, 17 RCTs, n=2,503). One study aimed to prepare adolescents for tonsillectomy and demonstrated improvements in satisfaction and knowledge but no difference in pain scores or anxiety (O'Conner-Von 2008 **Level II**, n=69, JS 3). The other study prepared adults for postoperative self-care after outpatient surgical procedures and found reductions in postoperative pain intensity the night and day afterwards (Goldsmith 1999 **Level II**, n=195 [only 80 at follow-up], JS 2).

An innovative use of web technology used an assessment process to individualise content of education and use persuasive educational techniques to effect changes in response to pain after cardiac surgery (Martorella 2012 **Level II**, n=60, JS 3). The 30-min web-based intervention uses a virtual nurse to guide the patient followed by two face-to-face 5-min booster sessions. In the experimental group, patients did not experience less intense pain but they reported significantly less pain interference when breathing/coughing and used more analgesia.

A web-based intervention program providing daily postural advice and exercise instructions with daily email reminders and personalised log over 9 mth to 100 office workers with subacute low-back pain (of 6 wk duration) was effective in improving QoL, behavior change, function and pain compared to standard care (del Pozo-Cruz 2013 **Level II**, n=100, JS 2).

3.1.2 Staff

Appropriate education of medical and nursing staff is essential if more sophisticated forms of analgesia (eg PCA or epidural analgesia) are to be managed safely and effectively and if better results are to be gained from conventional methods of pain relief (Macintyre 2015 **NR**). Medical and nursing staff education may take several forms; the evidence for any benefit or the best educational technique is varied and inconsistent. Education may also include the provision of guidelines and accompanying changes to practice to enable good outcomes from education. Organisational approaches may improve pain and other symptoms.

Improvements in nursing knowledge and ability to manage epidural analgesia followed the reintroduction of an epidural-education program using an audit/guideline/problem-based teaching approach, accompanied by practical assessments (Richardson 2001 **Level III-3**). Pain documentation in surgical wards (Ravaud 2004 **Level III-1**; Karlsten 2005 **Level III-2**) and ICUs (Arbour 2003 **Level IV**; Erdek 2004 **Level III-3**) was also improved by education programs. Implementation of a quality-improvement program led to improvements in nurses' knowledge and assessment of pain using pain-rating scales; however, while the number of patients assessed increased, there was no improvement in pain relief (Hansson 2006

Level III-2). However, others have shown benefit to patients. A quality-improvement system, which included education and guidelines as well as systems to improve practice, resulted in significant improvements in postoperative pain, nausea, vomiting and fatigue (Usichenko 2013 **Level III-3**).

Improvements in postoperative pain relief, assessment of pain and prescribing practices can result from staff education as well as the introduction of medical and nursing guidelines (Gould 1992 **Level III-2**; Harmer 1998 **Level III-3**). In EDs, education of junior medical staff improved patient pain relief (Jones 1999 **Level III-3**) and implementation of an education program and guidelines for pain management improved analgesia and patient satisfaction (Decosterd 2007 **Level III-2**). Personalised feedback forms given to anaesthetists have been shown to increase the use of PCA, NSAIDs, epidural morphine and nerve blocks (Rose 1997 **Level III-3**).

A number of studies have shown the benefits of education and/or guidelines on improved prescribing patterns both in general terms (Humphries 1997 **Level III-3**; Ury 2002 **Level III-3**) and specifically for NSAIDs (May 1999 **Level III-3**; Figueiras 2001 **Level III-2**; Ray 2001 **Level II**, n=209, JS 2), paracetamol (acetaminophen) (Ripouteau 2000 **Level III-3**) and pethidine (meperidine) (Gordon 2000 **Level III-3**). Use of an electronic decision-support system significantly improved adherence to guidelines for the prescription of postoperative nausea and vomiting (PONV) prophylaxis for patients at high risk of PONV (Kooij 2008 **Level III-3**).

A systematic review of educational endeavours to improve medical student and junior doctor prescribing shows improvements in written tests or clinical scenarios (Ross 2009 **Level III-3 SR**, 15 studies, n unspecified). One intervention in particular, the *Good Prescribing Guide* developed by the World Health Organization (WHO), is the only model widely used and has shown to consistently (four "before-and-after" studies) improve prescribing practice in tests but has not been tested widely in patient care.

Education programs may not always be successful in improving nursing staff knowledge or attitudes (Dahlman 1999 **Level III-3**) or pain relief (Knoblauch 1999 **Level IV**). In rural and remote settings, distance and professional isolation could affect the ability of healthcare staff to receive up-to-date education about pain relief. However, similarities between urban and rural nurses' knowledge and knowledge deficits relating to acute pain management have been reported (Kubecka 1996 **Level IV**) and a tailored education program in a rural hospital improved the management of acute pain (Jones 1999 **Level III-3**). An education program delivered to nurses in rural and remote locations and focusing on acute pain, chronic pain and cancer pain improved understanding of pain management (Linkewich 2007 **Level III-2**). Early attempts at using online education for nurses to improve pain management were not widely taken up. A model (using e-learning and problem-based approaches) has been proposed and has had some initial success (Keyte 2011 **NR**).

While the focus of most research has been on the impact of education on the efficacy of pain treatments, there remains much work to be done on establishing the role of education in patient monitoring and safety.

Physiotherapists have recognised the need for more education about acute and subacute pain incorporating a biopsychosocial approach to prevent long-term disability and pain. However, an 8-d university course about how to identify and address psychosocial risk factors attended by practicing musculoskeletal physiotherapists led to no improvement in their patients being treated for musculoskeletal problems (Overmeer 2011 **Level II**, n=42, JS 2). The authors suggest that this type of teaching may need to be incorporated at an earlier stage of learning or by other methods if an impact on practice is to be made.

A narrative review on undergraduate medical education describes many attempts around the world to improve the curricula of medical schools (Vadivelu 2012 **NR**). Unfortunately acute pain management is often neglected.

Key messages

1. There is no good evidence in favour of general education for acute neck pain having significant effects on any relevant outcomes (**N**) (**Level I** [Cochrane Review]).
2. Short educational interventions in acute whiplash injury reduce pain and disability and enhance recovery and mobility (**N**) (**Level I** [PRISMA])
3. There is no good evidence in favour of preoperative education having significant effects on outcomes such as pain, length of stay, patient satisfaction, postoperative complications, mobility and expectations in most postoperative settings (**N**) (**Level I**).
4. There is no good evidence in favour of general education for acute back pain having significant effects on any relevant outcomes (**N**) (**Level III-1 SR**).
5. Targeted reassurance in acute back pain by physicians in primary care can result in improved changes in psychological factors such as fear, worry, anxiety, catastrophisation and healthcare utilisation (**N**) (**Level III-1 SR**).
6. Educational interventions in cancer pain patients improve knowledge, attitudes and pain control (**N**) (**Level III-1 SR**).
7. Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief (**U**) (**Level II**).
8. Specific pain education in specific surgical settings may result in decreased pain, opioid use and less healthcare utilisation (**N**) (**Level II**).
9. Written information given to patients is better than verbal information given at the time of the interview (**S**) (**Level III-2**).
10. While evidence for the benefit of patient education in terms of better pain relief is inconsistent, structured preoperative education may be better than routine information (**S**) (**Level III-2**).
11. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**S**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Successful management of acute pain requires close liaison between all personnel involved in the care of the patient (**U**).

☑ More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

3.2 Organisational requirements

It is recognised that patients should be able to access best-practice care, including appropriate assessment of their pain and effective pain management strategies (ANZCA 2010 **GL**; ASA 2012 **GL**). However, effective acute pain management will, to a large extent, depend not only on the medicines and techniques available but also on the systems involved in their delivery (Macintyre 2015 **NR**). Even simple methods of pain relief can be more effective if proper attention is given to education (see Section 3.1), prescribing, administration, documentation, monitoring of patients and the provision of appropriate policies, protocols and guidelines (Gould 1992 **Level III-3**). The incorporation of pain measurement and clinical assessment for all patients, not only those under the care of an APS, will aid pain management for all the patients throughout an institution (Gordon 2008 **NR**). Standardised clinical observation charts including pain and sedation scores and other vital signs are an important step in ensuring safe provision of effective analgesia (Macintyre 2009 **NR**). In many institutions, an APS will assume responsibility for managing more advanced methods of pain relief such as PCA and epidural analgesia.

3.2.1 General requirements

Guidelines to enhance patient outcomes and standardise analgesic techniques (eg selection of medicines and their concentrations, dose and dose intervals), monitoring requirements, choice of equipment, and responses to inadequate or excessive analgesic doses or other complications may lead to consistency of practice. This can potentially improve patient safety and analgesic efficacy, regardless of the technique used (Counsell 2008 **NR**; Macintyre 2009 **NR**; Macintyre 2015 **NR**). These guidelines should be evidence-based wherever possible.

Marked improvements in conventional methods of pain relief have followed the introduction of guidelines for parenteral opioid administration (Gould 1992 **Level III-3**; Humphries 1997 **Level III-3**). However, it is the implementation of guidelines not their development that remains the greatest obstacle to their use. Compliance with available guidelines is highly variable and may be better in larger and university-affiliated hospitals (Nasir 2011 **Level IV**; Carr 1998 **Level IV**). Resource availability, particularly staff with pain management expertise, and the existence of formal quality-assurance programs to monitor pain management are positive predictors of compliance with guidelines (Jiang 2001 **Level IV**).

Different types of surgery require different types of analgesic regimens. Common and minor surgical procedures often result in high pain scores, which are frequently undertreated (eg laparoscopic appendicectomy, cholecystectomy, and haemorrhoidectomy) (Gerbershagen 2013, **Level IV**, n=70,764). The adoption of procedure-specific methods and the use of analgesic combinations may help to optimise analgesia and reduce adverse effects (Joshi 2013 **NR**) (see Section 8.1.1). A hospital-wide approach can be incorporated into postoperative enhanced-recovery programs (White 2010 **NR**) (see Section 3.2.3).

Professional bodies in a number of countries have issued guidelines for the management of acute pain (ASA 2012 **GL**; ANZCA 2013a **GL**; ANZCA 2013b **GL**; RCA 2014 **GL**).

The success of an APS and patient treatment depends not only on good clinical care but also on a positive organisational culture. This should follow the key principles of effective change management. A series of semistructured interviews of healthcare professionals identified key areas that need to be addressed for well-organised care. These include structural issues, political issues, cultural change, educational challenges, leadership and motivation, and technological challenges (Bate 2008 **NR**; Powell 2009 **NR**).

3.2.2 Acute pain services

There is a very wide diversity of APS structures, with no consensus as to the best model and no agreed definition of what might constitute such a service (Counsell 2008 **NR**). Some are "low-cost" nurse-based (Shapiro 2004 **Level IV**; Rawal 2005 **NR**), others are anaesthetist-led but rely primarily on APS nurses as there may not be daily clinical participation by an anaesthetist (Harmer 2001 **NR**; Nagi 2004 **NR**) and some are comprehensive and multidisciplinary services with APS nursing staff, sometimes pharmacists or other staff and daily clinical input from, and 24-h cover by, anaesthetists (Ready 1988 **Level IV**; Macintyre 1990 **Level IV**; Schug 1993a **NR**). The development of specific paediatric pain services has also been described (Kost-Byerly 2012 **NR**) and is an emerging field (Finley 2014 **NR**).

Larger hospitals and those with university affiliations are more likely to have a formal APS and use protocols (Nasir 2011 **Level IV**). When advanced modalities such as epidural analgesia and peripheral nerve block (PNB) infusions are used, the APS is most commonly anaesthetist-led. An economic evaluation of a physician-led APS has shown it to be cost-effective even for patients having IV-PCA after intermediate grade surgical procedures (Lee 2010 **Level II**, n=423, JS 2) (see Section 3.3.2).

The degree of medical input varies enormously. A UK survey reported that while 90% of hospitals reported having an APS, dedicated medical staff sessions did not exist in 37%, were limited to one or two per wk in 40% and in only 4% were there five or more sessions (Nagi 2004 **NR**). In training hospitals in Australia, 91% of hospitals accredited for anaesthetic training had an APS run from the department of anaesthesia with daily input from medical staff, although consultant anaesthetist sessions (one session is 0.5 d) varied from zero in 27%, just

one or two a wk in a further 22%, four to six per wk in 22% and ten per wk in 15% (Roberts 2008 **Level IV**). A more recent Dutch survey showed again that 90% of hospitals have an APS of variable organisational structure; important tasks of the APS were regular patient rounds and checking complex pain techniques (100%), supporting quality improvement of pain management (87%), pain education (100%) and pain research (21%) (van Boekel 2015 **Level IV**). However, a survey repeated in Denmark from 2000–2009 showed a surprising decline of APSs in parallel to increased usage of enhanced-recovery programs (Nielsen 2012 **Level IV**). In the USA, APSs were more common in university/academic hospitals (96%) than in Veterans' Affairs hospitals (69%) with the lowest rate in private hospitals (47%) (Nasir 2011 **Level IV**). Formal written postoperative pain protocols were more common in hospitals with an APS but overall only 55% of hospitals had such protocols. In Germany, 81% of the hospitals surveyed stated that they had an APS; however, only 45% met quality criteria defined by the authors (Erlenwein 2014 **Level IV**). In contrast to the USA data above, 97% of the hospitals had written acute pain protocols for surgical patients but only 51% on nonsurgical wards.

Some APSs supervise primarily "high-tech" forms of pain relief while others have input into all forms of acute pain management in an institution and will work towards optimising traditional methods of pain relief so that all patients in that institution benefit (Breivik 2002 **NR**; Counsell 2008 **NR**; Macintyre 2015 **NR**). Increasingly, APSs are also called on to deal with much more complex pain management issues (eg acute-on-chronic pain, acute pain after SCI or other major trauma, and resulting from a multitude of medical illnesses) and more complex patients (eg opioid-tolerant patients, older patients) (Counsell 2008).

Individual publications assessing the benefits of an APS have reported that the presence of an APS reduced pain scores (Gould 1992 **Level III-3**; Harmer 1998 **Level III-3**; Miaskowski 1999 **Level IV**; Sartain 1999 **Level III-3**; Salomaki 2000 **Level III-3**; Bardiau 2003 **Level III-3**; Stadler 2004 **Level III-3**) and adverse effects (Schug 1993a **Level IV**; Stacey 1997 **Level III-3**; Miaskowski 1999 **Level IV**; Sartain 1999 **Level III-3**). A review of publications (primarily audits) looking at the effectiveness of APSs (77% were physician-based, 23% nurse-based) concluded that the implementation of an APS is associated with a significant improvement in postoperative pain and a possible reduction in postoperative neurological symptoms (PONS) but that it was not possible to determine which model was superior (Werner 2002 **Level IV**). The authors comment, however, that it is not possible to assess the contribution of factors such as an increased awareness of the importance of postoperative analgesia, the use of more effective analgesic regimens (eg epidural analgesia), the effects of APS visits and better strategies for antiemetic therapy.

Possible benefits of an APS are summarised in Table 3.1.

Given the heterogeneity of APS models and types of patients and pain treated, as well as variation in the quality of published studies, it is difficult to meaningfully analyse the benefits or otherwise of an APS. Although systematic reviews have been attempted (McDonnell 2003 **Level III-3 SR**, 15 studies, n unspecified; NICS 2003 **Level III-3 SR**, 32 studies, n unspecified), the poor quality of the studies looking at the effectiveness or otherwise of APSs and the many different types of APS, means that a proper meta-analysis cannot be performed.

In addition, the above studies looked at outcome in terms of immediate pain and adverse effects in postoperative patients only. It is possible that an APS may benefit patients in other ways.

Combination of an APS with a physician-based critical-care outreach team, which systematically reviewed high-risk postoperative patients for 3 d after their return to a general ward, showed a significant improvement in postoperative outcome with decrease in serious adverse effects from 23–16 events per 100 patients and 30-d mortality from 9–3% (Story 2006 **Level III-2**). Finally, members of an APS may also be more likely to recognise the early onset of neuropathic pain associated with surgery, trauma or medical disease and institute the appropriate treatment (Counsell 2008 **NR**).

3.2.2.1 Safety

Unidimensional management of acute pain can lead to adverse outcomes including opioid-induced ventilatory impairment (OIVI) (Vila 2005 **Level III-3**; Macintyre 2011 **NR**). Structural changes in an APS can minimise such effects (Story 2006 **Level III-2**). Implementation of root-cause analysis for critical incidents improved the safety of patients looked after by an APS; this approach reduced the overall event rate (1.47 vs 2.35%) with specific effects on the rate of respiratory depression (0.41 vs 0.71%), severe hypotension (0.78 vs 1.34%) and PCA pump programming errors (0.0 vs 0.08%) (Paul 2014 **Level III-3**) (see also Sections 6.6 and 6.8).

Table 3.1 Possible benefits of an acute pain service

Benefit	References
Better pain relief	Gould 1992; Harmer 1998; Gear 1999; Sartain 1999; Salomaki 2000; Werner 2002; Bardiau 2003; Stadler 2004
Lower incidence of adverse effects	Schug 1993b; Stacey 1997; Miaskowski 1999; Sartain 1999; Werner 2002
Lower postoperative morbidity/mortality	Story 2006
Management of analgesic techniques that may reduce the incidence of persistent pain after surgery	Obata 1999; Senturk 2002; Gehling 2003
Cost-effective patient care	Lee 2010

Key messages

1. Implementation of an acute pain service may improve pain relief and reduce the incidence of adverse effects (**U**) (**Level III-3**).
2. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**U**) (**Level III-3**).
3. Even "simple" techniques of pain relief can be more effective if attention is given to education, documentation, patient assessment and provision of appropriate guidelines and policies (**U**) (**Level III-3**).
4. Implementation of root-cause analysis to follow up critical incidents improved the safety of patients under care of an acute pain service (**N**) (**Level III-3**)

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Successful management of acute pain requires close liaison between all personnel involved in the care of the patient (**U**).

☑ More effective acute pain management will result from appropriate education and organisational structures for the delivery of pain relief rather than the analgesic techniques themselves (**U**).

☑ Appropriate institutional support and engagement is important for the effective implementation of an acute pain service (**N**).

☑ Procedure-specific analgesic protocols can help optimise analgesia for the individual patient while reducing adverse effects (**N**).

3.3 Economic considerations in acute pain management

Economic evaluation of healthcare can be described as the "comparative analysis of alternative courses of action in terms of their costs and consequences" (Drummond 2008 **NR**). The aim of health economics is to maximise health benefits relative to the resources available. An economic assessment of acute pain can be of the overall service provision (eg an APS) or of an individual technique (eg PCA).

While the costs of healthcare are relatively easy to measure, the value of healthcare is harder to quantify (Goldman 2014 **NR**). Often, the benefits of healthcare are limited to those occurring within the healthcare system, however there may be other significant benefits in society that should also be included (eg return to full employment, long-term disability due to pain) (Drummond 2008 **NR**).

There are several types of economic assessment that are commonly used in the literature. These have important differences; there is a consensus agreement on their definitions (Husereau 2013 **GL**; Drummond 2005 **NR**) (see Table 3.2).

Table 3.2 Definitions of health economic assessment measures

Cost-effectiveness analysis	Consequences are measured in natural units, such as life years gained, disability days avoided or cases detected
Cost-utility analysis	Consequences are measured in terms of preference-based measures of health, such as quality-adjusted life years (QALY) or disability-adjusted life years (DALY)
Cost-benefit analysis	Consequences are valued in monetary units
Cost-minimisation analysis	Consequences of compared interventions are equivalent (in terms of clinical efficacy and tolerability) and only relative costs are compared
Cost-outcome description	Costs measured in monetary value and health effects measured in natural units (eg ICU days saved, patient satisfaction etc)

In the literature, these terms may be used interchangeably without correct adherence to their definitions. No single assessment measure is superior to another and health economists debate the merits of each. In addition, issues of social equity, needs and priorities should also be part of the decision-making process (McGregor 2003 **NR**; Schlander 2009 **NR**; Phillips 2009 **NR**).

In contrast to most commodities, healthcare is a "credence good" (Emons 1997 **NR**); ie patients or consumers/stakeholders find it difficult or impossible to determine the utility of a treatment prior to its consumption. They have to rely on the knowledge of healthcare experts when choosing a treatment. This situation is also referred to as "asymmetry of knowledge".

Patients value pain relief highly; a survey of 2 million USA inpatients found that "how well their pain was controlled" was the second most important factor in recommending a hospital (PressGaney 2009 **Level IV**). When healthcare funding occurs without regard to patients' values, then funding for formal APSs becomes limited (Sun 2010 **NR**).

A consistent risk factor for development of CPSP is poorly controlled postoperative pain (see Section 1.4). CPSP is an economic burden on society. An economic report in 2007 found that the total cost of chronic pain in Australia was $34.4 billion and that much of chronic pain originates as acute pain (Access Economics 2007). Chronic pain interferes with return to employment, requires ongoing medical treatment with its inherent costs and may require carers at an additional cost. CPSP is common after many types of surgical procedures: examples include limb amputation, thoracotomy, breast surgery and inguinal hernia repair (see also Section 1.4).

Economic assessment of pain relief requires direct and indirect evaluation of both the costs and the benefits. Assessment of subjective experiences, such as a reduction in pain scores, can be assigned a monetary value using techniques such as "willingness to pay" and "human capital approaches" (Kumar 2006 **NR**). These monetary values are then used in performing a cost-benefit analysis. An economic analysis needs to include the assessment of a treatment in comparison with the alternatives eg IV PCA vs *pro re nata* (prn; as needed) opioid analgesia. Direct costs can include the cost of equipment, medicines and staff. Indirect costs can include

duration of hospital stay, use of ICU, development of persistent pain and treatment of adverse effects. Potential benefits include reduction in pain intensity, minimisation of pain-related adverse effects, improved fast-track recovery and compliance with rehabilitation, and earlier return to work (White 2007 **NR**).

3.3.1 Economic evaluation of patient-controlled analgesia

The direct and indirect costs of PCA for pain relief after three common types of surgery have been assessed (Palmer 2014 **Level III-3**). This evaluation used data from a large administrative healthcare database (Premier 2015). Further cost estimates of adverse effects were derived from the literature. Use of PCA after total knee arthroplasty, hip arthroplasty and open abdominal surgery was evaluated. The costs included PCA-pump usage, setup costs, IV extension set, medicine, fluid for IV coinfusion and pump. The total of these costs (standardised to USA$ in 2012) during the first 48 h after surgery were $204, $196 and $243 respectively. Additionally, cost estimates for particular adverse effects in the first 48 h of PCA use were calculated. These costs were phlebitis ($2.18), healthcare worker needle-stick injury ($1.67) and IV PCA programming error ($35.52). The assessment of costs for PCA programming errors did not include newer pumps that have software for mitigation of programming errors (ie "smart pumps"). The cost of other adverse effects, such as respiratory depression or nausea and vomiting, were not included in this assessment.

The costs and rates of harmful and nonharmful errors due to the use of IV PCA were estimated from two large safety-reporting databases in the USA (Meissner 2009 **Level IV**). The datasets included medication errors (MEDMARX) and device errors (MAUDE). A cost-accounting methodology was used that included direct, indirect and opportunity costs. These were estimated from published literature, expert consensus, physician billing charges and staff labour rates (standardised to USA$ in 2006). The estimated average cost of a PCA adverse effect in the medication error dataset was $733, whereas the cost related to a pump error was $552. If an error led to patient harm, this was 120–250 times more costly than a nonharmful error. For medication incidents, the most expensive harm-causing error was due to poor communication ($8,984 per incident). The two most expensive pump-related errors were operator error ($5,756) and those of indeterminate cause ($6,120). The estimated annual USA error rates per 10,000 patients treated with PCA were 407 for PCA medication errors and 17 for PCA device errors.

3.3.2 Economic evaluation of acute pain services

A systematic review of the economic evaluations of APSs has been performed (Lee 2007 **Level IV SR,** 9 studies, n=14,774). Five of the studies were of nurse-based, anaesthetist-supervised services. Out-of-pocket expenses and loss of productivity due to absence from work were not included. No study went beyond 5 d. Monetary values were standardised to USA$ in 2005. The cost of an anesthetist-led APS ranged from $31.73–$100.37/patient/d. The cost of a nurse-based, anaesthetist-supervised APS ranged from $3.70–$50.77/patient/d. The cost savings from a shorter ICU stay were $9.90/patient/d. The cost-savings from a shorter duration of hospital stay were $11.40/patient/d. Savings from reduced nursing time were also identified. Data was not available to compare the economics of a nurse-based, anaesthetist-supervised APS with an anaesthesiologist-led APS. No studies were of high quality or included all costs and benefits associated with APS care.

An RCT for cost-effectiveness of APS care (anaesthesiologist-led, nurse-based) compared APS patient care (IV PCA plus adjuvants) with conventional ward analgesia for patients having major surgery (Lee 2010 **Level II**, n=423, JS 2). Regional analgesic techniques were not included. Of patients in the APS group, 86% had 1 d or more of highly effective pain relief compared with 75% in the conventional care group. Costs were higher in the APS group when compared with the conventional group by USA$ 46/d. Cost-effectiveness was determined using a "willingness-to-pay" methodology, which assigns a monetary value to pain relief. The cost to be 95% certain of attaining 1 d of highly effective pain relief per patient was $USA 546.

The cost-utility analysis of a nurse-based APS has been performed (Stadler 2004 **Level III-3**). The interventions used in this APS were implementation of guidelines, use of multimodal

analgesia, optimum use of systemic opioids as well as NSAIDs and paracetamol, along with information pamphlets to patients. In 1.5% of patients, PCA was used; patients receiving epidural analgesia were not included. The patient population was a large tertiary hospital that included all surgical subspecialties. Cost-utility was assessed using a measure of "postoperative pain days averted" (PPDA), which is a health-state scale conceptually similar to the QALY. The PPDA measure summarises treatment outcome in terms of time spent with lower pain scores. A value of "1" represents a state of no pain and a value of "0" represents worst pain imaginable. For postoperative d 1–3, PPDA values were 0.075 (1.8 h), 0.05 (1.2 h) and 0.0375 (0.9 h) respectively. The incremental cost of pain management by the APS, compared to no APS, was 19 Euro/patient/d. The effectiveness of the APS may have been different if more advanced methods of pain relief had been used. Measuring PPDA alone may have missed other benefits from improved pain relief (ie QoL surveys such as Short Form 12 of the Medical Outcomes Study [SF-12]).

3.3.3 Economic benefit related to improved patient outcomes

While not intended as economic assessments, there are studies that have measured patient outcomes, other than pain, that are related to an economic outcome. These are similar to a cost-effectiveness analysis (see Table 3.2).

A systematic review of patient outcome after epidural analgesia showed a reduction in the incidence of costly adverse effects. These included reduced risk of atrial fibrillation, supraventricular tachycardia, deep vein thrombosis, respiratory depression, atelectasis, pneumonia, ileus and PONV and improved recovery of bowel function (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044) (see Section 5.6). These must be balanced against the increase in adverse effects associated with epidural analgesia such as hypotension, pruritus, urinary retention and motor block.

One study examined the effect on patient outcome when an APS provided additional advice on patient care during their usual ward round (Story 2006 **Level III-3**, n=590). Examples of advice include oxygen therapy, IV fluid management, physiotherapy, analgesia or calling the medical emergency team. This APS intervention resulted in a reduction of serious adverse effects (from 23–16/100 patients) and reduced 30-d mortality (9–3%).

Key messages

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Patients value well-controlled pain highly (**N**).
- ☑ Long-term economic consequences from the progression of acute to chronic pain can be significant (**N**).
- ☑ Costs from PCA errors can be considerable; the most common high-cost errors arise from staff communication error and operator error (**N**).
- ☑ There are different measures of economic assessment and analysis used in healthcare; no one method is most appropriate (**N**).

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4. ANALGESIC MEDICINES

4.1 Opioids

Opioids not have only systemic effects but can bind to opioid receptors in the spinal cord or in the periphery.

4.1.1 Systemic opioids

Opioids remain the mainstay of systemic analgesia for the treatment of moderate to severe acute pain.

4.1.1.1 Choice of systemic opioid

All full opioid agonists given in equianalgesic doses produce the same analgesic effect (McQuay 1991 **NR**), although accurate determination of equianalgesic doses is difficult due to interindividual variabilities in kinetics and dynamics (Gammaitoni 2003 **NR**). Equianalgesic conversion dose tables are often used to assist in the change from one opioid to another. However, such tables are based largely on single-dose studies in opioid-naïve subjects and may not be as relevant when conversions are made after repeated doses of an opioid have been given (either in the acute pain or chronic pain setting) and do not take into account incomplete cross-tolerance and patient-specific factors (Weschules 2008a **NR**). Care must be taken when opioid rotations are undertaken based on such tables alone without consideration of clinical factors because this carries a significant risk of toxicity and even fatality (Webster 2012 **NR**).

In general there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of adverse effects between any of the pure agonist opioids, although the results of individual studies are inconsistent. However, for pharmacokinetic and other reasons, some opioids may be better in some patients (Woodhouse 1999 **Level II**, n=82, JS 4). Comparisons of the different opioids are commonly done in patients using PCA (see Section 6.3.1 for these comparisons).

While the data to support the concept of opioid rotation originate from cancer pain (Quigley 2004 **Level IV** [Cochrane] **SR**, 52 studies, n unspecified; Mercadante 2011 **Level III-2 SR**, 31 studies, n unspecified), it may be a useful strategy in the management of acute pain in patients with intolerable opioid-related adverse effects who are unresponsive to treatment and in opioid-tolerant patients (see Section 10.6).

4.1.1.2 Specific opioids

The efficacy of various opioids administered by the different routes used in the management of acute pain is discussed in detail in Chapter 5. The following section describes other relevant aspects of selected opioid agents including tramadol.

Buprenorphine

Buprenorphine is a semisynthetic derivative of thebaine, an alkaloid of opium and a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist with high receptor affinity and slow dissociation from the mu-receptor (Johnson 2005 **NR**). Buprenorphine shows biphasic pharmacokinetics with an initial distribution half life of around 2–3 h and a terminal half life of around 24 h; two-thirds of the medicine is excreted unchanged, mainly in faeces, while the remaining one-third is metabolised predominantly in the liver and gut wall via glucuronidation to an inactive metabolite, buprenorphine-3-glucuronide, and via CYP3A4 to norbuprenorphine, which has 40 times less analgesic effect than buprenorphine (Kress 2009 **NR**). Onset of effect is slower than for many other opioids; using experimental pain stimuli, the time to peak effect after administration of an IV bolus dose of buprenorphine was 70–90 min (Yassen 2006 **Level III-3**).

In clinically relevant doses, buprenorphine behaves like a full mu-opioid receptor agonist and, in animals as well as humans, in low doses (ie transdermally [TD]) there also appears to be no antagonism of other concurrently administered mu-agonist medicines (Pergolizzi 2010 **NR**).

There is a ceiling effect for respiratory depression but not for analgesia (Dahan 2005 **Level III-2**; Dahan 2006 **Level III-2**). The risk of respiratory depression is low compared with morphine, methadone, hydromorphone and fentanyl, even in the doses used for the treatment of opioid addiction, as long as concurrent sedative medications are not given (Kress 2009 **NR**). However, even buprenorphine alone can cause fatal respiratory depression (Selden 2012 **Level IV**). Should buprenorphine-induced respiratory depression occur, complete reversal with naloxone is possible (Pergolizzi 2010 **NR**), although higher than usual doses and a longer duration infusion of naloxone are required (van Dorp 2006a **Level III-2**; Boom 2012 **NR**).

In animal models of pain, buprenorphine appears to have good efficacy for neuropathic pain (Hans 2007 **NR**). In the clinical setting, case reports have suggested that buprenorphine is effective in peripheral (Licina 2013 **Level IV**) and central neuropathic pain (Guetti 2011 **Level IV**).

Buprenorphine may also have a reduced tendency to cause opioid-induced hyperalgesia (OIH) (Lee 2011 **NR**). In patients in opioid-substitution programs, buprenorphine reduced pain thresholds less than methadone (Compton 2001 **Level IV**). Using experimental pain stimuli in humans, buprenorphine, unlike pure mu-opioid agonists, has been shown to be antihyperalgesic, which may be related in part to its kappa-opioid antagonist activity (Koppert 2005 **Level II EH**, n=15, JS 4).

Withdrawal symptoms, which may be seen if the medicine is ceased after long-term treatment, are milder and more delayed in onset (≥72 h) than other opioids (Kress 2009 **NR**). There is also less neonatal abstinence syndrome (NAS) in babies of mothers under buprenorphine vs methadone substitution (Jones 2012 **NR**).

Buprenorphine can be safely used in patients with renal impairment and has less immunosuppressive effect than pure mu-opioid agonists (Pergolizzi 2010 **NR**).

Codeine

Codeine is classified as a weak opioid. However, it is only a very weak mu-receptor agonist and its analgesic action depends on the metabolism of about 10% of the dose to morphine, via the CYP2D6 cytochrome P450 isoenzyme (Lotsch 2005 **NR**).

Over 100 allelic variants of CYP2D6 have been identified, resulting in wide variability in enzyme activity (Somogyi 2007 **NR**). Individuals carrying two wild-type alleles display normal enzyme activity and are known as extensive metabolisers; intermediate metabolisers are heterozygotes with two variant alleles known to decrease enzymatic capacity; and poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Stamer 2007a **NR**). In Caucasian populations, 8–10% of people are poor metabolisers; however 3–5% are ultrarapid metabolisers (Stamer 2007a **NR**; Madadi 2009 **Level III-2**). Those who are ultrarapid metabolisers (carriers of the CYP2D6 gene duplication) have significantly higher levels of morphine and morphine metabolites after the same dose of codeine (Kirchheiner 2007 **Level IV**).

There are large interethnic differences in the frequencies of the variant alleles. For example, the proportion of ultrarapid metabolisers is higher (up to 29%) in Middle Eastern and Northern African populations and lower (0.5%) in Asians (Stamer 2007b **NR**); the proportion of poor metabolisers is lower in Asians and African Americans (Holmquist 2009 **NR**; Yee 2013b **Level IV**).

A case-control study including a case of a newborn dying while breastfed by a mother taking codeine has highlighted that breastfed infants of mothers who are ultrarapid metabolisers are at increased risk of life-threatening CNS depression (Madadi 2009 **Level III-2**). A number of similar cases have been reported and health professionals and mothers of breastfeeding infants should be aware of this risk (Madadi 2008 **Level IV**). CYP2D6 genotyping predicts subjects with reduced metabolism to morphine but must be combined with additional phenotyping to accurately predict patients at risk of morphine toxicity (Lotsch 2009 **Level III-2**).

Death or OIVI has occurred after codeine treatment. Although rare, the risk is highest in children who are ultrarapid metabolisers, after they have undergone tonsillectomy, adenoidectomy, or both, as many of these have sleep-disordered breathing and are therefore more sensitive to opioids (Kelly 2012 **Level IV**; Racoosin 2013 **NR**; Friedrichsdorf 2013 **Level IV**).

The USA Food and Drugs Administration (FDA) now has a boxed warning applied to maternal postpartum use and children (<18 y) undergoing adenotonsillectomy with instruction "to prescribe an alternative analgesic for postoperative pain control" (FDA 2013). The European Medicines Agency has responded similarly (EMA 2013); as has the WHO in removing codeine from its tiered analgesic ladder for treatment of (persistent) pain in children (WHO 2012). Guidelines on this issue have been published (Crews 2014 **GL**) (see also Sections 1.7.3 and 9.4.4).

The principal metabolite of codeine is codeine-6-glucuronide, which has a similar low potency to the parent medicine and is renally excreted (Lotsch 2005 **NR**).

Dextropropoxyphene

Oral dextropropoxyphene 65 mg alone is a poorly effective analgesic in postoperative pain (NNT 7.7) (Collins 2000 **Level I** [Cochrane], 6 RCTs [dextropropoxyphene only], n=440). Dextropropoxyphene is often used in combination with paracetamol but this combination does not lead to better pain relief compared with paracetamol alone and increases the incidence of dizziness (Li Wan Po 1997 **Level I**, 26 RCTs, n=2,231).

The use of this compound is discouraged, not only because of its low efficacy but also because of a number of risks related to its use (Barkin 2006 **NR**). These include QT-interval prolongation and possibility of Torsades des Pointes (TdP) and cardiogenic death. This is exacerbated by complex pharmacokinetics (particularly in the elderly) with the risk of accumulation of dextropropoxyphene and its metabolite nordextropropoxyphene, leading to CNS, respiratory and cardiac depression (Davies 1996 **NR**).

In line with many other developed countries, the Therapeutics Goods Administration (TGA) in Australia decided in November 2011 to remove the registration of dextropropoxyphene (Buckley 2013 **NR**). However, due to a number of appeals by the manufacturer, the medication has not yet been removed from the market and is still available with a number of precautions (TGA 2013).

Diamorphine

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to monoacetylmorphine (MAM) and morphine (Miyoshi 2001 **NR**); diamorphine and MAM are more lipid-soluble than morphine and penetrate the CNS more rapidly. It is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine.

There was no difference between parenteral diamorphine and morphine in terms of analgesia and adverse effects after hip surgery (Robinson 1991 **Level II**, n=40, JS 4) and between parenteral diamorphine and pethidine for labour analgesia (Wee 2014 **Level II**, n=484, JS 4). Epidurally administered diamorphine resulted in a longer time to first PCA use and lower total 24-h morphine requirements compared with the same dose given as an intramuscular (IM) injection (Green 2007 **Level II**, n=60, JS 4). Intranasal (IN) diamorphine has been used as an analgesic for acute pain in children attending EDs (Kendall 2015 **Level IV**). Here peak morphine plasma concentrations were higher and occurred earlier when diamorphine was administered IV vs IN (Kidd 2009 **Level IV**).

Dihydrocodeine

Dihydrocodeine is a semisynthetic derivative of codeine and has similar mu-opioid agonist activity. However, unlike codeine, inhibition of CYP2D6 by quinine does not alter its analgesic effect, even though the CYP2D6-dependant active metabolite, dihydromorphine, has a much higher mu-opioid receptor affinity than the parent medicine (Lotsch 2005 **NR**). Orally administered, it has around twice the potency of codeine and one-sixth the potency of morphine (Leppert 2010 **NR**).

Fentanyl

Fentanyl is a highly potent phenylpiperidine derivative, structurally related to pethidine. It is metabolised almost exclusively in the liver to minimally active metabolites. Less than 10% of unmetabolised fentanyl is renally excreted. Fentanyl is commonly used in the treatment of

acute pain, especially when its lack of active metabolites and fast onset of action may be of clinical benefit (Grape 2010 **NR**). The fast onset is the result in particular of its high lipophilicity (octanol:water partition coefficient >700); this leads to a transfer half-life of 4.7–6.6 min between plasma and CNS (Lotsch 2013 **NR**) (see also Section 5.4.1).

Hydromorphone

Hydromorphone is a derivative of morphine that is approximately five times as potent as morphine. The main metabolite of hydromorphone is hydromorphone-3-glucuronide (H3G), a structural analogue of morphine-3-glucuronide (M3G). Like M3G (see below), H3G is dependent on the kidney for excretion, has no analgesic action and can lead to dose-dependent neurotoxic effects (Smith 2000 **NR**; Wright 2001 **NR**; Murray 2005 **NR**).

Hydromorphone is an effective strong opioid analgesic with similar efficacy and adverse effects as other strong opioids (Quigley 2002 **Level I** [Cochrane], 36 RCTs [acute pain], n=2,521). It provides slightly better clinical analgesia than morphine with similar adverse effects (Felden 2011 **Level I**, 8 RCTs, n=1,004).

Methadone

Methadone is a synthetic opioid commonly used for the maintenance treatment of patients with an addiction to opioids and in patients with chronic pain. It is commercially available as a racemic mixture of R- and L-enantiomers but it is the R-enantiomer that is responsible for most, if not all, its mu-opioid receptor-mediated analgesic effects (Lugo 2005 **NR**; Fredheim 2008 **NR**).

It has good oral bioavailability (70–80%), high potency and long duration of action and a lack of active metabolites (Lugo 2005 **NR**). It is also a weak NMDA-receptor antagonist and monoamine (5HT and noradrenaline [norepinephrine]) reuptake inhibitor and has a long and unpredictable half-life (mean of 22 h; range 4–190 h) leading to an increased risk of accumulation (Weschules 2008b **NR**). Therefore it is of limited use for acute pain treatment. Dose conversion is complex and depends on many factors including absolute doses of other opioids and duration of treatment.

Methadone is metabolised primarily by the cytochrome P450 group of enzymes, in particular 3A4 and to a lesser extent by CYP 1A2, 2D6, 2D8, 2C9/2C8, 2C19 and 2B6 (Kapur 2011 **NR**). Over 50 drug-drug interactions with methadone are described. Concurrent administration of other medicines that are CYP450 inducers may increase methadone metabolism and lower methadone blood levels (eg carbamazepine, rifampicin, phenytoin, St John's wort [*Hypericum perforatum*] and some antiretroviral agents) leading to potential reduced efficacy or even withdrawal. Conversely, medicines that inhibit CYP450 (eg other antiretroviral agents, some selective serotonin-reuptake inhibitors [SSRIs], grapefruit juice and antifungal agents) may lead to raised methadone levels and an increase in adverse effects or overdose (Fredheim 2008 **NR**) (see Section 8.6.8 for interactions in patients with human immunodeficiency virus [HIV]).

High-dose methadone has been associated with prolonged QT intervals (see below).

Morphine

Morphine remains the standard against which other opioids are compared. Morphine-6-glucuronide (M6G) and M3G, the main metabolites of morphine, are formed by morphine glucuronidation, primarily in the liver. M6G is a mu-opioid receptor agonist that crosses the blood-brain barrier more slowly than morphine (De Gregori 2012 **NR**). It contributes to such a large extent to morphine analgesia in patients with both normal (85% of the effect after parenteral and up to 95% after oral administration) and impaired (98% of the effect) renal function, that morphine could be regarded as a prodrug to M6G (Klimas 2014 **NR**). M6G also has other morphine-like effects including respiratory depression (van Dorp 2006b **NR**; Dahan 2008b **NR**). M3G has very low affinity for opioid receptors, has no analgesic activity and animal studies have shown that it may be responsible for the neurotoxic symptoms (not mediated via opioid receptors), such as hyperalgesia, allodynia and myoclonus, sometimes associated with high doses of morphine (Lotsch 2005 **NR**).

Clinical trials have investigated M6G as an analgesic agent after a variety of different types of surgery. It was more effective than placebo (Romberg 2007 **Level II**, n=42, JS 3; Smith 2009 **Level II**, n=201, JS 4) and in some trials as effective as morphine (Cann 2002 **Level II**, n=144, JS 4; Hanna 2005 **Level II**, n=100, JS 3), although withdrawal due to insufficient analgesia was higher in another (Binning 2011 **Level II**, n=249, JS 5); this is possibly due to a slower onset of effect of M6G. However, in the clinical setting of titration of IV morphine to postoperative analgesia, the kinetics of morphine and its metabolites had only limited value in explaining the analgesic effects of morphine (Hammoud 2011 **Level IV**), which is an effective approach to early postoperative pain (Aubrun 2012 **NR**).

Excellent pain relief was also obtained after IT administration of 100 or 125 mcg M6G in patients after hip replacement surgery, but there was a high incidence (10%) of late respiratory depression (9–12 h after the dose was given) requiring treatment with naloxone, and a high incidence of nausea (76–88%) and vomiting (60–64%) (Grace 1996 **Level II**, n=75, JS 5).

The incidence and severity of nausea and vomiting as well as the need for antiemetics was less with M6G than with morphine (Cann 2002 **Level II**, n=144, JS 4; Binning 2011 **Level II**, n=249, JS 5). In healthy volunteers, morphine 0.15 mg/kg and M6G 0.2 mg/kg resulted in similar reductions in ventilatory response to carbon dioxide (CO_2) (Romberg 2003 **Level III-1 EH**).

Both M6G and M3G are dependent on the kidney for excretion. Impaired renal function, the oral route of administration (first-pass metabolism), higher doses and increased patient age are predictors of higher M3G and M6G concentrations (Faura 1998 **Level IV**; Klepstad 2003 **Level IV**) with the potential risk of severe long-lasting sedation and respiratory depression.

Oxycodone

Oxycodone contributes the majority of drug effect and is metabolised primarily to noroxycodone by CYP3A (≈80%) and by CYP2D6 to oxymorphone (Lalovic 2006 **PK**). Oxymorphone is more potent than oxycodone as a mu-receptor agonist (14 times) and has a higher receptor affinity (40 times) and may contribute to the overall analgesic effect of oxycodone (Samer 2010b **Level II EH**, n=10 [5-arm cross over], JS 5); noroxycodone, the major metabolite, is only a weak mu-receptor agonist (Coluzzi 2005 **NR**; Lalovic 2006 **NR**).

The dependence of oxymorphone concentrations on CYP2D6 activity and its high potency explains the impact of CYP2D6 polymorphism on oxycodone's pharmacodynamics and pharmacokinetics (Samer 2010b **Level II EH**, n=10 [5-arm cross over], JS 5). Ultrafast metabolisers experience better analgesic effects and higher toxicity, while poor metabolisers experience less analgesic effect. However, in acute postoperative pain, CYP2D6 genotype had no influence on oxycodone requirements (Zwisler 2010 **Level III-3**; Crews 2014 **GL**).

These findings mean also that drug-drug interactions can influence the efficacy of oxycodone (Samer 2010a **Level II EH**, n=10 [cross over], JS 5). This is particularly true for CYP2D6 ultrafast metabolisers but also can be influenced by CYP3A inhibitors such as ketoconazole, which increases the efficacy and toxicity of oxycodone. Therefore, use of a CYP3A inhibitor in an ultrafast CYP2D6 metaboliser is a potentially dangerous combination.

Animal studies have shown that oxycodone is actively taken up into the brain, resulting in a brain concentration that is up to six times that of free plasma levels (Bostrom 2008 **PK**); this may explain the discrepancies between its poorer mu-receptor affinity compared to morphine but its higher potency (Olkkola 2013 **NR**). In general anaesthesia, oxycodone showed a significant dose-dependent respiratory depressant effect measured by reduced minute ventilation, which was significantly more than that of comparable doses of morphine (Chang 2010 **Level II**, n=54, JS 4).

Overall oxycodone has a faster onset of action than morphine, better oral bioavailability, longer duration of action, fewer concerns about metabolites and lower rate of adverse effects (Olkkola 2013 **NR**). There is an increasing use of oxycodone in the perioperative setting based on these pharmacological properties (Kokki 2012 **NR**).

Pethidine

Pethidine (meperidine) is a synthetic opioid with decreasing use worldwide due to multiple disadvantages compared to other opioids. Despite a common belief that it is the most effective opioid in the treatment of renal colic, it was no better than morphine (O'Connor 2000 **Level II**, n=103, JS 5) or hydromorphone (Jasani 1994 **Level II**, n=73, JS 4). Pethidine and morphine also had similar effects on the sphincter of Oddi and biliary tract and there was no evidence that pethidine was better in the treatment of biliary colic (Latta 2002 **NR**).

Pethidine induced more nausea and vomiting than morphine when used parenterally in the ED (Silverman 2004 **Level III-3**) and in the first 2 h after gynaecological surgery (Ezri 2002 **Level II**, n=200, JS4). Pethidine use postoperatively was associated with an increased risk of delirium in the postoperative period in comparison to other opioids (Fong 2006 **Level III-2 SR**, 3 studies, n=877).

Accumulation of its active metabolite, norpethidine (normeperidine), is associated with neuroexcitatory effects that range from nervousness to tremors, twitches, multifocal myoclonus and seizures (Simopoulos 2002 **Level IV**). Impaired renal function increases the half-life of norpethidine; therefore patients with poor renal function are at increased risk of norpethidine toxicity. Naloxone does not reverse and may increase the problems related to norpethidine toxicity.

Overall, the use of pethidine should be discouraged in favour of other opioids in adults (Latta 2002 **NR**) and in the paediatric setting (Benner 2011 **NR**).

Remifentanil

Remifentanil is an unusual opioid with very fast onset of effect (<1 min) and extremely short duration of action due to rapid metabolisation by nonspecific esterases (Parashchanka 2014 **NR**). It is mainly used as a component of anaesthesia; the use as an analgesic has primarily been studied in the setting of labour analgesia (Devabhakthuni 2013 **NR**) (see Section 10.1.3.1).

Tapentadol

Tapentadol is a combined mu-agonist and noradrenaline-reuptake inhibitor (Tzschentke 2014 **NR**). In contrast to tramadol, it has no relevant functional serotonin-reuptake inhibition and no active metabolites (Raffa 2012 **NR**). Elimination is by glucuronidation; impaired hepatic function may require dose adjustment (Xu 2010 **PK**). Although in humans it has a 20-fold lower affinity for the mu-receptor than morphine, it is only three times less potent as an analgesic due to its dual mechanism of action. The effect of tapentadol as a noradrenaline-uptake inhibitor on descending pathways of pain inhibition has been confirmed in diabetic neuropathy, where tapentadol use increased conditioned pain modulation (Niesters 2014b **Level II**, n=24, JS 5). This mechanism of action suggests benefits in neuropathic pain (Vinik 2014 **Level II**, n=318, JS 5) but tapentadol also showed efficacy in nociceptive and inflammatory-pain models (Schiene 2011 **NR**) including postoperative pain (Lee 2014b **Level II**, n=352, JS 5).

Data in the setting of a number of chronic pain conditions show similar or superior efficacy to conventional opioids with reduced rates of gastrointestinal adverse effects such as nausea, vomiting and constipation leading to reduced rates of treatment discontinuation (Riemsma 2011 **Level I**, 42 RCTs, n unspecified). There is no effect on heart rate or blood pressure due to noradrenaline-reuptake inhibition in doses up to the maximum recommended 500 mg/d, even in patients with hypertension and/or on antihypertensives (Biondi 2014 **Level II**, *post hoc* analysis of 3 RCTs, n=1,464). Despite widespread use of this analgesic in the USA and Europe for a number of years, there are only two reported cases of an overdose death (Kemp 2013 **CR**; Franco 2014 **CR**).

Although a controlled medicine in all countries, tapentadol shows a lower rate of abuse and diversion than oxycodone and hydrocodone and a rate comparable to tramadol (Dart 2012 **Level IV**). Rates of doctor shopping were higher for oxycodone (OR 3.5; 95%CI 2.8 to 4.4) (Cepeda 2013b **Level III-2**) and rates of abuse lower for tapentadol (OR 0.35; 95%CI 0.21 to 0.58) (Cepeda 2013a **Level III-2**).

Tramadol

Tramadol is commonly referred to as an atypical centrally acting analgesic because of its combined effects as an opioid agonist and a serotonin- and noradrenaline-reuptake inhibitor (Raffa 1992; Raffa 2012 **NR**). Although an effective analgesic, it may not provide adequate pain relief if used as the sole agent for the management of moderate to severe acute pain at the currently recommended doses (Thevenin 2008 **Level III-1**). However, compared to a variety of strong opioids (morphine, fentanyl, oxycodone, pethidine) when administered by PCA, tramadol had comparable analgesic efficacy (Murphy 2010 **Level I**, 12 RCTs, n=782). Tramadol is an effective treatment for neuropathic pain with a NNT of 3.8 (Hollingshead 2006 **Level I** [Cochrane], 6 RCTs, n=399).

Tramadol given with morphine to patients immediately after surgery was shown to be morphine-sparing but the combination was infra-additive (Marcou 2005 **Level II**, n=90, JS 3; Thevenin 2008 **Level III-1**).

The (+) enantiomer of tramadol is the stronger inhibitor of serotonin reuptake and the (-) enantiomer the more potent inhibitor of noradrenaline reuptake; tramadol is metabolised by CYP2D6 and the resultant active metabolite O-desmethyltramadol (M1) is a more potent mu-opioid receptor agonist than the parent drug (Lee 1993 **NR**). Patients who are poor metabolisers get less analgesic effect from tramadol (Stamer 2003 **Level III-2**) (see also Section 1.7.3).

Coadministration with other medicines that inhibit CYP2D6 may also influence the effectiveness of tramadol. For example, pretreatment with paroxetine in healthy extensive metabolisers reduced the hypoalgesic effect of tramadol in an experimental pain model (Laugesen 2005 **Level II EH**, n=16 [4-way cross over], JS 5). Inhibition of $5HT_3$ receptors by ondansetron also decreased the analgesic effect of tramadol (Arcioni 2002 **Level II**, n=59, JS 5; De Witte 2001 **Level II**, n=40, JS 3), although this may be more a pharmacokinetic interaction (Hammonds 2003 **NR**).

Tramadol's adverse-effect profile is different from other opioids. The risk of respiratory depression is significantly lower at equianalgesic doses (Tarkkila 1997 **Level II**, n=36, JS 4; Tarkkila 1998 **Level II**, n=36, JS 4; Mildh 1999 **Level II EH**, n=8 [cross over], JS 5) and it does not depress the hypoxic ventilatory response (Warren 2000 **Level II EH**, n=20 [cross over], JS 5). However, in a large series of tramadol overdoses (n=525), mainly due to deliberate self-harm or abuse, 3.6% experienced apnoea and required respiratory support or naloxone use (Hassanian-Moghaddam 2013 **Level IV**). The mean time to presentation was 7.7 h (range 1–24 h); the mean dose causing apnoea was 2,125 mg (range 200–4,600 mg), significantly higher than in those not experiencing apnoea (1,383 mg; range 100–6,000 mg). One death in each group was reported. Significant respiratory depression has also been described in a patient with severe renal failure, most likely due to accumulation of the metabolite M1 (Barnung 1997 **CR**).

There is a risk of inducing serotonin toxicity when tramadol is combined with other serotonergic medicines, in particular SSRIs (Nelson 2012 **NR**). However, despite the widespread use of both medicines, there are only very few case reports on this interaction. The interaction might be complex, as SSRIs are often CYP2D6 inhibitors and can thereby increase tramadol concentrations. This might also mean that poor CYP2D6 metabolisers are at an increased risk of this interaction (Nelson 2012 **Level IV**). Furthermore, administration of tramadol to elderly patients in the postoperative period was a risk factor for delirium (Brouquet 2010 **Level IV**).

Tramadol has less effect on gastrointestinal motor function than morphine (Wilder-Smith 1997 **Level II**, n=10 [cross over], JS 5; Wilder-Smith 1999a **Level II**, n=30, JS 5; Wilder-Smith 1999b **Level II**, n=62, JS 5; Lim 2001 **Level II**, n=101, JS 5). Nausea and vomiting are the most common adverse effects and occur at rates similar to morphine (Radbruch 1996 **NR**; Lim 2001 **Level II**, n=101, JS 5), although an increased rate in comparison to a variety of strong opioids (morphine, fentanyl, oxycodone, pethidine) occurs with PCA use (OR 1.52; 95%CI 1.07 to 2.14) (Murphy 2010 **Level I**, 12 RCTs, n=782). The incidence of pruritus was reduced with tramadol (OR 0.43; 95%CI 0.19 to 0.98).

Tramadol did not increase the incidence of seizures compared with other analgesic agents (Jick 1998 **Level III-2**; Gasse 2000 **Level III-2**). Seizures were reported in tramadol intoxication, mainly

due to deliberate self-harm or abuse, with recurrent seizures in 7 and 11.7% of patients (Shadnia 2012 **Level IV**; Hassanian-Moghaddam 2013 **Level IV**). The low rate of recurrence does not justify the prophylactic use of an anticonvulsant after an initial seizure (Shadnia 2012 **Level IV**).

Finally, tramadol has a much lower abuse and misuse potential than conventional opioids, as recently reconfirmed by an expert committee on drug abuse of the German government (Radbruch 2013 **GL**); this is in line with previous findings and tramadol's status as a noncontrolled drug in most countries.

4.1.1.3 Determinants of opioid dose

Interpatient opioid requirements vary greatly (Macintyre 1996 **Level IV**) and opioid doses therefore need to be titrated to suit each patient. Reasons for variation include patient age and gender, genetic differences and psychological factors as well as opioid tolerance (see Section 4.1.4 below).

Patient age

Age, rather than patient weight, appears to be a better determinant of the amount of opioid an adult is likely to require for effective management of acute pain. There is clinical and experimental evidence of a two-fold to four-fold decrease in opioid requirements as patient age increases (Burns 1989 **Level IV**; Macintyre 1996 **Level IV**; Gagliese 2000 **Level IV**; Coulbault 2006 **Level IV**; Gagliese 2008 **Level IV**). The decrease in opioid requirement is not associated with reports of increased pain (Burns 1989 **Level IV**; Macintyre 1996 **Level IV**).

This age-related decrease in opioid requirement appears mainly due to differences in pharmacodynamics or brain penetration rather than systemic pharmacokinetic factors (Scott 1987 **Level IV**; Minto 1997 **Level IV**; Macintyre 2008b **NR**) (see Section 10.2).

Gender

In general, females report more severe pain than males with similar disease processes or in response to experimental-pain stimuli (Hurley 2008 **NR**). This is more complicated than initially thought; in experimental-pain settings, women have lower pressure pain thresholds than men with no difference for cold and ischaemic pain (Racine 2012a **Level IV SR**, 122 studies, n unspecified). Temporal summation, allodynia and secondary hyperalgesia may be more pronounced in women than in men (Racine 2012b **Level IV SR**, 129 studies, n unspecified). In acute pain, there is more a difference in pain perception than pain sensitivity (Ravn 2012 **Level IV**).

Evidence for differences of opioid responses in the acute pain setting varies. Across all studies in acute clinical pain with mu opioids there is no association between gender and opioid response, however with PCA use there is greater analgesic effect in women (ES 0.22; 95%CI 0.02 to 0.42) (Niesters 2010 **Level I**, 25 RCTs, n unspecified). The effect is even more pronounced with morphine PCA (ES 0.36; 95%CI 0.17 to 0.56) and is similar in experimental-pain settings (ES 0.35; 95%CI 0.01 to 0.69). Likely explanations are interactions between oestrogen and opioid receptors (Lee 2013 **NR**).

While response to opioids may differ, both the degree and direction of variation depend on many variables (Dahan 2008a **NR**; Campesi 2012 **NR**). This variation as well as other known and unknown factors involved in the very large interpatient differences in opioid requirements seen clinically, means that gender cannot be used as a basis for opioid-dose alteration and confirms the need to titrate doses to effect for each patient.

Genetics

Genetic variability may also affect a patient's response to opioids (see Section 1.7.3).

Psychological factors

The effect of psychological factors such as anxiety on opioid requirements is contradictory (see Section 1.2). Behavioural and psychological aspects associated with opioid tolerance and addiction are discussed in Sections 10.6 and 10.7.

4.1.1.4 Adverse effects of opioids

Common opioid-related adverse effects are sedation, pruritus, nausea, vomiting, slowing of gastrointestinal function and urinary retention. Meta-analyses have shown that the risk of adverse effects from opioids administered by PCA is similar to the risks from traditional methods of systemic opioid administration, with the exception of pruritus, which is increased in patients using PCA (Hudcova 2006 **Level I** [Cochrane] 55 RCTs, n=3,861).

However, there may be differences in the routine clinical setting (Cashman 2004 **Level IV SR**, 165 studies, n≈20,000; Dolin 2005 **Level IV SR**, 165 studies, n≈20,000). The following incidences (means) were associated with the use of PCA opioids: respiratory depression 1.2–11.5% (using decreased respiratory rate and oxygen desaturation, respectively, as indicators), nausea 32%, vomiting 20.7%, pruritus 13.8% and excessive sedation 5.3%. The incidences reported for IM opioid analgesia were: respiratory depression 0.8–37% (using the same indicators), nausea 17%, vomiting 21.9%, pruritus 3.4% and excessive sedation 5.2%.

Clinically meaningful opioid-related adverse effects are dose-related. There was an increased risk of 0.9% for nausea and 0.3% for vomiting for every 1 mg increase in PCA-morphine consumption after surgery (Marret 2005 **Level I**, 22 RCTs, n=2,307). In a later prospective evaluation of the incidence of nausea and vomiting in elderly surgical inpatients (requiring a length of stay >2 d and no PONV prophylaxis), there was also a direct correlation between increasing opioid dose and the incidence of both nausea and vomiting (Roberts 2005 **Level IV**). In patients after laparoscopic cholecystectomy performed on an ambulatory basis, once a threshold dose was reached (≈10 mg morphine equivalent/d), every further 3–4 mg increase of morphine-equivalent dose/d was associated with one additional meaningful adverse effect or patient-day with such an event (Zhao 2004 **Level II**, n=193, JS 5).

Opioid-related adverse effects in surgical patients were associated with increased length of stay in hospital and total hospital costs; the use of opioid-sparing techniques can be cost-effective (Philip 2002 **NR**; Oderda 2007 **Level III-2**; Barletta 2012 **NR**). In a large cohort study (n=37,031), postsurgical patients experiencing an opioid-related adverse effect had a 55% longer hospital stay, 47% higher costs, 36% increased risk of readmission and 3.4 times higher risk of inpatient mortality (Kessler 2013 **Level III-2**). Similar results were found in the analysis of a large national hospital database (n=319,898) (Oderda 2013 **Level III-2**). Identifying patients at high risk of opioid-related adverse effects using clinical and demographic parameters is possible (Minkowitz 2014b **Level III-3**; Minkowitz 2014a **Level III-2**); identification of such high-risk patients enabled reduction of adverse effects and hospital costs.

Opioid-induced ventilatory impairment

OIVI is a more appropriate term to describe the effects of opioids on ventilation than respiratory depression alone (Macintyre 2011 **NR**). It encompasses the respiratory depression caused by opioids (decreased central CO_2 responsiveness resulting in hypoventilation) and elevated partial pressure of carbon dioxide in arterial blood [$PaCO_2$]) (Boom 2012 **NR**) but also the depressed consciousness (decreased arousal and protection) and the subsequent upper airway obstruction (associated with lower airway motor tone) resulting from excessive opioid use. This combination is the most feared adverse effect of opioids, potentially with fatal consequences.

The most frequently reported risk factors for OIVI were female gender, sleep-disordered breathing, obesity, renal impairment, pulmonary disease and CYP450 enzyme polymorphisms, but patients without such risk factors can also develop OIVI (n=134) (Overdyk 2014 **Level IV**).

OIVI can usually be avoided by careful titration of the dose against effect and careful observation and monitoring. A variety of clinical indicators have been used to indicate OIVI caused by opioids; not all may be appropriate or sensitive.

A number of studies investigating hypoxia in the postoperative period in patients receiving opioids for pain relief have found that measurement of respiratory rate as an indicator of respiratory depression may be of little value and that hypoxaemic episodes often occur in the absence of a low respiratory rate (Catley 1985 **Level IV**; Jones 1990; Wheatley 1990 **Level IV**; Kluger

1992 **Level IV**). As respiratory depression is almost always preceded by sedation, the best early clinical indicator is increasing sedation (Ready 1988 **NR**; Vila 2005 **NR**; Macintyre 2011 **NR**).

Introduction of a numerical pain treatment algorithm in a cancer setting was followed by a review of opioid-related adverse effects. Use of this algorithm, in which opioids were given to patients in order to achieve satisfactory pain scores, resulted in a two-fold increase in the risk of respiratory depression (Vila 2005 **Level III-3**). Importantly, the authors noted that respiratory depression was usually not accompanied by a decrease in respiratory rate. Of the 29 patients who developed respiratory depression (either before or after the introduction of the algorithm), only 3 had a respiratory rates of <12 breaths/min but 27 (94%) had a documented decrease in their level of consciousness (Vila 2005 **Level III-3**). This study highlights the risk of titrating opioids to achieve a desirable pain score without appropriate patient monitoring.

In a review of PCA, case reports of respiratory depression in patients with obstructive sleep apnoea (OSA) were examined (Macintyre 2008a **NR**). It would appear that the development of respiratory depression might have been missed because of an apparent over-reliance on the use of respiratory rate as an indicator of respiratory depression; the significance of excessive sedation was not recognised (see Section 10.4).

In an audit of 700 acute pain patients who received PCA for postoperative pain relief, respiratory depression was defined as a respiratory rate of <10 breaths/min and/or a sedation score of 2 (defined as "asleep but easily roused") or more. Of the 13 patients (1.86%) reported with respiratory depression, 11 had sedation scores of at least 2 and, in contrast to the statements above, all had respiratory rates of <10 breaths/min (Shapiro 2005 **Level IV**).

These studies confirm that assessment of sedation is a more reliable way of detecting opioid-induced respiratory depression, although monitoring respiratory rate is still important.

Assessment of a patient's level of alertness was considered by the American Society of Anesthesiologists (ASA) Task Force on Neuraxial Opioids to be important in the detection of respiratory depression in patients given neuraxial opioids, as well as assessments of adequacy of ventilation and oxygenation (Horlocker 2009 **GL**). However, it was also recommended that a sleeping patient not be woken. In this situation it would be possible for increasing sedation to be missed unless the patient was at least roused. A workshop convened by the Anesthesia Patient Safety Foundation to discuss this issue in response to concerns about the safety of IV PCA, recommended "the use of continuous monitoring of oxygenation (generally pulse oximetry) and ventilation in nonventilated patients" (Weinger 2006-2007 **GL**). This was despite recognising the limitations of currently available monitors and despite the low sensitivity of continuous-pulse oximetry in patients given supplemental oxygen (common in many countries). The lack of agreed principles and evidence-based recommendations for monitoring were also acknowledged in American Society for Pain Management nursing guidelines on monitoring for opioid-induced sedation and respiratory depression (Jarzyna 2011 **GL**).

Oxygen saturation levels may not be a reliable method of detecting respiratory depression in the postoperative setting. In addition to the use of supplemental oxygen, there may be reasons other than opioids for hypoxaemia. For example, when measurement of oxygen saturation was used as an indicator of respiratory depression, the incidence was reported to be 11.5% in patients receiving PCA and 37% in those given IM opioids (Cashman 2004 **Level IV SR**, 165 studies, n≈20,000). However, the same authors showed that patients given IM opioids reported significantly more pain (moderate to severe pain in 67.2% and severe pain in 29.1% compared with 35.8% and 10.4% respectively in PCA patients), suggesting that these patients received much lower doses of opioids (Dolin 2002 **Level IV SR**, 165 studies, n≈20,000).

Increases in $PaCO_2$ are the most reliable way of detecting respiratory depression. Continuous monitoring of transcutaneous CO_2 for 24 h after major abdominal surgery showed that patients given IV PCA morphine had significantly higher CO_2 levels than those receiving epidural local anaesthetic/fentanyl infusions (Kopka 2007 **Level III-2**; McCormack 2008 **Level III-2**).

Alternative monitors include continuous noninvasive respiratory-volume monitoring, which was described as identifying at-risk patients with a significant drop in minute ventilation or

apnoeic/hypopnoeic episodes with high sensitivity (93%) and specificity (86%) (Voscopoulos 2014 **Level IV**).

Pharmacological strategies to reduce OIVI without affecting analgesia, eg by respiratory stimulants, have been investigated (Kimura 2014 **NR**; van der Schier 2014 **NR**).

Cardiac effects

The use of methadone has been linked to the development of prolonged QT interval with a risk of TdP and cardiac arrest (Mujtaba 2013 **NR**). Methadone has this effect due to inhibition of the cardiac-ion channel KCNH226 and the effect is dose-dependent. Most case reports of TdP in patients taking methadone have identified the presence of at least one other risk factor in addition to methadone (Justo 2006 **Level IV**; Fredheim 2008 **NR**). Risk factors include female gender, heart disease, other medicines with effects on the QT interval (eg tricyclic antidepressants [TCAs], antipsychotics, diuretics) or methadone metabolism, congenital or acquired prolonged QT syndromes, liver impairment and hypokalaemia (Fredheim 2008 **NR**; Mujtaba 2013 **NR**).

Of patients under substitution therapy receiving 60–100 mg/d methadone, 23% developed prolonged QT intervals during treatment compared with none of the buprenorphine patients taking 16–32 mg 3 times/wk (Wedam 2007 **Level II**, n=165, JS 5). In the methadone group, the QT interval continued to increase over time, even with stable doses.

There is as yet no consensus regarding the benefits or otherwise of obtaining an electrocardiogram (ECG) in patients prior to starting methadone, although it may be that the threshold for doing so should be lower in patients with other concomitant risk factors, including those receiving higher doses of methadone (Cruciani 2008 **NR**). Overall, guidelines targeting the prevention of death from methadone can only offer weak recommendations due to lack of good data (Chou 2014); a Cochrane review was unable to identify any studies suitable for inclusion (Pani 2013 **Level I** [Cochrane] 0 RCTs).

The use of dextropropoxyphene also carries a risk of TdP (Barkin 2006 **NR**) (see above). Similarly, higher doses of oxycodone were linked to prolonged QT intervals (Fanoe 2009 **Level III-2**).

Nausea and vomiting

Nausea and vomiting is a frequent adverse effect of opioid analgesia in a range of settings. PONV and its prevention have been studied the most extensively; hence the following discussion will focus on this data. PONV is common and related to opioid administration in a dose-dependent manner (Marret 2005 **Level I**, 22 RCTs, n=2,307; Roberts 2005 **Level IV**), although many other more relevant risk factors for PONV have also been identified (Apfel 2012 **Level IV SR**, 22 studies, n=95,154). Opioids are a risk factor for PONV (OR 1.39; 95%CI 1.20 to 1.60) but less so than female gender, history of previous PONV or motion sickness, inhalational anaesthesia and nonsmoking status. The biological mechanisms of PONV have not yet been completely unravelled (Horn 2014 **NR**).

Medicines used as components of multimodal analgesia and that are opioid-sparing may also reduce PONV. Opioid-sparing and a reduction in PONV has been shown with concurrent administration of gabapentin and pregabalin (Tiippana 2007 **Level I** [QUOROM], 22 RCTs, n=1,909; Zhang 2011 **Level I** [QUOROM] 11 RCTs, n=899), nsNSAIDs (Maund 2011 **Level I**, 43 RCTs [PONV], n unspecified), ketamine (Laskowski 2011 **Level I**, 70 RCTs, n=4,701) and lignocaine (Vigneault 2011 **Level I** [PRISMA], 29 RCTs, n=1,754; Sun 2012 **Level I** [PRISMA], 21 RCTs, n=1,108). For gabapentin, there is a specific effect on PONV in trials assessing this as a primary outcome (Guttuso 2014 **Level I**, 6 RCTs, n=773).

Opioid-sparing with no decrease in PONV is reported for paracetamol and coxibs (Maund 2011 **Level I**, 43 RCTs [PONV], n unspecified). However, paracetamol given IV preoperatively and intraoperatively reduces PONV; this effect is associated with improved analgesia, not reduced opioid requirements (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364).

Eight medicines effectively prevent PONV compared with placebo: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and

granisetron (Carlisle 2006 **Level I** [Cochrane], 737 RCTs, n=103,237). The authors conclude that evidence for differences between the medicines was unreliable due to publication bias. Despite limited data to compare adverse effects, droperidol was more sedative and headache more common after ondansetron. .

Scientific fraud by Yoshitaka Fujii has influenced this meta-analysis on the efficacy of antiemetics, in particular the efficacy of granisetron and ramosetron is overestimated by inclusion of 168 fraudulent RCTs by his group (Carlisle 2012 **Level I**, 534 RCTs, n unspecified). Ramosetron remains effective compared to placebo (but less than reported previously) and maintains a statistical, but clinically questionable, advantage over ondansetron (Mihara 2013 **Level I**, 12 RCTs, n=1,372).

The efficacy of various single compounds in reducing incidence of PONV in the first 24 h has been confirmed in updated meta-analyses; dexamethasone 4–5 mg IV (NNT 3.7), 8–10 mg IV (NNT 3.8) (De Oliveira 2013b **Level I** [PRISMA], 60 RCTs, n=6,696); droperidol ≤1 mg IV (NNT 3.5–5 for high-risk patients) (Schaub 2012 **Level I**, 25 RCTs, n=2,957); metoclopramide 10 mg IV (NNT 7.8) (De Oliveira 2012b **Level I** [PRISMA], 30 RCTs, n=3,328); perphenazine (Schnabel 2010 **Level I**, 11 RCTs, n=2,081); $5HT_3$-antagonists ondansetron, granisetron, tropisetron and dolasetron (Tang 2012 **Level I**, 85 RCTs, n=15,269) and TD hyoscine (scopolamine) (Apfel 2010 **Level I**, 25 RCTs, n=3,298).

NK1 receptor antagonists are a new class of antiemetics used in treatment and prophylaxis of PONV (George 2010 **NR**). After craniotomy, fosaprepitant 150 mg IV was significantly more effective than ondansetron 4 mg IV (6 vs 50% vomiting) (Tsutsumi 2014 **Level II**, n=64, JS 5). Oral aprepitant 80 mg reduced PONV for 48 h after gynaecological laparoscopic surgery compared to placebo (Jung 2013 **Level II**, n=120, JS 5) and, added to ondansetron, reduced the rate of postoperative vomiting in bariatric surgery patients for 72 h (Sinha 2014 **Level II**, n=125, JS 5).

Propofol (1 mg/kg) close to the end of surgery reduced PONV significantly compared to placebo (Kim 2014a **Level II**, n=107, JS 4). Caffeine (500 mg IV) was ineffective in preventing PONV and increased rates of nausea (Steinbrook 2013 **Level II**, n=136, JS 3).

Combinations of antiemetics may be more effective than one medicine given alone. Prophylaxis with the combination of a $5HT_3$-receptor antagonist and dexamethasone was associated with lower use of rescue antiemetics than $5HT_3$-receptor antagonist or dexamethasone alone (Kovac 2006 **Level I**, 49 RCTs, n=12,752), also after strabismus surgery in children (Shen 2014 **Level I**, 13 RCTs, n=2,006). Similarly, the combination of droperidol and ondansetron was additive (Chan 2006 **Level II**, n=400, JS 5). Other combinations that were more effective than either medicine given alone were cyclizine and granisteron (Johns 2006 **Level II**, n=960, JS 5), dexamethasone and haloperidol (Chu 2008a **Level II**, n=400, JS 5) and dexamethasone and dolasetron (Rusch 2007 **Level II**, n=242, JS 5). The addition of metoclopramide to dexamethasone also led to better PONV prophylaxis but, compared with dexamethasone 8 mg alone, only if doses of 25 mg and 50 mg metoclopramide were used; not 10 mg (Wallenborn 2006 **Level II**, n=3,140, JS 4).

Droperidol and, to a lesser extent, ondansetron may lead to prolonged QT intervals. Concerns about the potential for serious cardiac arrhythmias secondary to QT prolongation associated with administration of droperidol led to a “black box” warning by the USA FDA in 2001. Following this there has been a significant reduction in the use of this medicine, even though the warning was felt by many to be unwarranted (Habib 2008b **NR**). Mild QT prolongation can occur with anaesthesia and surgery. Saline and 0.625 and 1.25 mg IV droperidol were associated with similar QT prolongation in the postoperative period (White 2005 **Level II**, n=120, JS 5). Similarly, 1.25 mg droperidol did not prolong QT interval (Toyoda 2013 **Level II**, n=72, JS 3). A large review (Nuttall 2007 **Level III-3**) of surgical patients in the periods 3 y before (n=139,932) and 3 y after (n=151,256) the FDA black box warning merged anaesthesia database information with information from ECG and other databases as well as patients’ case notes, and recorded all patients who had documented prolonged QT intervals, TdP or death within 48 h of their surgery. Despite a reduction in the use of droperidol from 12–0% of patients following the warning, there was no difference in the incidence of QT prolongation, ventricular tachycardia, or death within 48 h of surgery and no clearly identified case of TdP

related to use of droperidol (Nuttall 2007 **Level III-3**). The authors concluded that for low-dose droperidol, the black box warning was "excessive and unnecessary". The scientific basis of the decision in favour of a black box warning has been questioned as a range of data show that the incidence of QT prolongation and TdP development is similar for low-dose droperidol and other compounds used to treat PONV (Halloran 2010 **NR**). The authors of guidelines for the management of PONV also express concerns about the FDA caution and state "due to the 2001 black box warning, droperidol is not the first choice for PONV prophylaxis in many countries" (Gan 2014).

Haloperidol has also been associated with QT prolongation and TdP (Habib 2008a **NR**). Using data from studies published up until 1988, a meta-analysis showed that haloperidol was also an effective antiemetic (Buttner 2004 **Level I**, 23 RCTs, n=1,468). Subsequent studies have confirmed its effectiveness compared with placebo (Aouad 2007 **Level II**, n=93, JS 4), ondansetron (no differences in efficacy, adverse effects or QT intervals) (Aouad 2007 **Level II**, n=93, JS 4; Lee 2007b **Level II**, n=90, JS 5; Rosow 2008 **Level II**, n=244, JS 2) and droperidol (equally effective) (Wang 2008b **Level II**, n=150, JS 5). Haloperidol/ondansetron was more effective than ondansetron alone (Grecu 2008 **Level II**, n=268, JS 3) and haloperidol/dexamethasone was also more effective than either medicine given alone (Chu 2008a **Level II**, n=400, JS 5; Wang 2012 **Level II**, n=135, JS 3), again with no difference in adverse effects or QT intervals. Compared with droperidol, the only advantage of haloperidol may be "that there is no black box warning" (Ludwin 2008 **NR**).

Dolasetron (IV and oral formulations) is contraindicated by the Canadian authorities for any therapeutic use in children and adolescents aged <18 y and the prevention or treatment of PONV in adults because of the risk of QT prolongation (Health Canada 2006). This age restriction is not limited to Canada but applies in a number of other countries including the UK. The effect of therapeutic doses of dolasetron (and ondansetron) on QT prolongation is, however, minimal (6% from baseline) (n=1,429) (Obal 2014 **Level III-3**); a case of prolonged QT interval has been reported after overdose (Rochford 2007 **CR**).

Acupuncture at the PC6 point has a beneficial effect on early vomiting (0–6 h) and nausea (0–24 h) (Cheong 2013 **Level I** [PRISMA], 30 RCTs, n=2,534). PC6 acupressure, PC6 electroacupoint stimulation, stimulation of other acupoints with or without PC6 reduced the number of cases of PONV for the first 24 h postoperatively. The study quality was low for studies of PC6 combined with other acupoints and for other acupoints. Acupuncture/acupressure is the only nonpharmacological intervention included in the PONV management guideline developed by Society for Ambulatory Anesthesiology, endorsed by ANZCA (Gan 2014 **GL**).

Aromatherapy with isopropyl alcohol is more effective than saline in reducing PONV (assessed by reduced rescue antiemetic requirements) but is less effective than standard antiemetics (Hines 2012 **Level I** [Cochrane], 9 RCTs/CCTs, n=402).

Supplemental oxygen (Fio2 80%) in the postoperative period does not reduce PONV (Orhan-Sungur 2008 **Level I**, 10 RCTs, n=1,729) but high inspired oxygen concentrations intraoperatively reduce PONV in patients receiving inhalational anaesthetics without prophylactic antiemetics (Hovaguimian 2013 **Level I**, 22 RCTs, n=7,001).

Guidelines on the prevention and management of PONV have been revised on the basis of the latest evidence (Gan 2014 **GL**).

Impairment of gastrointestinal motility

Opioids are well described as inducing constipation with chronic use (Ahmedzai 2006 **NR**). Opioids impair return of bowel function after surgery (Barletta 2012 **NR**). A daily dose of hydromorphone IV >2 mg was the most obvious risk factor for postoperative ileus (Barletta 2011 **Level IV**). Other risk factors were longer IV opioid use and postoperative ileus was a risk factor for prolonged hospital stay.

The peripheral-acting opioid antagonists alvimopan and methylnaltrexone are effective in reversing opioid-induced slowing of gastrointestinal transit time and constipation and alvimopan is an effective treatment for postoperative ileus (McNicol 2008 **Level I** [QUOROM], 22 RCTs, n=2,358); insufficient evidence exists about the efficacy or safety of naloxone

or nalbuphine. The efficacy of alvimopan has been confirmed in subsequent studies summarised in a review (Kraft 2010 **NR**). After radical cystectomy, alvimopan resulted in faster gastrointestinal recovery, shorter hospital stay and reduced incidence of postoperative ileus (7 vs 26%) with reduced resulting morbidity (8.4 vs 29.1%) without increased adverse effects (Lee 2014a **Level II**, n=280, JS 3). Naloxegol is another oral, peripherally acting, mu-receptor antagonist that results in improved bowel function without impairing opioid analgesia (Chey 2014 **Level II**, combined analysis of 2 identical RCTs, n=1,352).

A combined formulation of controlled-release (CR) oxycodone and naloxone has been studied. Compared with CR oxycodone alone in patients with chronic nonmalignant pain, the combination formulation resulted in similar analgesic efficacy but less bowel dysfunction (Lowenstein 2010 **Level II** [pooled analysis of 2 RCTs], n=578, JS 5). It has been suggested that these benefits were transferable to acute pain settings (Kuusniemi 2012 **NR**). This was not confirmed after laparoscopic hysterectomy where oxycodone/naloxone CR had no beneficial effect on constipation or other opioid adverse effects compared to oxycodone CR (Comelon 2013 **Level II**, n=85, JS 5). IV administration of the crushed combination resulted in reduced drug liking and other subjective effects (Colucci 2014 **Level II EH**, n=24, JS 3).

Urinary retention

Opioids cause urinary retention due to presumed central and peripheral mechanisms. Opioid antagonists reverse this effect; naloxone reversed opioid-induced urinary retention in 100% of patients, while the peripheral opioid antagonist methylnaltrexone IV was effective in 42% of study participants (Rosow 2007 **Level III-1**). These data suggest that at least part of the bladder dysfunction caused by opioids is peripherally mediated.

Premedication with gabapentin reduces urinary retention caused by opioids (NNT 7) (Tiippana 2007 **Level I** [QUOROM], 22 RCTs, n=1,909). This effect is most likely related to the opioid-sparing effect of gabapentin.

Pruritus

The mechanism of opioid-induced pruritus, which is particularly common after neuraxial opioid administration, is not fully understood but central mu-opioid receptor-mediated mechanisms are thought to be the primary cause (Ganesh 2007 **NR**). See also Section 4.1.2.

Naloxone, naltrexone, nalbuphine and droperidol are effective in the treatment of opioid-induced pruritus, although minimum effective doses remain unknown (Kjellberg 2001 **Level I**, 22 RCTs, n=1,477 patients); doses >2 mcg/kg/h of naloxone are more likely to lead to reversal of analgesic effects. Low-dose continuous naloxone (0.25–1 mcg/kg/h) has the best evidence (Miller 2011 **NR**).

Cognitive function and confusion

While opioids can be the cause of cognitive dysfunction, confusion and delirium, it is surprising that, after cardiac surgery, morphine 5 mg IM was superior to haloperidol 5 mg IM in treating delirium (Atalan 2013 **Level II**, n=53, JS 2). This suggests that undertreated pain is a relevant consideration. Similarly, in elderly patients after hip fracture repair, opioids were not an important predictor of postoperative delirium (Sieber 2011 **Level IV**).

The risk of delirium and/or changes in cognitive function has been compared in patients receiving different PCA opioids. There was no statistically significant difference in the rates of confusion between morphine and fentanyl (14.3 vs 14.3%) but there was less depression of cognitive function with fentanyl (Herrick 1996 **Level II**, n=96, JS 2). No differences in cognitive function were reported in patients receiving tramadol compared with morphine (Silvasti 2000 **Level II**, n=60, JS 4) or fentanyl (Ng 2006 **Level II**, n=30, JS 5) but cognition has been found to be poorer with hydromorphone when compared with morphine (Rapp 1996 **Level II**, n=61, JS 4). Tramadol has been identified as a risk factor for postoperative delirium in the elderly following abdominal surgery (Brouquet 2010 **Level IV**).

Pethidine use postoperatively was associated with an increased risk of delirium in the postoperative period in comparison to other opioids (Fong 2006 **Level III-2 SR**, 3 studies, n=877).

Tolerance and hyperalgesia

In the absence of disease progression, a decrease in the effectiveness of opioid analgesia has traditionally been attributed to opioid tolerance. It is now known that administration of opioids can lead to both opioid-tolerance (a desensitisation of antinociceptive pathways to opioids) and, paradoxically, to OIH (a sensitisation of pronociceptive pathways leading to pain hypersensitivity) and that both these phenomena can significantly reduce the analgesic effect of opioids (Lee 2011 **NR**; Low 2012 **NR**). The mechanisms underlying the development of tolerance and OIH are still not fully understood but, as with neuropathic pain, are thought to include activation of the glutaminergic system via the NMDA receptor, as well as other transmitter and receptor systems (Mao 2008 **NR**; Lee 2011 **NR**).

It may be useful here to distinguish "pharmacological tolerance" (ie tolerance, as defined in Section 10.6.1 "the predictable and physiological decrease in the effect of a drug over time") and "apparent tolerance", where both tolerance and OIH contribute to a decrease in the effectiveness of opioids (Chang 2007 **NR**; Mao 2008 **NR**). The clinical significance of this mix, and the relevant contribution of pharmacological tolerance and OIH to apparent tolerance in any particular patient is difficult, if not impossible, to determine (Low 2012 **NR**). However, inadequate pain relief because of pharmacological tolerance may improve with opioid dose escalation, while improvements in analgesia in the presence of OIH may follow a reduction in opioid dose (Chang 2007 **NR**; Mao 2008 **NR**; Chu 2008b **NR**).

A formal diagnosis of hyperalgesia may require QST, that is, serial assessment of the responses to varying intensities of a nociceptive stimulus in order to determine pain thresholds (Mitra 2008 **NR**). QST before and after starting chronic opioid therapy may assist in the differentiation between OIH and pharmacological tolerance (Chu 2008b **NR**) but this is unlikely to become common practice in the acute pain setting. Furthermore, measures of QST were of limited usefulness to identify OIH; possibly the most useful measure is heat-pain sensitivity (Katz 2015 **Level IV SR**, 14 studies, n unspecified).

It is probable that the degree of OIH varies between opioids. Remifentanil in particular (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494) but also morphine, in high doses, may be more likely to result in OIH than some other opioids; experimental data and a very limited number of case reports have shown an improvement when morphine doses were reduced or a change to methadone, fentanyl or sufentanil was made (Angst 2006 **NR**). Similarly, it appears that opioids differ in their ability to induce tolerance. Medicines such as methadone, fentanyl and sufentanil promote receptor internalisation and thereby receptor recycling; in contrast, the activation of opioid receptors by morphine leads to little or no receptor internalisation and thereby increased risk of development of tolerance (Joo 2007 **NR**). The difference between opioids is one reason why opioid-rotation may be a useful strategy in the clinical setting in attempts to improve pain relief (see Section 10.6.3).

In addition to the many animal studies showing that opioid administration can lead to OIH (Angst 2006 **NR**), human studies have also investigated changes in pain sensitivity following long-term opioid use and reported increases in sensitivity to certain pain stimuli.

Patients taking methadone as part of a drug-dependence treatment program have been shown to have an increased sensitivity to cold pressor pain stimuli (Compton 2000 **Level IV**; Doverty 2001 **Level III-2**; Athanasos 2006 **Level III-2**). Similarly, pain sensitivity to cold pressor but not heat stimuli was noted in patients 1 mth after starting oral morphine therapy (Chu 2006 **Level III-2**) and to cold pressor but not electrical-pain stimuli in patients with chronic noncancer pain taking either methadone or morphine (Hay 2009 **Level III-2**). Similar degrees of hyperalgesia occurred in heroin users and patients in buprenorphine- and methadone-substitution programs (Compton 2012 **Level III-1**). Methadone-maintained subjects were shown to have a significant tolerance to remifentanil given by short-duration infusion, suggesting that opioid-tolerant patients may require significantly higher doses for the treatment of acute pain compared with opioid-naïve patients; dose-dependent increases in cold pressor tolerance were found (Hay 2009 **Level III-2**).

Severity of acute pain following a single subcutaneous (SC) injection of lignocaine was compared in patients taking opioids for chronic pain and opioid-naïve controls; pain and

unpleasantness scores were higher in those patients taking opioids and correlated with opioid dose and duration of treatment (Cohen 2008 **Level III-2**).

In the setting of postoperative pain, high intraoperative doses of opioids resulted in higher postoperative pain intensity than controls at 1 h (MD 9.4/100; 95%CI 4.4 to 14.5), at 4 h (MD 7.1/100; 95%CI 2.8 to 11.3) and at 24 h (MD 3/100; 95%CI 0.4 to 5.6) and higher postoperative morphine use over 24 h (SMD 0.7; 95%CI 0.37 to 1.02) (Fletcher 2014 **Level I** [PRISMA], 27 RCTs, n=1,494). These results are mainly influenced by remifentanil due to limited data with other opioids. The ability of intraoperative remifentanil specifically to induce acute opioid tolerance and OIH has been reviewed (Kim 2014b **NR**). It is not yet clear whether this "apparent acute tolerance" is due to pharmacological tolerance or OIH (Low 2012 **NR**).

These effects of remifentanil may be dose-dependent but were also ameliorated by propofol anaesthesia vs sevoflurane anaesthesia (Shin 2010 **Level II**, n=214, JS 5). NMDA-receptor antagonists (mainly ketamine but also magnesium and amantadine) reduce the development of these effects of remifentanil (Wu 2015 **Level I** [QUOROM], 14 RCTs, n=729); this assessment is based on reduced postoperative pain scores and opioid requirements and increased time to first analgesic request and satisfaction scores. These results negate a preceding less rigorous meta-analysis (Liu 2012b **Level I**, 14 RCTs, n=623). In an experimental setting, propranolol infusion reduced the size of area of secondary hyperalgesia induced by remifentanil to being not significantly different from control (Chu 2012 **Level II EH**, n=10 [cross over], JS 4). In animal experiments, the effects of gabapentin and ketamine on fentanyl-induced hyperalgesia were supra-additive (Van Elstraete 2011 **BS**).

There are case reports of patients with cancer and chronic noncancer pain and taking high doses of opioid who developed OIH and whose pain relief improved following reduction of their opioid dose or after a change was made to another opioid (Angst 2006 **NR**; Chu 2008b **NR**); however there have been no similar reports from an acute pain setting.

The clinical relevance of the phenomenon of OIH remains under discussion (Tompkins 2011 **NR**). (See also Section 10.7.1.)

Tolerance to adverse effects of opioids

Tolerance to the adverse effects of opioids also occurs; tolerance to sedation, cognitive effects, nausea and respiratory depression can occur reasonably rapidly but there is little, if any, change in miosis or constipation (Chang 2007 **NR**).

Key messages

1. Dextropropoxyphene has low analgesic efficacy (**U**) (**Level I** [Cochrane Review]).
2. Tramadol is an effective treatment for neuropathic pain (**U**) (**Level I** [Cochrane Review]).
3. Droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron are effective in the prevention of postoperative nausea and vomiting (**S**) (**Level I** [Cochrane Review]).
4. PC6 acupuncture, PC6 acupressure and PC6 electroacupoint stimulation reduce postoperative nausea and vomiting (**N**) (**Level I** [PRISMA]).
5. Opioids in high doses, in particular remifentanil, can induce hyperalgesia and/or acute tolerance (**S**) (**Level I** [PRISMA]).
6. Paracetamol given intravenously preoperatively and intraoperatively reduces postoperative nausea and vomiting; this effect is associated with improved analgesia, not reduced opioid requirements (**N**) (**Level I** [PRISMA]).
7. Alvimopan, methylnaltrexone (**S**) (**Level I** [QUOROM]) and naloxegol (**N**) (**Level II**) reduce opioid-induced slowing of gastrointestinal transit time and constipation; alvimopan is an effective treatment for postoperative ileus.
8. NMDA-receptor antagonists reverse the acute tolerance and/or hyperalgesia induced by remifentanil (**N**) (**Level I** [QUOROM]).

9. Haloperidol, perphenazine and transdermal scopolamine are effective in the prevention of postoperative nausea and vomiting (**N**) (**Level I**).
10. The incidence of clinically meaningful adverse effects (nausea, vomiting) of opioids is dose-related (**S**) (**Level I**).
11. Gabapentin, pregabalin, nonselective NSAIDs, systemic lignocaine and ketamine are opioid-sparing medications and reduce opioid-related adverse effects (**S**) (**Level I**).
12. Paired combinations of $5HT_3$ antagonist, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**U**) (**Level I**).
13. Naloxone, naltrexone, nalbuphine and droperidol are effective treatments for opioid-induced pruritus (**U**) (**Level I**).
14. Opioids administered by PCA, in particular morphine, show higher analgesic efficacy in females than in males (**N**) (**Level I**).
15. Tapentadol has similar efficacy to opioids with a reduced rate of gastrointestinal adverse effects (nausea, vomiting, constipation) (**N**) (**Level I**).
16. Neurokinin-1 receptor antagonists (fosaprepitant, aprepitant) are effective in the prevention of postoperative nausea and vomiting (**N**) (**Level II**).
17. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
18. Pethidine is not superior to morphine or hydromorphone in treatment of pain of renal colic (**S**) (**Level II**).
19. Morphine-6-glucuronide is an effective analgesic (**U**) (**Level II**).
20. In the management of acute pain, one opioid is not superior to others but some opioids are better in some patients (**U**) (**Level II**).
21. High doses of methadone can lead to prolonged QT interval (**U**) (**Level II**).
22. Opioid antagonists are effective treatments for opioid-induced urinary retention (**N**) (**Level III-1**).
23. Pethidine use was associated with an increased risk of delirium in the postoperative period compared to other opioids (**N**) (**Level III-2 SR**)
24. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**U**) (**Level III-2**).
25. Tapentadol has lower rates of abuse and doctor shopping than oxycodone (**N**) (**Level III-2**).
26. Opioid-related adverse effects in the postoperative period result in increased length of hospital stay, costs and rates of readmission (**N**) (**Level III-2**).
27. Assessment of sedation is a more reliable way of detecting early opioid-induced ventilatory impairment than a decreased respiratory rate (**U**) (**Level III-3**).
28. The evidence for significant QT prolongation and risk of cardiac arrhythmias following low-dose droperidol, haloperidol and dolasetron is weak (**N**) (**Level III-3**).
29. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).
30. Impaired renal function and the oral route of administration result in higher levels of the morphine metabolites morphine-3-glucuronide and morphine-6-glucuronide with increased risk of sedation and respiratory depression (**S**) (**Level IV**).
31. CYP2D6 ultrarapid metabolisers are at increased risk of codeine toxicity (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Opioid-induced ventilatory impairment is a more appropriate term to describe the effects of opioids on ventilation as it encompasses the central respiratory depression caused by opioids and also the depressed consciousness and the subsequent upper airway obstruction resulting from excessive opioid use (**N**).
- ☑ The use of pethidine and dextropropoxyphene should be discouraged in favour of other opioids (**S**).

4.1.2 Neuraxial opioids

Opioid receptors were described in the spinal cord of the rat in 1976 (Pert 1976 **BS**) and the same year a potent analgesic effect of directly applied IT morphine was reported in these animals (Yaksh 1976 **BS**). Opioid analgesia is spinally mediated via presynaptic and postsynaptic receptors in the substantia gelatinosa in the dorsal horn (Yaksh 1981 **BS**). Spinal opioid receptors are 70% mu, 24% delta and 6% kappa (Treman 2001 **NR**); with 70% of all mu and delta receptors being presynaptic (predominantly small primary afferents) and commonly colocated, with kappa being more commonly postsynaptic. Opioid-mediated antinociception may be further augmented by descending inhibition from mu-opioid-receptor activation in the periaqueductal area of the brain, which may be potentiated by neuraxial opioids. In addition to this, a local anaesthetic action has been described for pethidine (meperidine) that may contribute to the clinical effect when administered IT (Jaffe 1996 **BS**). The first clinical use of IT morphine was for analgesia in cancer patients (Wang 1979 **Level IV**).

Neuraxial opioids may cause respiratory depression, sedation, nausea, vomiting, pruritus, urinary retention and decreased gastrointestinal motility. Depending on type and dose of the opioid, a combination of spinal and systemic (supraspinal) mechanisms may be responsible for these adverse effects. Many of these effects are more frequent with morphine and are to some extent dose-related (Dahl 1999 **Level I**, 15 RCTs, n=535; Cole 2000 **Level II**, n=38, JS 4). Late onset respiratory depression (>2 h after administration), which is believed to be a result of the cephalad spread of opioids to the medulla within the cerebrospinal fluid (CSF), is also seen more commonly with hydrophilic opioids such as morphine and hydromorphone and appears to match the time taken for trigeminal analgesia, which is approximately 6–12 h after administration (Cousins 1984 **NR**; Saltan 2011 **NR**; Bujedo 2014 **NR**). The incidence of respiratory depression with the lipophilic opioid fentanyl given via the epidural route has been reported to be 1.4% (with 0.4% requiring naloxone) (Scott 1995a **Level IV**) but, given IT, fentanyl or sufentanil are likely to be lower risk than the hydrophilic opioids morphine and hydromorphone (Horlocker 2009 **GL**). Risk factors for respiratory depression include higher doses (>300 mcg morphine), increasing age, obesity and coadministration of systemic opioids or sedatives (Saltan 2011 **NR**). Although dose-response analyses are not always clear, it is suggested that neuraxial opioids have a ceiling effect for analgesia, with optimal single-injection morphine doses (balancing risk-benefit) of 50–150 mcg IT and 2.5–3.75 mg via epidural route (Saltan 2011 **NR**).

Tolerance to the development of spinal opioid analgesia can develop rapidly. Low-dose mu and delta opioid antagonists can prevent tolerance development and restore morphine IT analgesia in animals (Abul-Husn 2007 **BS**). In an animal model, bolus doses increased nociceptive thresholds for 3–5 h followed by delayed hyperalgesia with a lower threshold lasting 1–2 d, an effect prevented by coadministration of ketamine (Van Elstraete 2005 **BS**). The clinical implications of single-dose neuraxial opioid administration in regard to the potential development of OIH or tolerance is uncertain. IT fentanyl added to bupivacaine and morphine for Caesarean delivery was associated with higher pain scores (the authors suggesting acute tolerance) but no difference in 24 h morphine consumption (Carvalho 2012 **Level II**, n=40, JS 5). Adding fentanyl to IT local anaesthesia for Caesarean delivery improved anaesthesia conditions but was associated with a 60% increase in morphine consumption between 6 and 24 h (Cooper 1997 **Level II**, n=60, JS 2). IT sufentanil was associated with wound hyperalgesia

(at 48 h), with a preventive effect demonstrated by addition of 150 mcg IT clonidine (Lavand'homme 2008a **Level II**, n=96, JS 5).

4.1.2.1 Intrathecal opioids

The lipid solubility of opioids largely determines the speed of onset and duration of IT analgesia; hydrophilic medicines (eg morphine) have a slower onset of action and longer half-lives in CSF with greater dorsal horn bioavailability and greater cephalad migration compared with lipophilic opioids (eg fentanyl) (Bernards 2003 **NR**; Bujedo 2014 **NR**).

Safety studies and widespread clinical experience with morphine, fentanyl and sufentanil have shown no neurotoxicity or behavioural changes at normal clinical IT doses (Hodgson 1999 **NR**). Other opioid agonists or partial agonists do not have animal or human safety data. Tramadol (10, 25 mg) administered IT with bupivacaine produces similar extension of spinal analgesia and prolonged postoperative analgesia compared to comparative doses of fentanyl (10, 25 mcg) for Caesarean delivery (Subedi 2013 **Level II**, n=80, JS 5) and appendectomy (Afolayan 2014 **Level III-1**).

Early clinical studies used very high IT morphine doses (ie ≥500 mcg). However adequate postoperative analgesia with fewer adverse effects may be obtained with significantly less morphine; although at lower doses there is not a clear dose-response relationship for some adverse effects or pain relief (Meylan 2009 **Level I**, 27 RCTs, n=1,205). Another meta-analysis comparing IT morphine doses <300 mcg, ≥300 mcg and placebo reported a greater risk of respiratory depression and of nausea and vomiting with the higher but not lower doses of morphine, while the incidence of pruritus was increased for all doses (Gehling 2009 **Level I,** 28 RCTs, n=1,314). Low doses of IT morphine are effective in prolonging local anaesthetic block or reducing the dose of local anaesthetic required for spinal anaesthesia with reduction in adverse effects and improved recovery (Popping 2012 **Level I** [PRISMA], 55 RCTs; n=3,338; Popping 2013 **Level I** [PRISMA], 28 RCTs; n=1,393); in combination with bupivacaine, IT morphine was associated with more respiratory depression than IT fentanyl (3.4 vs 0.4%).

When combined with low-dose bupivacaine for Caesarean delivery, 100 mcg IT morphine produced analgesia comparable with doses as high as 400 mcg, with significantly less pruritus (Girgin 2008 **Level II**, n=100, JS 4). A single dose of morphine (100 mcg) added to a spinal anaesthetic for Caesarean delivery prolonged the time to first postoperative analgesic administration resulting in at least 11 h of effective analgesia (Dahl 1999 **Level I**, 15 RCTs, n=535). Adverse effects included pruritus (43%), nausea (10%) and vomiting (12%). The rate of respiratory depression was low (see below). Sufentanil (2 RCTs) and fentanyl (8 RCTs) showed no analgesic benefit. No differences in pain reported or analgesia use was detected when comparing 100 mcg to 50 mcg IT morphine for Caesarean delivery, although pruritus was more common in the higher-dose group (Carvalho 2013 **Level II**, n=130, JS 4).

IT morphine added to bupivacaine for postoperative analgesia following abdominal hysterectomy reduced IV PCA morphine consumption compared to placebo, with no benefit of 300 mcg compared to 200 mcg (Hein 2012 **Level II**, n=144, JS 5).

The addition of 10 mcg sufentanil to 400 mcg IT morphine did not potentiate postoperative analgesia or reduce intraoperative opioid requirements in patients undergoing major colorectal surgery (Culebras 2007 **Level II**, n=80, JS 5). The addition of IT fentanyl to low-dose spinal bupivacaine for anorectal surgery resulted in more pruritus but lower mean recovery and discharge times, with fewer analgesic requests in the fentanyl group (Gurbet 2008 **Level II**, n=40, JS 3). IT sufentanil provided shorter postoperative analgesia (mean 6.3 h) than IT morphine (mean 19.5 h) with no difference in adverse effects (Karaman 2006 **Level II**, n=54, JS4). In another comparison of IT morphine (100 mcg) and IT pethidine (10 mg) for analgesia following Caesarean delivery in a nonblinded study, patients receiving morphine had longer analgesia and fewer intraoperative adverse effects than the pethidine group but experienced more pruritus (Kumar 2007 **Level II**, n=60, JS 2). Pethidine 25 mg added to lignocaine with adrenaline spinal anaesthesia had quicker onset with higher sensory block and more prolonged time to significant pain (≥4/10, 9.6 h) compared to fentanyl 25 mcg (6.3 h) or placebo (2.1 h) (Farzi 2014 **Level II**, n=195, JS 5).

For more information on effectiveness and adverse effects related to the use of IT opioids see Section 5.7.

4.1.2.2 Epidural opioids

The behaviour of epidural opioids is also governed largely by their lipid solubility. The greater sequestration of lipid soluble opioids into epidural fat and slow rerelease back into the epidural space means that elimination from the epidural space is prolonged, resulting in relatively smaller fractions of medicine reaching the CSF (Bernards 2003 **NR**). Lipophilic opioids (eg fentanyl) have a faster onset but shorter duration of action compared with hydrophilic opioids (eg morphine) (de Leon-Casasola 1996 **NR**; Bernards 2004 **NR**; Bujedo 2014 **NR**).

A meta-analysis of randomised studies involving epidural opioids, mostly in combination with local anaesthetics, found no differences in VAS pain scores at any time after surgery between opioids, although there was a higher rate of nausea and vomiting (OR 1.95; 95%CI 1.14 to 3.18) with morphine compared to fentanyl (Youssef 2014 **Level I** [PRISMA], 24 RCTs, n=1,513). No studies directly compare epidural morphine and fentanyl alone for postoperative analgesia.

Morphine is the least lipid soluble of the opioids administered epidurally; it has the slowest onset and offset of action (Cousins 1984 **NR**) and the highest bioavailability in the spinal cord after epidural administration (Bernards 2004 **NR**). As morphine has a prolonged analgesic effect, it can be given by intermittent bolus dose or infusion; the risk of respiratory depression may be higher and analgesia less effective with bolus dose regimens (de Leon-Casasola 1996 **NR**). The low lipid solubility makes level of administration of epidural morphine not a relevant factor; eg after blunt chest wall trauma there was no difference in any outcome between thoracic and lumbar epidural morphine administration (Hakim 2012 **Level II**, n=55, JS 3).

The evidence that epidural fentanyl acts via a spinal rather than systemic effect is conflicting and it has been suggested that any benefit when comparing epidural with systemic fentanyl alone is marginal (Wheatley 2001 **NR**; Bernards 2004 **NR**). However, the conflicting results may be due to differing techniques of administration. A lumbar epidural infusion of fentanyl appears to produce analgesia by uptake into the systemic circulation, whereas a bolus dose of fentanyl produces analgesia by a selective spinal mechanism (Ginosar 2003 **Level IV**). Thoracic epidural administration does appear to produce greater spinal analgesia, an effect more pronounced with coadministration with adrenaline, which provides a supra-additive effect possibly via both pharmacokinetic (via vasoconstriction, increasing amount of epidural fentanyl available to spinal cord site of action) and pharmacodynamic (via apha-2 adrenoceptor antinociceptive) mechanisms (Niemi 2013 **NR**). Less intraoperative fentanyl is required when administered via a thoracic epidural catheter compared to IV administration for colon surgery, with longer time to first postoperative analgesia request (Sadurni 2013 **Level II**, n=30, JS 4). There is no evidence of benefit of epidural vs systemic administration of alfentanil or sufentanil (Bernards 2004 **NR**).

Pethidine is effective when administered epidurally by bolus dose, continuous infusion and by patient-controlled epidural analgesia (PCEA). It is more lipid soluble than morphine (but less than fentanyl and its analogues); thus its onset and offset of epidural analgesic action is more rapid than morphine (Ngan Kee 1998 **Level IV**). The analgesic effect of smaller doses appears to be spinally mediated but systemic effects are likely after larger doses; in smaller doses it is not known whether the local anaesthetic properties of pethidine contribute significantly to pain relief (Ngan Kee 1998 **Level IV**). Epidural pethidine has been used predominantly in the obstetric setting. After Caesarean delivery epidural pethidine resulted in better pain relief and less sedation than IV pethidine (Paech 1994 **Level II**, n=45, JS 5) but inferior analgesia compared with IT morphine, albeit with less pruritus, nausea and drowsiness (Paech 2000 **Level II**, n=144, JS 5).

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to MAM and morphine. Diamorphine and MAM are more lipid soluble than morphine and penetrate the CNS more rapidly, although it is MAM and morphine that are thought to be responsible for the analgesic effects of diamorphine (Miyoshi 2001). Epidural administration of diamorphine is common in the UK and is effective whether administered by intermittent bolus dose or infusion (McLeod 2005 **Level II**, n=62, JS 5).

The quality of epidural analgesia with hydromorphone is similar to morphine (Chaplan 1992 **Level II**, n=55, JS 5). In a comparison of epidural and IV hydromorphone, patients required twice as much IV hydromorphone to obtain the same degree of analgesia (Liu 1995 **Level II**, n=16, JS 3).

Extended-release epidural morphine

An extended-release (ER) suspension of morphine has been developed for epidural use (Depodur™) consisting of morphine molecules suspended in liposome complexes (lipofoam). ER epidural morphine (EREM) has been shown to be effective compared with placebo after hip arthroplasty (Viscusi 2005 **Level II**, n=200, JS 5; Martin 2006 **Level II**, n=126, JS 5) and, using doses of ≥10 mg, to lead to better pain relief compared with standard epidural morphine (4 or 5 mg) and a reduction in the need for supplemental analgesics up to 48 h after hip arthroplasty (Viscusi 2006 **Level III-1**), lower abdominal surgery (Gambling 2005 **Level II**, n=541, JS 4) and Caesarean delivery (Carvalho 2005 **Level II**, n=79, JS 3; Carvalho 2007 **Level II**, n=70, JS 5). A pooled analysis of six clinical studies described consistent prolonged pharmacokinetics when compared to immediate-release (IR) morphine preparation, with 25% higher peak plasma concentrations in women, mainly explained by differences in body weight (Viscusi 2009 **PK**).

EREM has provided superior analgesia compared to continuous femoral nerve block (FNB) after total knee arthroplasty; however, only at rest at 24 h (Johnson 2011 **Level II**, n=65, JS 3). There were no differences in functional outcomes and adverse effects except for more pruritus with EREM but patients reported greater satisfaction with EREM. In two patients, EREM was used successfully after multiple rib fractures (Ford 2012 **Level IV**). After lumbar spinal surgery, EREM provided similar analgesia with fewer adverse effects than epidural morphine (Vineyard 2014 **Level II**, n=60, JS 3).

Respiratory depression is more likely with EREM than IV PCA opioids (OR 5.74; 95%CI 1.08 to 30.5) (Sumida 2009 **Level I**, 3 RCTs, n=464). It has been recommended that the liposome preparation of Depodur® not be administered while local anaesthetics are present in the epidural space as this may cause early release of the morphine (Viscusi 2009 **PK**). When Depodur® was administered within 3–15 min of a 3 mL test dose of 1.5% lignocaine with adrenaline, higher maximum serum concentration (C_{max}) values for morphine were reported compared with C_{max} values when no lignocaine was administered; there was no difference in morphine C_{max} if the interval was >30 min. The C_{max} of morphine was unchanged when Depodur® doses were given 15, 30 and 60 min after an anaesthetic dose of epidural bupivacaine (20 mL of 0.25%) (Gambling 2009 **PK**) although, in a later study, peak plasma morphine concentration was increased when administered 1 h post a high volume anaesthetic dose (20–35 mL 2% lignocaine with adrenaline) after Caesarean delivery, with associated increased morphine-related adverse effects (Atkinson Rallis 2011 **Level II**, n=30, JS 3).

Key messages

Intrathecal

1. Intrathecal morphine and intrathecal fentanyl prolong spinal local anaesthetic block, with fentanyl being associated with fewer adverse effects (**N**) (**Level I** [PRISMA]).
2. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl or sufentanil after Caesarean delivery (**U**) (**Level I**).
3. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**U**) (**Level I**).

Epidural

4. Epidural morphine provides similar analgesia to epidural fentanyl when combined with local anaesthetic, although the incidence of nausea is greater with morphine (**N**) (**Level I** [PRISMA]).
5. Extended-release epidural morphine provides analgesia for up to 48 hours (**U**) (**Level II**), however it is associated with more respiratory depression than IV PCA following abdominal surgery (**S**) (**Level I**)

6. Epidural pethidine produces better pain relief and less sedation than IV pethidine after Caesarean delivery (**U**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ No neurotoxicity has been shown at normal clinical intrathecal doses of morphine, fentanyl and sufentanil (**U**).

☑ Neuraxial administration of bolus doses of hydrophilic opioids carries an increased risk of delayed sedation and respiratory depression compared with lipophilic opioids (**U**).

4.1.3 Peripheral opioids

Opioid receptors on sensory unmyelinated C-nerve fibres mediate antinociceptive effects in animal studies (Stein 1990 **NR**). In the presence of inflammation, opioid receptors are transported to the periphery and increased amounts of endogenous opioid peptides are present in infiltrating immune cells (Smith 2008 **NR**; Stein 2011 **NR**; Lesniak 2011 **NR**). Tissue inflammation leads to increased functionality of opioid receptors on peripheral sensory neurones and to local production of opioid peptides (Stein 2011 **NR**). While multiple mechanisms have been identified, inhibition of calcium and sodium channels appear prominent, which leads to reduced hyperexcitability of sensitised peripheral fibres and reduction in local release of proinflammatory neuropeptides (Koppert 1999 **EH**; Mousa 2007 **EH**). This is consistent with the clinical observation that peripheral opioids are more effective in the presence of inflammation.

4.1.3.1 Intra-articular

In experimentally induced synovitis in horses, intra-articular morphine reduced clinical and biological signs of inflammation compared to IV administration (Lindegaard 2010 **BS**). Intra-articular bupivacaine was less effective than morphine in providing analgesia in patients having "high inflammatory arthroscopic knee surgery", whereas bupivacaine was more effective than morphine in those having "low inflammatory surgery" (Marchal 2003 **Level II**, n=53, JS 5) (see also Section 5.8.2).

In clinical practice, morphine injected as a single dose into the knee intra-articular space produced analgesia that lasted up to 24 h but evidence for a peripheral rather than a systemic effect was inconclusive (Gupta 2001 **Level I**, 19 RCTs, n=1,166; Kalso 2002 **Level I**, 28 RCTs, n=1,067).

Confounding factors that hinder analysis include the pre-existing degree of inflammation, type of surgery, the baseline pain severity and the overall relatively weak clinical effect (Gupta 2001 **Level I**, 19 RCTs, n=1,166). When published trials were reanalysed taking these confounding factors into consideration, including the intensity of early postoperative pain, the data did not support an analgesic effect for intra-articular morphine following arthroscopy compared with placebo (Rosseland 2005 **Level I**, 9 RCTs, n=710); a large number of poor quality studies were excluded. Subsequent studies have confirmed that intra-articular opioids, particularly morphine, provide superior analgesia to no opioid/placebo but still fail to address the issue of a systemic vs a local (direct) effect (Garcia 2010 **Level III**; Eroglu 2010 **Level II**, n=60, JS 4; Hosseini 2012 **Level II**, n=60, JS 3; Arti 2013 **Level II**, n=140, JS 5).

The addition of intra-articular sufentanil to a mixture of ropivacaine and clonidine following anterior cruciate ligament repair provided no additional analgesic benefits (Armellin 2008 **Level II**, n=120, JS 5). A mixture of intra-articular bupivacaine and 100 mg tramadol resulted in better pain relief and lower rescue analgesic requirements than use of either medicine alone (Zeidan 2008 **Level II**, n=90, JS 5).

4.1.3.2 Perineural

There is no evidence for analgesic efficacy of peripheral opioids with perineural block by local anaesthetics (Picard 1997 **Level I**, 26 RCTs, n=952). However, pethidine (Ozturk 2009 **EH**) and, to a lesser extent, tramadol (Ozturk 2008 **EH**) have weak local anaesthetic-like effects if applied to the ulnar nerve.

4.1.3.3 Topical

While opioid receptors have been identified in the cornea and skin, topically applied opioids have not consistently demonstrated efficacy in pain states such as corneal ulceration (fentanyl) (Zollner 2008 **Level II**, n=40, JS 4), partial thickness burns (morphine) (Welling 2007 **Level II**, n=49, JS 5) or chronic skin ulceration (morphine) (Vernassiere 2005 **Level II**, n=18, JS 4).

The clinical use of topical opioids in palliative care for pain control in cutaneous lesions is reported as beneficial in three of six RCTs (Graham 2013b **Level IV SR**, 26 studies, n unspecified). A greater benefit was reported with inflammatory lesions than with vascular ulcers, suggesting an opioid anti-inflammatory role may be as important as a peripheral analgesic benefit.

Although commonly used, oral morphine mouthwash in chemotherapy-induced mucositis pain has only limited supporting evidence; a dose-response (beneficial) effect was seen in a small pilot study using 1 mg/mL and 2 mg/mL morphine mouthwash (Cerchietti 2003 **Level III-1**). Benefit was also evident for morphine mouthwash 30 mg every 3 h, with a local anaesthetic-based solution, in mucositis associated with chemoradiotherapy in head and neck cancer patients (Cerchietti 2002 **Level II**, n=26, JS 3). With oral morphine mouthwash (30 mg in 15 mL) for the treatment of mucositis pain, the act of mouthwashing was beneficial, with a trend to more benefit with morphine (Vayne-Bossert 2010 **Level II**, n=11, JS 5). Recruitment difficulties meant this trial was concluded before sufficient subjects were recruited based on power analysis (see also Section 8.6.7.7).

Key messages

1. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo when administered after surgery (**U**) (**Level I**).
2. Peripheral opioids administered with local anaesthetics perineurally have no analgesic effects (**N**) (**Level I**).
3. Evidence for a clinically relevant peripheral opioid effect with topical administration is inconclusive (**S**) (**Level I**).

4.2 Paracetamol

Paracetamol is the only remaining para-aminophenol used in clinical practice and is an effective analgesic (see below) and antipyretic. It is absorbed rapidly and well from the small intestine after oral administration with a bioavailability of between 63 and 89% (Oscier 2009 **NR**). It can also be given rectally and IV (see below and Chapter 5).

4.2.1 Mechanism of action

The mechanism of action of paracetamol remains unclear. In contrast to opioids, paracetamol has no known endogenous binding sites and, unlike NSAIDs, causes only weak inhibition of peripheral cyclooxygenase (COX) activity, with apparent selectivity for COX-2 (Graham 2013a **NR**). There is increasing evidence of an additional central antinociceptive effect. Although the mechanism of analgesic efficacy of paracetamol remains elusive, it may involve direct and indirect inhibition of central cyclooxygenases but the activation of the endocannabinoid system and spinal serotonergic pathways also appear to be essential (Graham 2013a **NR**). Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of COX activity (Mancini 2003 **BS**). As one of the mechanisms of action of paracetamol appears linked to the serotonergic system, it is possible that other medicines with serotonergic effects could affect pain relief. In volunteers, coadministration of tropisetron or granisetron blocked the analgesic effects of paracetamol (Pickering 2006 **EH**; Pickering 2008 **EH**). The significance of this in the clinical setting has not yet been elucidated.

4.2.2 Efficacy

Single doses of paracetamol are effective in the treatment of postoperative pain. The NNTs for a variety of doses, as well as combinations of paracetamol with other analgesic medicines such as codeine, are discussed and in Chapter 5 and listed in Table 5.1.

There is no good evidence for a dose-dependent analgesic effect of oral paracetamol; the effects of 500 mg (NNT 3.5; 95%CI 2.7 to 4.8), 600/650 mg (NNT 4.6; 95%CI 3.9 to 5.5) and 1,000 mg (NNT 3.6; 95%CI 3.2 to 4.1) show no statistically significant difference (Moore 2011 **Level I** [Cochrane], 53 RCTs, n=6,230). Paracetamol by all routes of administration has a statistically significant opioid-sparing effect on PCA-morphine consumption (MD over 24 h 6.3 mg; 95%CI -9.0 to -3.7), although this effect is inferior to nsNSAIDs and coxibs (Maund 2011 **Level I**, 60 RCTs, n unspecified).

Paracetamol IV is also an effective analgesic after surgery with an NNT of 4.0 (95%CI 3.5 to 4.8) over 4 h and an NNT of 5.3 (95%CI 4.2 to 6.7) over 6 h (Tzortzopoulou 2011 **Level I** [Cochrane], 36 RCTs, n=3,896). When paracetamol is used an adjunct to opioid analgesia, opioid requirements are reduced by 30% over 4 h after a single IV dose. For orthopaedic surgery specifically, IV paracetamol has similar benefits (Jebaraj 2013 **Level I** [PRISMA], 8 RCTs, n unspecified).

Paracetamol given IV perioperatively reduces PONV (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). This effect is correlated to pain relief achieved but not to reduced opioid consumption and was most pronounced when IV paracetamol was given prophylactically before surgery (OR 0.54; 95%CI 0.40 to 0.74).

Paracetamol is superior to placebo for migraine (NNT 12 for pain-free response at 2 h) and reaches the efficacy of sumatriptan when combined with 10 mg metoclopramide (Derry 2013a **Level I** [Cochrane] 11 RCTs, n=2,942). In episodic tension-type headache (TTH), paracetamol is as effective as low-dose NSAIDs (Yoon 2012 **Level I**, 6 RCTs, n=2,162). Paracetamol is also superior to placebo for postpartum perineal pain (OR 2.14; 95%CI 1.59 to 2.89) (Chou 2013 **Level I**, 10 RCTs, n=1,377).

The combination of paracetamol and NSAIDs is more effective than either paracetamol or NSAID alone (Ong 2010 **Level I**, 21 RCTs, n=1,909). This in particular is shown for the combination of paracetamol and ibuprofen in the setting of wisdom tooth removal (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241).

A combination of 1,000 mg paracetamol with 130 mg caffeine is more effective than paracetamol alone (OR 1.12; 95%CI 1.05 to 1.19) in a range of painful conditions with no safety concerns (Palmer 2010 **Level I** [QUOROM], 8 RCTs, n=2,510).

Combinations of paracetamol with opioids such as codeine, tramadol or hydrocodone show increased efficacy (see Section 5.1.1.1.).

4.2.3 Adverse effects

Paracetamol has fewer adverse effects than NSAIDs and can be used when the latter are contraindicated (eg patients with a history of renal impairment, asthma or peptic ulcers). The risk of hepatotoxicity from therapeutic doses (maximum 4 g/24 h) is not supported by current data (Dart 2007 **Level IV SR**, 791 studies, n=40,202). The higher number of findings in the retrospective vs the prospective studies suggests that some of these cases may be inadvertent overdoses. Similar safety has also been shown in a paediatric population with no cases of liver disease, need for antidote or transplantation, or death (95%CI 0.000 to 0.009) and only 0.031% of cases (95%CI 0.015 to 0.057) with major or minor hepatic adverse effects (Lavonas 2010 **Level IV SR**, 62 studies, n=32,414). In conclusion, hepatotoxicity from therapeutic doses of paracetamol is extremely rare (Graham 2013a **NR**).

It is commonly recommended that paracetamol should be used with caution or in reduced doses in patients with active liver disease, history of heavy alcohol intake and glucose-6-phosphate dehydrogenase deficiency. However, therapeutic doses of paracetamol are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol (Graham 2013a **NR**). In subjects who consume alcohol, no elevation of alanine aminotransferase

levels was noted with up to 4 g/d of paracetamol for at least 4 d (Rumack 2012 **Level I** [PRISMA], 5 RCTs, n=551); no cases of hepatic failure or death were observed in any published prospective trial of moderate to heavy drinkers. In patients newly abstinent after abusing alcohol, therapeutic doses of paracetamol had no effect on parameters of liver function (Dart 2010 **Level II**, n=142, JS 5).

There is no evidence that patients who have depleted glutathione stores (eg patients who are malnourished or who have cirrhosis, hepatitis C or HIV) are at increased risk of liver dysfunction when exposed to therapeutic doses of paracetamol (Benson 2005 **NR**; Graham 2013a **NR**). However there is a potential association between acute liver failure and therapeutic paracetamol doses in paediatric patients with myopathies (Ceelie 2011 **Level IV**).

Paracetamol overdose is a common cause of acute liver failure (Graham 2013a **NR**); in the USA 30,000 patients are hospitalised every year for paracetamol overdose, of which >50% are unintentional and 17% result in hepatotoxicity (Blieden 2014 **NR**). In a multiethnic Asian population, the hepatotoxicity rate was lower at 7.3% (Marzilawati 2012 **Level IV**). Treatment should be with acetylcysteine; there is no obvious advantage of IV over oral administration (Green 2013 **Level III-3 SR**, 16 studies, n=5,164). Treatment delays increase the incidence of hepatotoxicity.

A cohort study of 19,163 newly diagnosed chronic kidney disease patients had an increased risk of end-stage renal disease with paracetamol use (OR 2.92; 95%CI 2.47 to 3.45) and higher risk with increasing dose exposure (p for trend <0.001) (Kuo 2010 **Level III-2**).

Paracetamol may interact with warfarin to increase the International Normalised Ratio (INR) (with doses >2 g/d over several days) (Hughes 2011 **Level IV SR**, 5 studies, n unspecified).

Epidemiological studies have looked at an association between paracetamol use and a number of conditions without being able to show a causal relationship. However, an association has been found for renal cancer (OR 1.28; 95%CI 1.15 to 1.44), similar to NSAIDs (Choueiri 2014 **Level III-2 SR**, 20 studies, n=579,285). The association with ovarian cancer was a protective one; reduced odds ratio (OR 0.82; 95%CI 0.74 to 0.92) compared to nonuse and further reduction with long-term (≥10 y), high-intensity paracetamol use (OR 0.45; 95%CI 0.24 to 0.86) (Baandrup 2014 **Level III-2**). The overall effect of paracetamol on blood pressure remains unclear; observational studies (n=155,910) show a variable association between paracetamol use and increased hypertension but RCTs (n=152) have inconsistent results (Turtle 2013 **Level III-3 SR**, 10 studies, n=156,062). In children, exposure to paracetamol was associated with an increase in the incidence of asthma (pooled OR 1.63; 95%CI 1.46 to 1.77) (Etminan 2009 **Level III-3 SR**, 19 studies, n=425,140). There are also claimed associations between the use of paracetamol in pregnancy and subsequent asthma in childhood (OR 1.21; 95%CI 1.02 to 1.44) (Eyers 2011 **Level III-2 SR**, 6 studies, n=28,038), as well as with later hyperkinesic disorder (HR 1.37; 95%CI 1.19 to 1.59), use of attention deficit hyperactivity disorder (ADHD) medications (HR 1.29; 95%CI 1.15 to 1.44) or having ADHD-like behaviors at age 7 y (RR 1.13; 95%CI 1.01 to 1.27) (Liew 2014 **Level III-2**).

Caution should be used with interpretation of such retrospective analyses because of the possible effect of unknown or unmeasured confounding factors; the relevance to use limited to an acute situation is also unclear.

Key messages

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects is comparable to placebo (**U**) (**Level I** [Cochrane Review]).
2. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related adverse effects (**U**) (**Level I**).
3. Hepatotoxicity with therapeutic doses of paracetamol is extremely rare (**N**) (**Level IV**) and not associated with alcohol consumption (**N**) (**Level I** [PRISMA]).

4.3 Nonselective NSAIDs and coxibs

4.3.1 Systemic nonselective nonsteroidal anti-inflammatory drugs

The term NSAIDs is used to refer to both nsNSAIDs and coxibs (COX-2 selective inhibitors). NSAIDs have a spectrum of analgesic, anti-inflammatory and antipyretic effects and are effective analgesics in a variety of acute pain states. Many effects of NSAIDs can be explained by inhibition of prostaglandin synthesis in peripheral tissues, nerves and the CNS (Botting 2006 **NR**). However, NSAIDs and aspirin may have other mechanisms of action independent of any effect on prostaglandins, including effects on basic cellular and neuronal processes. Prostaglandins are produced by the enzyme prostaglandin endoperoxide synthase, which has both COX and hydroperoxidase sites. Subtypes of the COX enzyme have been identified; the "constitutive" COX-1 and the "inducible" COX-2; a COX-3 is also being investigated (Simmons 2004 **NR**; Gajraj 2005 **NR**; Botting 2006 **NR**; Kam 2009 **NR**).

Prostaglandins regulate many physiological functions including gastric mucosal protection, bronchodilation, renal tubular function and intrarenal vasodilation. Production of endothelial prostacyclin leads to vasodilation and prevents platelet adhesion, whereas thromboxane, produced from platelets by COX, results in platelet aggregation and vasoconstriction. With the exception of prostacyclin synthesis (mediated largely through COX2), such physiological roles are mainly regulated by COX-1 and this is the basis for many of the adverse effects associated with nsNSAID use. Tissue damage induces COX-2 production leading to synthesis of prostaglandins that result in inflammation, peripheral sensitisation of nociceptors and consequently increased pain perception. COX-2 induction within the spinal cord plays a role in central sensitisation. COX-2 may also be "constitutive" in some tissues, including the kidney, cardiovascular system and brain and is overexpressed in some cancers (Kam 2009 **NR**).

NSAIDs are reversible COX inhibitors with the exception of aspirin, which binds covalently and acetylates the enzyme irreversibly. In platelets, the enzyme cannot be replenished leading to prolonged inhibition of platelet function with minimal inhibition of endothelial prostacyclin; this confers cardiovascular protection at low dosages of aspirin. Nonselective NSAIDs are "nonselective" COX inhibitors that inhibit both COX-1 and COX-2. The coxibs have been developed to inhibit selectively, but not specifically, COX-2 (Simmons 2004 **NR**; Gajraj 2005 **NR**; Botting 2006 **NR**).

4.3.1.1 Efficacy

Single doses of oral nsNSAIDs are effective in the treatment of pain after surgery (Moore 2011 **Level I** [Cochrane], ≈350 RCTs, n≈45,000). For a list of NNTs for each medicine see Table 5.1. However, while useful analgesic adjuvants, they are often inadequate as the sole analgesic agent in the treatment of severe postoperative pain (Cepeda 2005 **Level II**, n=1,003, JS 5).

They are also effective analgesics in chronic low-back pain (Chung 2013 **Level I** [PRISMA], 25 RCTs, n=5,935), renal colic (Holdgate 2005 **Level I** [Cochrane], 20 RCTs, n=1,613), primary dysmenorrhoea (Marjoribanks 2010 **Level I** [Cochrane], 73 RCTs, n=5,165), migraine (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473); Derry 2013b **Level I** [Cochrane], 5 RCTs, n=1,356), acute ankle sprains (van den Bekerom 2015 **Level I**, 28 RCTs, n unspecified) and biliary colic (Colli 2012 **Level I**, 11 RCTs, n=1,076).

Nonselective NSAIDs are integral components of multimodal analgesia (Kehlet 1997 **NR**; Buvanendran 2009 **NR**; Young 2012 **NR**). When given in combination with IV PCA morphine after surgery, nsNSAIDs result in better analgesia, reduced opioid consumption (MD over 24 h 10.2 mg; 95%CI -11.7 to -8.7) and a lower incidence of PONV (OR 0.70; 95%CI 0.53 to 0.88) (Maund 2011 **Level I**, 60 RCTs, n unspecified). Similar findings were made in the paediatric setting (Michelet 2012 **Level I**, 27 RCTs, n=985).

The combination of paracetamol and NSAIDs is more effective than paracetamol or NSAID alone (Ong 2010 **Level I**, 21 RCTs, n=1,909). This is particularly well documented for the combination of paracetamol and ibuprofen in the setting of wisdom tooth removal (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241).

Administration of ketorolac to patients with rib fractures reduced the incidence of pneumonia (OR 0.14; 95%CI 0.04 to 0.46) and reduced requirements for ICU admission and ventilation (Yang 2014 **Level III-2**). The perioperative use of rectal indomethacin for endoscopic retrograde cholangiopancreatography (ERCP) reduces the risk of post-ERCP pancreatitis (OR 0.49; 95%CI 0.34 to 0.71) compared with placebo (NNT 17) (Ahmad 2014 **Level I**, 4 RCTs, n=1,422).

In cancer surgery, initial data suggested benefits of intraoperative use of nsNSAIDs in breast cancer patients (reduced recurrence rate and lower mortality) and in lung cancer patients (lower metastases risk and longer survival) (Forget 2013 **Level III-2**). In breast cancer surgery, intraoperative administration of nsNSAIDs (ketorolac or diclofenac) was associated with an improved disease-free survival (HR 0.57; 95%CI 0.37 to 0.89) and better overall survival (HR 0.35; 95%CI 0.17 to 0.70) (Forget 2014 **Level III-2**).

4.3.1.2 Adverse effects

Nonselective NSAID adverse effects are more common with long-term use; the major concerns relate to the gastrointestinal, renal and cardiovascular systems. In the perioperative and acute period, the main concerns are renal impairment, interference with platelet function, wound and bone healing and peptic ulceration or bronchospasm in individuals at risk. Certain risks are accentuated in the perioperative period because of pre-existing comorbidities, concurrent medications, haemodynamic disturbances, fluid shifts, activation of the neurohumoral stress response and deficient enteral feeding.

In general, the risk and severity of nsNSAID-associated adverse effects is increased in elderly people (Pilotto 2003 **Level III-2**; Juhlin 2005 **Level II**, n=14, JS 4). For this reason, opioids are sometimes used in preference to NSAIDs. A cohort study of elderly patients (n=12,840) with arthritis (mean age 80 y) started on nsNSAIDs, coxibs or opioids challenges the assumption that opioids are safer in that population, showing increased rates of fracture, hospital admission and all-cause mortality in the opioid cohort and similar or higher rates of cardiovascular, renal and gastrointestinal adverse effects (Solomon 2010 **Level III-2**). Overall the nsNSAID cohort appeared to have the lowest risk for adverse effects.

Renal function

Renal prostaglandins regulate tubular electrolyte handling, modulate the actions of renal hormones and maintain renal blood flow and glomerular filtration rate in the presence of circulating vasoconstrictors. The adverse renal effects of chronic nsNSAID use are common and well recognised. In some clinical conditions, including hypovolaemia, dehydration and major surgery, high circulating concentrations of the vasoconstrictors angiotensin II, noradrenaline and vasopressin increase production of intrarenal vasodilators including prostacyclin; maintenance of renal function may then depend on prostaglandin synthesis and thus can be sensitive even to brief nsNSAID administration (McDowell 2014 **NR**).

In patients with normal preoperative renal function, nsNSAIDs causes a clinically insignificant and transient decrease in creatinine clearance on d 1 after surgery, and there are no differences between patients given diclofenac, ketorolac, indomethacin (indometacin) or ketoprofen (Lee 2007a **Level I** [Cochrane], 23 RCTs, n=1,459). The risk of adverse renal effects of nsNSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents including angiotensin-converting enzyme (ACE) inhibitors (Juhlin 2005 **Level II**, n=14, JS 4), IV contrast media and aminoglycosides (RCA 1998 **Level IV**). Of note, a trial of naproxen following cardiac surgery was stopped because of an increased rate of renal failure (7.3 vs 1.3%) (Horbach 2011 **Level II**, n=161, JS 5). This is confirmed by an analysis of a French pharmacovigilance database, which showed that acute renal failure caused by drug interactions between NSAIDs and ACE inhibitors, angiotensin-receptor blockers or diuretics was a common issue (Fournier 2014 **Level IV**).

Nephrectomy may not represent an independent risk factor for renal failure as a continuous infusion of ketorolac for 24 h after laparoscopic donor nephrectomy had no significant effect on renal function for up to 18 mth postoperatively (Grimsby 2014 **Level II**, n=111, JS=3).

In a nested case-control study of new NSAID users (n=1,459,271), the risk of acute kidney injury, defined as a creatinine increase >50%, increased with a decrease in COX2 selectivity (Lafrance 2009 **Level III-2**). The risk ratios were 1.11 for diclofenac (95%CI 0.84 to 1.48), 1.72 for naproxen (95%CI 1.52 to 1.95), 2.07 for ketorolac (95%CI 1.78 to 2.41), 2.25 for ibuprofen (95%CI 2.04 to 2.49) and 3.64 for high-dose aspirin (95%CI 2.46 to 5.37). Using multiple NSAIDs appeared to have higher risk (RR 2.90; 95%CI 2.62 to 3.22). A cohort study of newly diagnosed chronic kidney disease patients (n=19,163) had an increased risk of end-stage renal disease with aspirin use (OR 1.96; 95%CI 1.62 to 2.36) and nsNSAID use (OR 1.56; 95%CI 1.32 to 1.85) and higher risk with increasing dose exposure (p for trend <0.001) (Kuo 2010 **Level III-2**).

With proper selection and monitoring, the incidence of NSAID-induced perioperative renal impairment is low and NSAIDs need not be withheld in patients with normal preoperative renal function (Lee 2007a **Level I** [Cochrane], 23 RCTs, n=1,459).

Platelet function

Nonselective NSAIDs inhibit platelet function. In line with previous findings, the rate of surgery-related bleeding was 2.4% after nsNSAIDs compared to 0.4% with placebo (Maund 2011 **Level I**, 6 RCTs [bleeding], n=695). In a larger previous meta-analysis, after a variety of different operations, the use of nsNSAIDs showed a significant increase in risk of severe bleeding from 0–1.7% compared with placebo (NNH 59) (Elia 2005 **Level I**, 52 RCTs, n=4,893).

This was also found in the HIPAID study after hip replacement, where the ibuprofen group had an increased risk of major bleeding complications (OR 2.09; 95%CI 1.00 to 4.39) (Fransen 2006 **Level II**, n=902, JS 5). After otorhinolaryngological surgery in an outpatient setting, tenoxicam increased bleeding at the surgical site compared to placebo (Merry 2004 **Level II**, n=1,001, JS 5). After gynaecological or breast surgery, the nsNSAID diclofenac was associated with more blood loss than the coxib rofecoxib (Hegi 2004 **Level II**, n=50, JS 5). In contradiction to the more general meta-analyses and a ketorolac-specific one in tonsillectomy (Chan 2014 **Level III-2 SR** [PRISMA], 10 studies, n=1,357), perioperative ketorolac did not increase the rate of postoperative bleeding (OR 1.1; 95%CI 0.61 to 2.06) (Gobble 2014 **Level I**, 27 RCTs, n=2,314).

Bleeding after tonsillectomy is of clinical significance but occurs infrequently; studies have been small to date and results remain contradictory. In contrast to previous meta-analyses (Marret 2003 **Level I**, 7 RCTs, n=505; Moiniche 2003 **Level I**, 25 RCTs, n=970), a subsequent meta-analysis found no statistically significant increase of any outcome related to bleeding with the perioperative use of nsNSAIDs in tonsillectomy (Riggin 2013 **Level I**, 46 RCTs, n=4,878). This was found for most severe bleeding outcome (OR 1.30; 95%CI 0.90 to 1.88), bleeding requiring reoperation (OR 1.32; 95%CI 0.59 to 2.95), bleeding requiring readmission (OR 1.08; 95%CI 0.54 to 2.15), bleeding managed conservatively (OR 1.56; 95%CI 0.91 to 2.66) and secondary haemorrhage (OR 0.90; 95%CI 0.40 to 2.01). There was also no increased bleeding outcome in the paediatric subgroup of this meta-analysis (19 RCTs, n=1,747), which is in line with another meta-analysis in children only (OR 1.69; 95%CI 0.71 to 4.01) (Lewis 2013 **Level I** [Cochrane], 15 RCTs, n=1,101) (see also Section 9.4.2 for details).

The above meta-analysis (Riggin 2013 **Level I**, 46 RCTs, n=4,878) could not identify a specific risk for any nsNSAID including aspirin (3 RCTs, n=1,610) (OR 4.23; 95%CI 0.64 to 27.66) and ketorolac (8 RCTs; n=579) (OR 2.01; 95%CI 0.62 to 6.54). These findings are contradicted by a previous larger meta-analysis on aspirin (OR 1.94; 95%CI 1.09 to 3.42) (Krishna 2003 **Level I**, 7 RCTs, n=1,368) and a systematic review on ketorolac (Chan 2014 **Level III-2 SR** [PRISMA], 10 studies, n=1,357). The latter found an overall increased risk of bleeding post tonsillectomy with ketorolac (RR 2.04; 95%CI 1.32 to 3.15), which was also found in adults (3 studies, n=246) (RR 5.64; 95%CI 2.08 to 15.27) but not in children (7 studies, n=1,111) (RR 1.39; 95%CI 0.84 to 2.30).

It is important to note that the majority of studies included in these meta-analyses have used a single dose of NSAIDs compared to placebo. Multiple postoperative dosing for some days is routine clinical practice and has not yet been studied with regard to the issue of bleeding and surgical techniques are evolving.

Peptic ulceration

Chronic nsNSAID use is associated with peptic ulceration and bleeding and the latter may be exacerbated by the antiplatelet effect. All long-term nsNSAID regimens increase the risk of upper gastrointestinal complications (diclofenac RR 1.89; 95%CI 1.16 to 3.09; ibuprofen RR 3.97; 95%CI 2.22 to 7.10; naproxen RR 4.22; 95%CI 2.71 to 6.56) (Bhala 2013 **Level I**, 754 RCTs, n=353,809). The combination of an nsNSAID with an SSRI further increases the risk of upper gastrointestinal bleeding (Anglin 2014 **Level III-2 SR**, 19 studies, n>393,268).

Acute gastroduodenal damage and bleeding can also occur with short-term nsNSAID use; the risk is increased with higher doses, a history of peptic ulceration, use for >5 d and in elderly people (Strom 1996 **Level IV**). After 5 d of naproxen and ketorolac use in healthy elderly subjects, ulcers were found on gastroscopy in 20 and 31% of cases respectively (Harris 2001 **Level II**, n=17 [terminated due to high incidence of gastrointestinal ulcers in both nsNSAID groups], JS 4; Stoltz 2002 **Level II**, n=94, JS 4; Goldstein 2003 **Level II**, n=168, JS 4). Importantly, such endoscopic findings do not correlate with dyspeptic symptoms; these consequently cannot be relied upon as an indicator of potential harm (Dib 2014 **Level III-2**).

The relative risk of hospital admission for perforations, ulcers and bleeds associated with nsNSAIDs is estimated as 5.3 compared with people not consuming nsNSAIDs (Lanas 2003 **Level III-2**). Use of ketorolac and piroxicam carried the highest risk. Concurrent use of a proton-pump inhibitor (PPI) significantly reduced the incidence of nsNSAID-related peptic ulcer disease (Targownik 2008 **Level III-2**). However, concurrent use of a PPI and nsNSAID (diclofenac) was still associated with an increased risk of clinically significant upper or lower gastrointestinal adverse effects compared with coxib alone (RR 4.3; 95%CI 2.6 to 7.0) (Chan 2010b **Level II**, n=4,484, JS 5). Suppression of gastric acid by PPI to reduce nsNSAID-induced gastropathy may increase the risk of enteropathy lower in the gastrointestinal tract (Blackler 2014 **NR**).

Colonic diverticular bleeding is also increased by aspirin (RR 1.73; 95%CI 1.31 to 2.30) and other nsNSAIDs (RR 2.24; 95%CI 1.63 to 3.09) (Yuhara 2014 **Level III-2 SR**, 6 studies, n≈52,000).

Allergic reactions and NSAID-exacerbated respiratory disease

NSAIDs, especially nsNSAIDs, are one of the most common causes of drug-induced hypersensitivity reactions. Acute reactions include rhinitis, asthma, urticaria, angioedema and anaphylaxis, while delayed reactions include fixed drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, maculopapular reactions, pneumonitis, nephritis or aseptic meningitis (Kowalski 2011 **GL**). This guideline advises on classification, diagnosis and management.

Precipitation of bronchospasm by aspirin/nsNSAIDs is a recognised phenomenon in individuals with moderate asthma, chronic rhinosinusitis or nasal polyps. NSAID-exacerbated respiratory disease affects 10–15% of people with asthma and can be severe. It can lead to respiratory symptoms after exposure to nsNSAIDs (NNH 13) (Morales 2013 **Level I** [PRISMA], 14 RCTs, n=426). A history of NSAID-exacerbated respiratory disease is a contraindication to nsNSAID use, although there is no reason to avoid nsNSAIDs in other people with stable mild to moderate asthma or other forms of chronic obstructive pulmonary disease (COPD).

Bone healing

Evidence for an effect of nsNSAIDs on bone healing is conflicting. There is a statistically significant three-fold increase (95%CI 1.6 to 5.6) in nonunion in all studies but a statistically nonsignificant increase in studies of higher quality (7 spinal fusion studies) (OR 2.2; 95%CI 0.8 to 6.3) (Dodwell 2010 **Level III-2 SR** [PRISMA], 11 studies, n=12,051). In spinal fusion specifically, when used for <14 d, only high-dose ketorolac (>120 mg/d) lowered the success of spinal fusion (RR 2.87; 95%CI 1.53 to 5.38) but not standard doses of nsNSAIDs and coxibs (RR 1.39; 95%CI 0.74 to 2.61) (Li 2011 **Level III-2 SR**, 5 studies, n=1,403). A retrospective study (n=1,901) has shown increased nonunion, malunion and infection following long bone fracture in nsNSAID users (OR 2.2; 95%CI 1.15 to 4.10) (Jeffcoach 2014 **Level III-2**).

A structured review of 316 papers related to this topic concludes that "despite animal data showing suppression of bone healing by NSAIDs, … robust clinical evidence in human subjects does not exist at this time … and suitable clinical trials would likely prove difficult to undertake". The authors express the view that "there is not enough clinical evidence to deny patients with simple fractures the analgesic benefits of these compounds" (Kurmis 2012 **NR**).

Anastomotic leakage

There are concerns in the literature about perioperative NSAIDs increasing the risk of anastomotic leakage following bowel surgery.

There is no statistically significant difference between NSAID use and control with regard to anastomotic leakage (OR 2.16; 95%CI 0.85 to 5.53) (Burton 2013 **Level I** [PRISMA], 6 RCTs, n=480); however, there were insufficient numbers to permit analysis for COX-2 selectivity and the power of this meta-analysis may be insufficient to show a difference. A parallel systematic review of five RCTs (overlap 5 RCTs to above meta-analysis) and three retrospective database reviews comes to an opposite conclusion (Bhangu 2014 **Level III-2** [PRISMA], 8 studies, n=4,464); here nsNSAIDs increase the risk of anastomotic leak (OR 2.37; 95%CI 1.71 to 3.28) (n=3,074). However, the authors describe evidence of publication bias in funnel plots. Specific findings suggest an effect with diclofenac (OR 2.32; 95 %CI 1.66 to 3.25) (3 studies, n=2,869) but not with ketorolac (OR 3.10; 95 %CI 0.81 to 11.82; p=0.100) (3 studies, n=205).

A subsequent retrospective study (2004–2011) of 731 patients showed no significant association between perioperative ketorolac use and anastomotic leakage (OR 1.06; 95%CI 0.43 to 2.62) (Saleh 2014 **Level III-2**); smoking was identified as the only relevant risk factor in a multivariate analysis (OR 3.34; 95%CI 1.30 to 8.62). Another nested case-control study contradicted these findings, as it found no effect with any NSAID (OR 1.81; 95%CI 0.98 to 3.37) but a significant increase with ketorolac only (OR 2.09; 95%CI 1.12 to 3.89) (Subendran 2014 **Level III-2**).

Cardiovascular

Most publications looking at the risk of cardiovascular adverse effects associated with nsNSAID use also include information relating to risks with coxibs (see the more detailed discussion under Section 4.3.2 below).

For some years it has been known that ibuprofen may impede access of aspirin to platelet COX-1 and may abrogate the protective effect of aspirin (MacDonald 2003 **Level III-2**; Hudson 2005 **Level III-2**). Subsequent research indicates that a degree of inhibition may occur with most nsNSAIDs and even some coxibs; while not blocking COX-1, they may block aspirin from reaching it (Nalamachu 2014 **NR**). Impaired aspirin inhibition of platelet function is described in multiple studies for ibuprofen, flufenamic acid, mefenamic acid, piroxicam, nimesulide and dipyrone, while there is conflicting evidence with respect to naproxen, celecoxib, rofecoxib and sulindac, and no inhibition was seen with diclofenac, etoricoxib, ketorolac, ketoprofen, meloxicam or paracetamol (Meek 2013 **EH**; Polzin 2013 **Level III-2**; Saxena 2013 **EH**). The FDA issued a caution specifically about the concomitant use of aspirin and ibuprofen, which states that "at least 8 hours should elapse after ibuprofen dosing, before giving aspirin, to avoid significant interference" (FDA 2006).

Central nervous system

CNS effects of NSAIDs are poorly defined, but range from symptomatic adverse effects such as headache or dizziness through to possible disease modification in conditions such as Parkinson's disease and dementia (Auriel 2014 **NR**).

4.3.2 Cyclooxygenase-2 selective inhibitors

Coxibs selectively inhibit the inducible COX enzyme, COX-2, and relatively spare constitutive COX-1 (see above). The coxibs available at present are celecoxib, etoricoxib and parecoxib (the injectable precursor of valdecoxib). By sparing physiological tissue prostaglandin production while inhibiting inflammatory prostaglandin release, coxibs offer the potential for effective analgesia with fewer adverse effects than nsNSAIDs. However, as noted above, some constitutive physiological synthesis of prostaglandins is also mediated through COX-2, and coxibs may still inhibit COX-1 to some extent.

4.3.2.1 Efficacy

Coxibs are as effective as nsNSAIDs for postoperative pain (Moore 2011 **Level I** [Cochrane], ≈350 RCTs, n≈45,000) and chronic low-back pain (Chung 2013 **Level I** [PRISMA], 25 RCTs, n=5,935). NNTs are comparable with those for nsNSAIDs for the treatment of moderate to severe acute pain. For a list of NNTs for each medicine see Table 5.1.

When given in combination with opioids after surgery, coxibs show reduced opioid consumption similar to nsNSAIDs (MD over 24 h -10.9 mg; 95%CI -12.8 to -9.1) but no significant reductions in pain scores or opioid-related adverse effects (Maund 2011 **Level I**, 60 RCTs, n unspecified).

After total knee arthroplasty, use of coxibs in the perioperative period reduces pain scores, opioid consumption, PONV and pruritus and improves range of motion without increased blood loss (Lin 2013 **Level I**, 8 RCTs, n=571). Continuation of coxibs for 6 wk postoperatively resulted in ongoing improved analgesia and reduced opioid consumption with improved rehabilitation conveying benefits on knee flexion for up to 1 y (Schroer 2011 **Level II**, n=107, JS 5). The risk-benefit ratio for coxibs as a discharge medication after orthopaedic surgery is superior to that for nsNSAIDs (Roberts 2012 **Level I** [PRISMA], 23 RCTs, n unspecified).

Pain relief at rest and on movement and satisfaction were improved when oral celecoxib was added to thoracic PCEA using local anaesthetic and opioid (Senard 2010 **Level II**, n=40, JS 5).

Timing of administration may not be critical. A comparison of celecoxib, started preoperatively vs postoperatively and continued for 3 d after surgery, showed opioid-sparing effect and improved patient satisfaction in both patient groups compared with placebo, with no advantage for preoperative administration (Sun 2008 **Level II**, n=120, JS 4). Similarly, in patients undergoing hip arthroplasty, preoperative administration of parecoxib offered no advantage compared with postoperative use; opioid sparing was again seen in both groups compared with placebo (Martinez 2007 **Level II**, n=62, JS 5). Pain relief was also no better when parecoxib was given before incision compared with administration at the end of surgery in patients undergoing colorectal surgery (Lee 2008 **Level II**, n=60, JS 5).

4.3.2.2 Adverse effects

Renal function

COX-2 is constitutively expressed in the kidney and is highly regulated in response to alterations in intravascular volume. COX-2 has been implicated in maintenance of renal blood flow, mediation of renin release and regulation of sodium excretion (Cheng 2004 **Level IV**; Kramer 2004 **Level IV**).

A single dose of 80 mg of parecoxib had no effect on any parameter of renal function in patients with ASA physiological status I–II <60 y of age undergoing laparoscopic hysterectomy (Puolakka 2009 **Level II**, n=30, JS 5) and only transient changes were seen after 3 d treatment with parecoxib 40 mg daily in elderly patients undergoing major orthopaedic surgery (Koppert 2006 **Level II**, n=75, JS 5). As with nsNSAIDs, a statistically significant increased risk of renal failure was reported following administration of coxibs in cardiac surgery patients (NNH 73) (Elia 2005 **Level I**, 3 RCTs [cardiac surgery], n=803); this use is now contraindicated as discussed below.

With chronic use, etoricoxib and nsNSAIDs (naproxen and ibuprofen) have similar low risks with regard to effects on renal function (Curtis 2004 **Level I**, 8 RCTs, n=4,770).

Analysis of the effects of different coxibs on renal function showed heterogeneity within the class as rofecoxib was associated with increased risk of renal dysfunction, while celecoxib was not (Zhang 2006 **Level I**, 114 RCTs, n=116,094).

In a nested case-control study of new NSAID users (n=1,459,271), the risk of acute kidney injury (defined as a creatinine increase >50%) increased with decrease in COX-2 selectivity (Lafrance 2009 **Level III-2**). The risk ratio was lowest at 0.96 for celecoxib (95%CI 0.63 to 1.47). A cohort study of newly diagnosed chronic kidney disease patients (n=19,163) found no increased risk of end-stage renal disease with celecoxib use but with rofecoxib use (OR 1.98; 95%CI 1.15 to 3.40) (Kuo 2010 **Level III-2**).

Platelet function

Platelets express only COX-1, not COX-2, and as a corollary coxibs do not impair platelet function (Munsterhjelm 2006 **Level II EH**, n=18, JS 4). After total knee arthroplasty, no increase in bleeding was seen when coxibs vs placebo were used (Lin 2013 **Level I**, 8 RCTs, n=571). The use of a coxib was associated with less surgical blood loss in comparison with an nsNSAID after mastectomy and hysterectomy (Hegi 2004 **Level II**, n=50, JS 5).

Cardiovascular effects

Information relating to the cardiovascular risks associated with the use of nsNSAIDs and coxibs is mainly derived from long-term treatment data with regular dosing and may not reflect the risk of short-term use in the acute pain setting (Jones 2005 **NR**). A detailed review of the issues in the perioperative setting has been published; it addresses also rare adverse effects such as arrhythmias (Gerstein 2014 **NR**).

In acute pain management, short-term use of coxibs (parecoxib or valdecoxib) after noncardiac surgery does not increase the risk of cardiovascular adverse effects (Schug 2009 **Level I**, 32 RCTs, n=8,511). Similarly, short-term use of other NSAIDs (meloxicam, ketorolac, celecoxib for a mean of 3 d) after lower limb total joint replacement (n=10,873) did not increase the risk of myocardial infarction postoperatively compared to nonuse (adjusted OR 0.95; 95%CI 0.5 to 1.8) (Liu 2012a **Level III-2**).

However, an increase in the incidence of cerebrovascular and cardiovascular events has been reported in patients given parecoxib, then valdecoxib, after CABG surgery (Furberg 2005 **Level I**, 2 RCTs, n=2,098). The FDA has contraindicated the use of all NSAIDs in the immediate postoperative period following CABG surgery (FDA 2005b). A subsequently performed retrospective observational study with ketorolac has not identified these concerns (Oliveri 2014 **Level III-2**).

Overall, the situation with regard to cardiovascular risks in the chronic setting remains unclear. In a comparison, there was no difference in the incidence of cardiovascular complications with nsNSAIDs compared with coxibs (Moore 2007 **Level I**, 148,406 patients-years of exposure). In this meta-analysis, both cardiovascular and gastrointestinal adverse effects were evaluated and celecoxib and valdecoxib were the only medicines associated with lower risk than (pooled) nsNSAIDs on both measures. In a subsequent meta-analysis, major coronary or vascular events were increased by coxibs, diclofenac and ibuprofen but not naproxen (Bhala 2013 **Level I**, 54 RCTs, n=353,809).

Naproxen has generally been associated with a lower risk of myocardial infarction (Trelle 2011 **Level I**, 31 RCTs, n=116,429) and the American Heart Association has identified naproxen as the preferred nsNSAID for long-term use in patients with or at high risk of cardiovascular disease (Antman 2007 **GL**), although the FDA has not endorsed this in the USA. Once daily administration of celecoxib eg 400 mg (RR 1.1; 95%CI 0.6 to 2.0) was associated with a lower cardiovascular risk than giving 400 mg as divided doses of 200 mg twice daily (RR 1.8; 95%CI 1.1 to 3.1) (Solomon 2008 **Level I**, 6 RCTS, n=7,950), possibly justifying this as an alternative to naproxen (Trelle 2011 **Level I**, 31 RCTs, n=116,429).

All NSAIDs approximately double the risk of congestive heart failure (Bhala 2013 **Level I**, 54 RCTs, n=353,809). An increased risk of atrial fibrillation (RR 1.76; 95%CI 1.07 to 2.88) has been documented, even with relatively brief exposure (Krijthe 2014, **Level III-2**). However, this study has been criticised due to an extremely low event rate.

In comparison with a historical cohort, the use over a 10-mth period of parecoxib and valdecoxib 40 mg daily for 2–3 wk was associated with an increase in the rate of vascular free flap failure from 7–29%, then falling to 4% after these medicines were no longer used (n=180) (Al-Sukhun 2006 **Level III-3**). These retrospective data, which are subject to potential confounding factors, are supported by one study in rats showing harmful effect of parecoxib on flap survival (Ren 2013 **BS**), which did not occur with celecoxib (Wax 2007 **BS**).

A retrospective cohort study using ketorolac after head and neck free flaps found no bleeding complications and no increased risk of free flap failure (Schleiffarth 2014 **Level III-2**).

Gastrointestinal

Short-term use of parecoxib/valdecoxib, as required to treat acute pain, results in gastroscopic ulcer rates similar to placebo in elderly patients at increased risk (Harris 2001 **Level II**, n=17 [terminated due to high incidence of gastrointestinal ulcers in both nsNSAID groups], JS 4; Stoltz 2002 **Level II**, n=94, JS 4; Goldstein 2003 **Level II**, n=168, JS 4). This contrasts with increased rates of ulceration with nsNSAIDs in the same setting.

Gastrointestinal bleeding complications are less likely with chronic use (24 wk) of coxibs compared with nsNSAIDs, even when the latter are combined with a PPI (Chan 2010b **Level II**, n=4,484, JS 5). A meta-analysis (including this RCT) shows a reduced risk of major gastrointestinal events, including gastric perforation, obstruction, and bleeding with 2–24 wk coxib therapy compared to nsNSAIDs/PPI (RR 0.38; 95%CI 0.25 to 0.56) (Jarupongprapa 2013 **Level I**, 9 RCTs, n=7,616). This rate reduction was only significant for patients at high risk of gastrointestinal complications or with longer term use. Coxib use was associated with less diarrhoea (RR 0.56; 95%CI 0.35 to 0.9) but an increased rate of dyspepsia (RR 1.58; 95%CI 1.26 to 1.98) compared to nsNSAIDs/PPI. With regard to specific compounds, the incidence of gastrointestinal bleeding complications was lowest with celecoxib and valdecoxib (Moore 2007 **Level I**, 148,406 patient-years of exposure).

The best gastroprotective strategy was the combination of a coxib and a PPI (Targownik 2008 **Level III-2**). In high-risk populations (previous admission with gastrointestinal bleeding), ulcer recurrence could be completely avoided even in long-term therapy by combining a coxib (celecoxib) with a PPI (40 mg/d esomeprazole) (Chan 2007 **Level II**, n=273, JS 5).

Allergic reactions and NSAID-exacerbated respiratory disease

Patients with anaphylactoid reactions (n=33) to dipyrone and nsNSAIDs (mainly propyphenazone and diclofenac) tolerated oral challenges with rofecoxib and celecoxib (Quiralte 2004 **Level IV**).

Coxibs, administered at analgesic doses, do not produce bronchospasm in patients with NSAID-exacerbated respiratory disease (Morales 2013 **Level I** [PRISMA] 14 RCTs, n=426).

Bone healing

At present, data on the effect of coxibs on bone healing are mainly restricted to animal models, where they undoubtedly affect bone remodelling (Kurmis 2012 **NR BS**). Celecoxib after hip arthroplasty reduced the frequency and severity of heterotopic bone formation (Lavernia 2014 **Level III-2;** Oni 2014 **Level III-2**). There is no good evidence of any clinically significant inhibitory effect of coxibs on bone healing (Gerstenfeld 2004 **NR**; Bandolier 2004 **NR**; Kurmis 2012 **NR**).

Anastomotic leakage

A systematic review identifies no increased risk of anastomotic leakage with use of coxibs (OR 2.32; 95%CI 0.71 to 7.63) (4 studies, n=1,223) and specifically with celecoxib (OR 3.24; 95%CI 0.53 to 19.77) (2 studies, n unspecified) (Bhangu 2014 **Level III-2** [PRISMA], 8 studies, n=4,464).

Key messages

Efficacy of systemic NSAIDs

1. Nonselective NSAIDs are effective in the treatment of acute postoperative pain, renal colic, migraine, primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]), acute ankle sprain (**N**) (**Level I**) and chronic low-back pain (**N**) (**Level I** [PRISMA]).2. Coxibs are effective in the treatment of acute postoperative pain (**U**) (**Level I** [Cochrane Review]) and chronic low-back pain (**N**) (**Level I** [PRISMA]).
3. Nonselective NSAIDs and coxibs are effective analgesics of similar efficacy for acute pain (**U**) (**Level I** [Cochrane Review])
4. Nonselective NSAIDs given in addition to paracetamol improve analgesia compared with either medicine given alone (**S**) (**Level I**), in particular ibuprofen combined with paracetamol (**N**) (**Level I** [Cochrane Review]).
5. The risk-benefit ratio for coxibs as a discharge medication after orthopaedic surgery is superior to that for nonselective NSAIDs (**N**) (**Level I** [PRISMA]).
6. Nonselective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea and vomiting (**W**) (**Level I**).
7. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related adverse effects (**U**) (**Level I**), except after total knee arthroplasty, where they reduce pain scores and adverse effects and improve outcomes (**N**) (**Level I**).

Adverse effects of systemic NSAIDs

8. With careful patient selection and monitoring, the incidence of NSAID-induced perioperative renal impairment is low (**S**) (**Level I** [Cochrane Review]).
9. Nonselective NSAIDs may increase the risk of any bleeding-related outcome after tonsillectomy in adults (**W**) (**Level I**) but not in children (**U**) (**Level I** [Cochrane Review]); in particular, there is an increase in bleeding complications with aspirin in adults and children (**U**) (**Level I**) and with ketolorac in adults only (**N**) (**Level III-2** [PRISMA]).
10. Nonselective NSAIDS, but not coxibs, may cause bronchospasm in individuals known to have NSAID-exacerbated respiratory disease (**S**) (**Level I** [PRISMA]).
11. Coxibs and nonselective NSAIDs are associated with similar rates of adverse cardiovascular effects, in particular myocardial infarction; naproxen may be associated with a lower risk than other nonselective NSAIDs and celecoxib may be associated with a lower risk than other coxibs and nonselective NSAIDs overall (**U**) (**Level I**).
12. Short-term use of parecoxib (**U**) (**Level I**) and other NSAIDs (**N**) (**Level III-2**) compared with placebo does not increase the risk of cardiovascular adverse effects after noncardiac surgery.
13. Use of parecoxib followed by valdecoxib after coronary artery bypass graft surgery increases the incidence of cardiovascular and cerebrovascular effects and is therefore contraindicated (**S**) (**Level I**).
14. Perioperative nonselective NSAIDs increase the risk of minor and major bleeding after surgery compared with placebo (**S**) (**Level I**).
15. Coxibs do not impair platelet function; this leads to perioperative blood loss being reduced in comparison with nonselective NSAIDs (**U**) (**Level II**) and comparable to placebo after total knee arthroplasty (**N**) (**Level I**).
16. Coxibs and nonselective NSAIDs have similar adverse effects on renal function (**U**) (**Level I**), although increased COX-2 selectivity may be associated with less risk of acute kidney injury (**N**) (**Level III-2**), which is confirmed for celecoxib (**N**) (**Level I**).

17. Short-term use (5–7 days) of coxibs results in gastric ulceration rates similar to placebo and lower than nonselective NSAIDs (**U**) (**Level II**).
18. The protective effects of low-dose aspirin are reduced by concomitant administration of some NSAIDs, in particular ibuprofen (**N**) (**Level III-2**).
19. The risk of adverse renal effects of nonselective NSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension and use of other nephrotoxic agents including angiotensin-converting enzyme inhibitors (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Adverse effects of nonselective NSAIDs are significant and may limit their use (**U**).

☑ The effects of NSAIDs on bone healing and anastomotic leakage (after colorectal surgery) remain unclear (**N**).

4.3.3 Nonsystemic nonsteroidal anti-inflammatory drugs

4.3.3.1 Intra-articular

Following arthroscopy, intra-articular nsNSAIDs such as tenoxicam and ketorolac result in improved pain relief after surgery (Romsing 2000 **Level I**, 7 RCTs [intra-articular], n unspecified). Compared with systemic administration, intra-articular nsNSAIDs (4 RCTs) showed a pain score reduction of 20/100 (95%CI 13 to 26) and a 50–65% reduction in supplementary analgesic requirements over 24 h. In contrast, when intra-articular nsNSAIDs were compared with intra-articular placebo, two of three studies showed no significant analgesic benefit. More recent studies do not enable differentiation of the effect of intra-articular NSAIDs from other components in the injected solution. No long-term follow-up looking at any effect on cartilage or bone healing from intra-articular injection of nsNSAIDs or coxibs has been undertaken.

4.3.3.2 Wound infiltration

Infiltration of the surgical wound with local anaesthetic/nsNSAID compared with local anaesthetic and IV nsNSAID showed no analgesic difference in three of five studies (overall WMD -6/100; 95%CI -19 to 6); similarly, wound infiltration with local anaesthetic/nsNSAID compared with local anaesthetic/placebo showed no analgesic benefit in four of five studies (Romsing 2000 **Level I**, 10 RCTs [wound], n unspecified).

4.3.3.3 Local infiltration analgesia

Local infiltration analgesia (LIA) involves the intraoperative periarticular infiltration of large volumes of local anaesthetic combined with a variety of adjuvants typically including an alpha2 agonist/vasoconstrictor, an opioid and/or an anti-inflammatory agent. The majority of investigations into the effectiveness of LIA in acute pain management following hip or knee arthroplasty fail to separate out the components of the mixture and some protocols also use catheter-based "top-up" regimens of varying composition. The lack of appropriate systemic comparators further complicates analysis of the role of the individual components. Ketorolac is the most frequently used nsNSAID in the LIA mixture. A systematic review identified no RCTs enabling a comparison of the efficacy of systemic vs periarticular administration of nsNSAIDs as a component of LIA in hip arthroplasty (Andersen 2014a **Level I** [PRISMA], 27 RCTs [hip], n=756).

In knee arthroplasty, one study compared epidural analgesia and two LIA groups: one with IV ketorolac and morphine (group A) and one with ketorolac and morphine in the LIA mixture (group B) in addition to ropivacaine and adrenaline (Spreng 2010 **Level II**, n=66, JS 5). Repeat intra-articular injection of ropivacaine and either intra-articular ketorolac or IV ketorolac occurred at approximately 24 h. Group B patients had a lower morphine consumption over 72 h than group A, although this was not associated with a difference in opioid-related adverse effects. There was a minimal analgesic benefit of group B over group A in pain at rest over 72 h after postanaesthesia care unit (PACU) discharge (mean reduction 5.3/100;

95%CI 0.25 to 10.3) but no significant difference in pain on knee flexion. The use of morphine in the initial dose in group B makes the specific role of ketorolac less obvious. Also in knee arthroplasty patients, LIA (ropivacaine/ketorolac/adrenaline) was compared with FNB (with a catheter infusion of local anaesthetic for 24 h) and systemic ketorolac (Affas 2011 **Level II**, n=40, JS 2). There was no significant difference in pain scores or morphine consumption over 24 h between groups.

4.3.3.4 Intravenous regional analgesia

Ketorolac 60 mg in combination with local anaesthetic for IV regional analgesia (IVRA) demonstrated longer time to first analgesia request compared with local anaesthetic IVRA with either IV ketorolac or IV placebo following minor upper limb procedures (Reuben 1995 **Level II**, n=60, JS 2). However, pain scores were low overall and this study was not blinded. Ketorolac 60 mg added to local anaesthetic for IVRA or infiltrated into the wound provided superior analgesia for up to 2 h following tourniquet release compared to patients receiving no ketorolac (Reuben 1996 **Level II**, n=60, JS 3). Again, pain scores were low for all groups and there was no separate parenteral dose of ketorolac. When varying doses of ketorolac were added to IVRA for hand surgery, a linear dose-response relationship from 5–20 mg was found; between 20 and 60 mg, there appeared to be no additional analgesic benefit (Steinberg 1998 **Level II**, n=75, JS 3). With IVRA doses of ≥20 mg compared with doses <20 mg, time to first analgesia was prolonged and pain scores were significantly lower for up to 2 h following tourniquet release. There was no comparison with ketorolac administered as a separate parenteral dose.

Overall, no conclusion can be drawn regarding a specific benefit of adding ketorolac to IVRA over parenteral administration by a separate route.

4.3.3.5 Nerve block

Parecoxib/ropivacaine improved quality and duration of brachial plexus block compared to placebo/ropivacaine and ropivacaine with IV parecoxib (Liu 2013 **Level II**, n=150, JS 5).

4.3.3.6 Topical

In adult patients with acute pain resulting from strains, sprains or sports injuries, topical diclofenac, ibuprofen, ketoprofen and piroxicam were found to be of similar efficacy, with an overall NNT for 50% reduction in pain of 4.5 (95%CI 3.9 to 5.3), whereas indomethacin and benzydamine were not significantly better than placebo (Massey 2010 **Level I** [Cochrane] 47 RCTs, n=3,455). The rate of systemic adverse effects with the topical NSAIDs was low and did not differ from placebo. The rate was also lower than with the same oral NSAID although there was limited data on direct comparison.

Diclofenac spray gel 3 times/d (Predel 2013 **Level II**, n=236, JS 4) or diclofenac gel at least 2 times/d (Predel 2012 **Level II**, n=242, JS 4) also had superior outcomes to placebo in ankle sprain. There are also statistically significant improvements vs placebo in a diclofenac patch formulation for soft tissue injuries (Kuehl 2010 **Level I**, 6 RCTs [of 8 studies included], n=1,371).

There was a small but significant reduction of pain with the use of topical NSAIDs for traumatic corneal abrasions (Calder 2005 **Level I**, 3 RCTs, n=459).

Topical NSAIDs were of limited efficacy in lateral elbow pain, providing short-term functional improvement for up to 2 wk (Pattanittum 2013 **Level I** [Cochrane], 8 RCTs, n=301). The overall quality of included studies was poor and findings heterogeneous. No comparisons with oral NSAIDs were included.

There is insufficient evidence to differentiate between routes of administration of NSAIDs in the treatment of acute low-back pain (Roelofs 2008 **Level I** [Cochrane], 65 RCTs, n=11,237).

Topical application of diclofenac results in tissue levels that are higher and plasma levels that are lower compared with oral administration (Zacher 2008 **Level I**, 19 RCTs, n>3,000). Topical NSAIDs were associated with fewer gastrointestinal adverse effects but more local skin irritation (Klinge 2013 **Level I**, 6 RCTs, n=600).

Microgranules containing flurbiprofen 8.75 mg provided better pain relief and reductions in difficulty in swallowing for sore throat than placebo with fast onset (1 min) and long duration (6 h) (Russo 2013 **Level II**, n=373, JS 5).

Key messages

1. Topical NSAIDs (except indomethacin) are effective in treating acute strains, sprains or sports injuries with systemic adverse effects comparable to placebo (**S**) (**Level I** [Cochrane Review]).
2. The efficacy of nsNSAIDs for peri or intra-articular injection as a component of local infiltration analgesia compared with systemic administration remains unclear (**N**) (**Level I** [PRISMA]).
3. Topical NSAIDs are effective analgesics for traumatic corneal abrasions (**U**) (**Level I**).
4. Intra-articular nonselective NSAIDs may provide more effective analgesia following arthroscopy than with IV administration (**N**) (**Level I**).

4.4 Local anaesthetics and other membrane stabilisers

4.4.1 Systemic local anaesthetics and other membrane stabilisers

4.4.1.1 Acute pain

Perioperative IV lignocaine (lidocaine) infusions in a wide dose range are opioid-sparing and significantly reduce pain scores at rest and during activity, nausea, vomiting and duration of ileus after abdominal surgery and also reduce length of hospital stay (Vigneault 2011 **Level I** [PRISMA], 29 RCTs, n=1,754; Sun 2012 **Level I** [PRISMA], 21 RCTs, n=1,108). Perioperative IV administration of lignocaine also has a preventive analgesic effect (extending beyond 5.5 half-lives of lignocaine, ie >8 h after cessation of administration) after a wide range of operations (Barreveld 2013a **Level I**, 16 RCTs, n=678).

IV lignocaine has a potentially an analgesic effect in procedural pain in burns (Wasiak 2012 **Level I** [Cochrane], 1 RCT, n=45).

The efficacy of lignocaine in the treatment of acute migraine is unclear. Analgesia provided by IV lignocaine was similar to dihydroergotamine but not as effective as chlorpromazine (Bell 1990 **Level II**, n=90, JS 4) and in one trial no better than placebo (Reutens 1991 **Level II**, n=25, JS 3). Results for IN lignocaine are conflicting showing significant benefit (Maizels 1996 **Level II**, n=53, JS 2) and no effect (Blanda 2001 **Level II**, n=49, JS 4).

Mexiletine improved pain relief and reduced analgesic requirements after breast surgery (Fassoulaki 2002 **Level II**, n=75, JS 3).

4.4.1.2 Chronic pain

The membrane stabilisers IV lignocaine and mexiletine have a similar analgesic effect on neuropathic pain of various origins, which is superior to placebo (WMD 10.6; 95%CI -14.5 to 6.7) (Tremont-Lukats 2005 **Level I,** 19 RCTs, n=706) and similar to various comparators (Challapalli 2005 **Level I** [Cochrane], 30 RCTs, n=1,142). There was strong evidence of benefit for use of membrane stabilisers in pain due to peripheral nerve trauma (Kalso 1998 **Level I**, 17 RCTs, n=450).

Currently, the use of membrane stabilisers for acute neuropathic pain can only be based on extrapolation of the above data.

Key messages

1. Perioperative intravenous lignocaine reduces pain and opioid requirements following abdominal surgery as well as nausea, vomiting, duration of ileus and length of hospital stay (**S**) (**Level I** [PRISMA]).
2. Perioperative intravenous lignocaine has a preventive analgesic effect (extending beyond 5.5 half-lives of lignocaine, ie > 8 hrs after cessation of administration) after a wide range of operations (**N**) (**Level I**).
3. Both IV lignocaine and mexiletine are effective in the treatment of chronic neuropathic pain. (**U**) (**Level I** [Cochrane]).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use membrane stabilisers including systemic lignocaine in the management of acute neuropathic pain (**U**).

4.4.2 Regional local anaesthetics

Local anaesthetics exert their effect as analgesics by blocking sodium channels and hence impeding neuronal excitation and/or conduction. Local anaesthetics differ predominantly by potency, duration of action and systemic toxicity.

4.4.2.1 Short-duration local anaesthetics

Lignocaine (lidocaine) is the most widely used short-duration local anaesthetic in acute pain management. Although the plasma half-life is approximately 90 min, the duration of local anaesthetic effect depends very much on site of administration, dose administered and the presence or absence of vasoconstrictors. Although lignocaine is hydrophilic, it is delivered in high concentrations and therefore usually diffuses well into nerve bundles, resulting in little separation of sensory and motor blocking actions (Covino 1998 **NR**).

The use of lignocaine in ongoing acute pain management is usually restricted to the short-term re-establishment of a local anaesthetic infusion block; it is unsuited to long-term (ie days) use because of the development of tachyphylaxis or acute tolerance (Mogensen 1995 **NR**). For example, continuous perineural infusions of lignocaine for 24 h resulted in less effective analgesia and more motor block than infusions of the long-acting local anaesthetic agent ropivacaine (Casati 2003c **Level II**, n=40, JS 4).

Mepivacaine is a short- to intermediate-duration local anaesthetic agent, structurally related to bupivacaine and ropivacaine. Its use is largely restricted to intraoperative anaesthesia.

4.4.2.2 Long-duration local anaesthetics

The three commonly used long-duration local anaesthetic agents, bupivacaine, levobupivacaine and ropivacaine, are structurally related (Markham 1996 **NR**; McLeod 2001 **NR**). Whereas bupivacaine is a racemic mixture of S- and R-enantiomers, levobupivacaine is the S-(or levo) enantiomer of bupivacaine; ropivacaine is likewise an S-enantiomer.

The issue with relative potency emerges with lower doses and concentrations of local anaesthetics. When doses are carefully titrated, a minimum local anaesthetic concentration (MLAC) can be found at which 50% of patients will achieve a satisfactory analgesic block. In obstetric epidural analgesia, two separate studies found the MLAC of bupivacaine was 0.6 times that of ropivacaine (Capogna 1999 **Level II**, n=87, JS 4; Polley 1999 **Level II**, n=83, JS 4). The motor-blocking potency showed a similar ratio of 0.66 (Lacassie 2003 **Level II**, n=60, JS 4).

When comparing bupivacaine with levobupivacaine, the “percentage” bupivacaine solution is by weight of bupivacaine hydrochloride, whereas the percentage levobupivacaine solution is for the active molecule alone. This means that the molar dose of equal “percentage concentration” is 13% higher for levobupivacaine (Schug 2001 **NR**). The sensory MLAC potency

ratio of levobupivacaine to bupivacaine is 0.98, although if correction is made for molar concentrations this falls to 0.87 (neither value being significantly different from unity) (Lyons 1998 **Level II**, n=60, JS 3). Levobupivacaine has been shown to have slightly less motor-blocking capacity than bupivacaine with a levobupivacaine/bupivacaine potency ratio for epidural motor block of 0.87 (95%CI 0.77 to 0.98) (Lacassie 2003 **Level II**, n=60, JS 4). Another labour epidural analgesia study has found no difference in MLAC between levobupivacaine and ropivacaine with a ropivacaine/levobupivacaine potency ratio of 0.98 (95%CI 0.80 to 1.20) (Polley 2003 **Level II**, n=83, JS 4).

4.4.2.3 Epidural local anaesthetics

For postoperative epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott 1995b **Level II**, n=30, JS 5; Schug 1996 **Level II**, n=36, JS 5). Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1% or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency.

The majority of studies find similar analgesic outcomes with postoperative epidural infusions based on these strengths (Jorgensen 2000 **Level II**, n=60, JS 3; Macias 2002 **Level II**, n=80, JS 5; Casati 2003b **Level II**, n=45, JS 5). Motor block is of clinical relevance in low-thoracic or lumbar epidural infusions and has been reported to be less intense with epidural ropivacaine than with bupivacaine (Zaric 1996 **Level II**, n=37, JS 3; Muldoon 1998 **Level II**, n=52, JS 4; Merson 2001 **Level II**, n=68, JS 4). However, this finding has not been supported by another study (Casati 2003b **Level II**, n=45, JS 5).

The relevance of dose, not concentration or volume of local anaesthetic infused, was confirmed in two trials. The same dose of a mixture of levobupivacaine in three different concentrations (0.5%, 0.25% and 0.15%) and sufentanil administered during continuous thoracic epidural infusion for thoracotomy resulted in similar efficacy and adverse effects (Mendola 2009 **Level II**, n=138, JS 3) as did two concentrations (0.15 and 0.5%) of levobupivacaine in another trial (Dernedde 2006 **Level II**, n=82, JS 4). Neither infusions of bupivacaine 0.125% nor ropivacaine 0.2% interfered with neurophysiological assessments after scoliosis surgery (Pham Dang 2008 **Level II**, n=18, JS 4). At concentrations of ≥0.5%, there were no significant differences in onset time and intensity or duration of sensory block between bupivacaine, levobupivacaine or ropivacaine used for epidural analgesia (Cheng 2002 **Level II**, n=45, JS 3; Casati 2003b **Level II**, n=45, JS 5).

Local anaesthetic/opioid combinations

The quality of pain relief from low-dose epidural infusions of plain local anaesthetic consistently benefits from the addition of opioids, most commonly fentanyl (Curatolo 1998 **Level I**, 18 RCTs [fentanyl/local anaesthetic], n unspecified; Walker 2002 **Level I**, 4 RCTs [epidural local anaesthetic/opioid combinations], n=226); this was confirmed by additional RCTs (Crews 1999 **Level II**, n=64, JS 3; Scott 1999 **Level II**, n=182, JS 5; Hubler 2001 **Level II**, n=109, JS 4; Senard 2002 **Level II**, n=60, JS 3). (For addition of other adjuvants see Sections 4.9 and 4.12.) Potential dose-sparing benefits are more obvious for local anaesthetic adverse effects (hypotension and motor block) than for opioid-related adverse effects (Walker 2002 **Level I**, 4 RCTs [epidural local anaesthetic/opioid combinations], n=226).

Comparisons of PCEA using ropivacaine 0.2%, ropivacaine 0.125% and levobupivacaine 0.125%, all with sufentanil 1 mcg/mL (6 mL background plus 2 mL bolus), showed no differences in pain relief or motor block; patients given 0.2% ropivacaine used similar volumes, thus receiving more total dose of local anaesthetic and the same amount of sufentanil (Sitsen 2007 **Level II**, n=63, JS 4). Similarly, there was no difference in analgesia and no motor block reported in a PCEA comparison of ropivacaine 0.05%, 0.075% and 0.1%, with fentanyl 4 mcg/mL and droperidol 25 mcg/mL added to all solutions (Iijima 2007 **Level II**, n=272, JS=4). In another comparison of PCEA 0.625% bupivacaine with fentanyl 3 mcg/mL and 0.15% ropivacaine alone, there was no difference in pain relief; patient satisfaction was lower with PCEA ropivacaine, even though it led to fewer opioid-related adverse effects (Pitimana-aree 2005 **Level II**, n=70, JS 3).

No studies directly compare fentanyl to morphine when added to local anaesthetic epidural infusions, although a single retrospective audit of the use of high-thoracic epidural following cardiac surgery suggested improved pain control and lowered infusion rate using ropivacaine 0.2% with morphine 20 mcg/mL compared with fentanyl 2 mcg/mL (Royse 2005 **Level III-3**). For information relating to the use of epidural local anaesthetics or opioid/local anaesthetic combinations for labour pain see Section 10.1.2.

4.4.2.4 Peripheral local anaesthetics

A number of studies have compared different local anaesthetics or doses of local anaesthetics used for continuous peripheral nerve block (CPNB).

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory block between bupivacaine, levobupivacaine or ropivacaine in sciatic (Casati 2002 **Level II**, n=50, JS 4), interscalene (Casati 2003a **Level II**, n=47, JS 5) or axillary brachial plexus blocks (McGlade 1998 **Level II**, n=61, JS 5). The intensity and duration of motor block is frequently less with ropivacaine compared with bupivacaine or levobupivacaine but this has little effect on the quality of block for surgery (McGlade 1998 **Level II**, n=61, JS 5; Casati 2003a **Level II**, n=47, JS 5). A comparison of three concentrations (0.1%, 0.2%, 0.3%) of ropivacaine for continuous FNB following total knee arthroplasty found that infusions of 0.2% and 0.3% ropivacaine had equivalent quality of postoperative analgesia (Brodner 2007 **Level II**, n=102, JS 4). After similar surgery, there was no difference in pain relief or motor block between patient-controlled FNB with 0.125% levobupivacaine and 0.2% ropivacaine (Heid 2008 **Level II**, n=60, JS 4).

Comparisons of two different patient-controlled CPNB regimens found different results depending on the location of the block; the regimens were ropivacaine at 4 mL/h 0.4% (bolus 2 mL) or 8 mL/h 0.2% (bolus 4 mL). For continuous popliteal nerve block, the larger volumes of the dilute local anaesthetic were more likely to cause an insensate limb (Ilfeld 2008 **Level II**, n=50, JS 3); for continuous interscalene nerve block there was no difference between the two solutions (Le 2008 **Level II**, n=50, JS 2) and for continuous infraclavicular nerve block the smaller volumes of the more concentrated local anaesthetic were more likely to cause an insensate limb (Ilfeld 2009 **Level II**, n=50, JS 3).

Another comparison of patient-controlled continuous interscalene block using 0.25% levobupivacaine, 0.25% ropivacaine and 0.4% ropivacaine reported less effective pain relief with the lower concentration of ropivacaine (Borghi 2006 **Level II**, n=72, JS 5). Continuous popliteal sciatic nerve block using 0.2% ropivacaine, 0.2% levobupivacaine and 0.125% levobupivacaine resulted in similar pain relief after foot surgery but fewer patients had complete recovery of motor function at 24 and 48 h with 0.2% levobupivacaine (Casati 2004 **Level II**, n=60, JS 5).

Skin infiltration

Increasing the pH of commercial lignocaine (to ≥7.35 by the addition of sodium bicarbonate prior to injection) reduces pain scores on injection for invasive procedures in cross-over studies (WMD -2/10; 95%CI -2.6 to -1.3) (10 RCTs) and in parallel design studies (WMD 1/10; 95%CI -1.4 to -0.4) (7 RCTs) (Cepeda 2010 **Level I** [Cochrane], 23 RCTs, n=1,067). The magnitude of the decrease in pain is larger when the solution contains adrenaline (WMD 2.5/10; 95%CI -3.2 to -1.7) (6 RCTs, n=232).

Warming the solution (to 37–43°C) assessed mostly in adults reduces pain on SC or intradermal injection overall (WMD -11/100; 95%CI -14 to -7) (18 RCTs, n=831) and when the local anaesthetic is buffered (WMD -7/100; 95%CI -12 to -3) (8 RCTs, n=412) Hogan 2011 **Level I** [PRISMA], 18 RCTs, n=831).

Local infiltration analgesia

A "cocktail" is most commonly used for periarticular LIA comprising a local anaesthetic, an alpha-2 agonist/vasoconstrictor, an opioid and an anti-inflammatory agent. The majority of investigations into the effectiveness of LIA in acute pain management following hip or knee arthroplasty fail to separate out the components of the mixture and some protocols use

"top-up" regimes of varying composition (Andersen 2014a **Level I** [PRISMA], 27 RCTs, n=1,644). In hip joint arthroplasty (n=756), multimodal systemic analgesia or neuraxial techniques (IT morphine or epidural analgesia) have similar analgesic efficacy compared to LIA; however in total knee joint arthroplasty, LIA provided superior analgesia to placebo (n=328). Compared with FNB, epidural analgesia or IT morphine, LIA provided similar or improved analgesia in the early postoperative period, but most trials had a high risk of bias due to different systemic analgesia regimens between groups. Overall, the use of wound catheters for postoperative administration of local anaesthetic following LIA was not supported in the included trials.

Despite the many studies of LIA, final interpretation is hindered by methodological insufficiencies in most studies, especially because of differences in use of systemic analgesia between groups. (See also Section 5.8.2.1.)

Slow-release preparations for local anaesthetics

Encapsulation of bupivacaine within liposomes in clusters of <100 microns diameter results in drug release into adjacent tissues for a number of days following injection, with peak plasma levels occurring 12–36 h after injection (Skolnik 2014 **NR**). Current indications from trial data have not raised any specific safety concerns (Viscusi 2014 **Level I**, 10 RCTs, n=823). A limited number of trials have been conducted with wound infiltration, perineural block and epidural administration (see Section 4.1.2.2 for ER epidural opioid preparations); most trials have demonstrated analgesic superiority over placebo for up to 72 h, however benefit over normal formulations of bupivacaine has not been shown (Tong 2014 **Level III-2 SR**, 5 studies, n unspecified). Trials to date have been relatively small and firm conclusions regarding the efficacy and indications for liposomal bupivacaine cannot yet be made.

4.4.3 Local anaesthetic toxicity

4.4.3.1 Direct toxicity

All local anaesthetics exhibit neurotoxicity if nerves are exposed to sufficiently high concentrations for a sufficiently long period. Lignocaine (5%) infused via lumbar subarachnoid microcatheters has been associated with case reports of cauda equina syndrome (Rigler 1991 **Level IV**; Schell 1991 **Level IV**). This suggested that high local concentrations of lignocaine were potentially neurotoxic and led to the technique falling into disfavour.

Transient neurological symptoms (TNS) is a clinical syndrome associated with spinal (IT) anaesthesia. Patients experience pain or muscle spasms in the buttocks or lower limbs following initial recovery from the spinal anaesthetic. The onset of symptoms is usually within 24 h of the procedure and it fully resolves spontaneously within a few days. Despite its name, there is no evidence that this condition is associated with actual neurologic pathology. A meta-analysis compared the frequency of TNS and neurological complications after spinal anaesthesia with lignocaine to other local anaesthetics (Zaric 2009 **Level I** [Cochrane], 16 RCTs, n=1,467); the overall incidence is 14.2% following lignocaine and the relative risk for developing TNS after spinal anaesthesia with lignocaine compared with other local anaesthetics (bupivacaine [7 RCTs], prilocaine [4 RCTs], procaine [2 RCTs], levobupivacaine [1 RCT], ropivacaine [1 RCT] and 2-chloroprocaine [1 RCT]) is 7.31 (95%CI 4.16 to 12.86); there is no association with baricity or lignocaine concentration in the individual studies that compared these factors. Mepivacaine (4 RCTs) gives similar results to lignocaine and was not included in the pooled analysis.

4.4.3.2 Systemic toxicity

There is consistent laboratory data showing that the S-enantiomers of the long-acting amide local anaesthetics exhibit less CNS or cardiac toxicity than the R-enantiomers or the racemic mixtures for doses resulting in equivalent sensory nerve conduction block. Defining relative toxicities for these agents is complex because it depends on the parameters measured (eg cardiac, CNS), the dose, route and species studied. There is lack of scientific data available to determine a safe maximal dose of local anaesthetic. However the upper limit of a dose should take into account patient weight, age and comorbidities. There is a pharmacokinetic

rationale to support fractional dosing by incremental injection of local anaesthetic in addition to identifying unintended intravascular injection.

The incidence of local anaesthetic systemic toxicity (LAST) has been quantified using a large registry database (25,336 peripheral nerve blocks [PNBs]), which identified 22 LAST episodes (0.87 per 1,000 blocks; 95%CI 0.54 to 1.3) over a 5-y reporting period (Barrington 2013 **Level IV**). The use of ultrasound (US) was associated with a reduced incidence of LAST (OR 0.23; 95%CI 0.088 to 0.59). This finding is consistent with a meta-analysis, which finds a significantly decreased risk of vascular puncture using US (RR 0.16; 95%CI 0.05 to 0.47) (Abrahams 2008 **Level I**, 13 RCTs, n=946). Factors associated with increased LAST events are paravertebral (OR 9.20; 95%CI 2.24 to 37.8) and upper limb (OR 4.80; 95%CI 1.23 to 18.7) blocks, the use of lignocaine compared with ropivacaine (OR 5.64; 95%CI 2.02 to 15.7) and larger doses of local anaesthetic (Barrington 2013 **Level IV**).

In blinded human-volunteer studies, CNS symptoms were detected at IV doses and plasma levels that were 25% higher for ropivacaine compared with bupivacaine (Scott 1989 **Level II EH,** n=12, JS 2) and 16% higher for levobupivacaine than bupivacaine (Bardsley 1998 **Level II EH**, n=14, JS 3). Although these data show that CNS toxicity might occur less frequently or be less severe with the S-enantiomers, all local anaesthetics are toxic. A rapid IV bolus of any of these agents may overwhelm any of the more subtle differences found at lower plasma concentrations.

Severe myocardial depression and refractory ventricular fibrillation have been described as the hallmark of accidental IV administration of moderately large doses of bupivacaine. This has been attributed to the slow dissociation of bupivacaine from the myocardial sodium channel, which is less marked with levobupivacaine and ropivacaine (Mather 2001 **NR**). Animal studies confirm that higher systemic doses of ropivacaine and levobupivacaine are required to induce ventricular arrhythmias, circulatory collapse or asystole (Ohmura 2001 **BS**), with the ranking of toxicity risk being bupivacaine > levobupivacaine > ropivacaine (Groban 2001 **NR**).

Controlled human studies are only possible when looking at surrogate endpoints such as ECG changes or myocardial depression and suggest a similar ranking of effect (Scott 1989 **Level II EH**, n=12, JS 5; Knudsen 1997 **Level II EH**, n=12, JS 5; Bardsley 1998 **Level II EH**, n=14, JS 5), with bupivacaine being the most toxic and levobupivacaine being less toxic and similar to ropivacaine (Stewart 2003 **Level II EH**, n=14, JS 5).

Successful resuscitation from a massive overdose is of greater relevance in clinical practice. A canine study investigating resuscitation and survival following local anaesthetic-induced circulatory collapse showed survival rates of 50%, 70% and 90% with bupivacaine, levobupivacaine and ropivacaine respectively (Groban 2001 **NR**).

Case reports of accidental toxic overdose with ropivacaine suggest that outcomes are more favourable and resuscitation more straightforward (in particular requiring less cardiovascular support) than with racemic bupivacaine (Pham-Dang 2000 **CR**; Chazalon 2003 **CR**; Huet 2003 **CR**; Klein 2003 **CR**; Soltesz 2003 **CR**; Khoo 2006 **CR**; Kimura 2007 **CR**; Hubler 2010 **CR**; Weiss 2014 **CR**).

Total plasma levels of local anaesthetic tend to rise during the first 48 h of postoperative infusion, although free levels remain relatively low (Emanuelsson 1995 **EH PK**; Scott 1997 **Level IV**). Thus, in published studies, toxicity due to systemic absorption from epidural or perineural infusions has not been a problem. However, the risk of accidental absolute overdose with postoperative infusions suggests that the less toxic agents should be used in preference and that the doses administered should be the minimum needed for efficacy.

Lipid emulsion therapy

Lipid emulsion therapy is advocated for the treatment of LAST. There is basic scientific evidence and many case reports to support the use of IV lipid emulsion therapy for LAST resulting in cardiovascular collapse (Felice 2008 **Level IV**; Cave 2014 **Level IV**). Animal experimental data (Weinberg 2003 **BS**; Weinberg 1998 **BS**) has been supported by case reports of successful resuscitation following bupivacaine (Rosenblatt 2006 **CR**), ropivacaine (Litz 2006 **CR**), levobupivacaine (Foxall 2007 **CR**) mepivacaine/prilocaine (Litz 2008 **CR**) and mepivacaine/bupivacaine (Warren 2008 **CR**) toxicity.

The mechanism of action of the lipid emulsion may be due to partitioning of local anaesthetic within the emulsion itself (acting as a "lipid sink")(Weinberg 2006 **NR**), mitochondrial substrate enhancement in the myocardium (Weinberg 2000 **BS**) and/or a direct inotropic effect (Fettiplace 2014 **BS**). Uncertainties relating to dosage, efficacy and adverse effects (Cave 2014 **Level IV**) still remain and therefore it is recommended to administer lipid emulsion only after advanced cardiac life support, including adrenaline administration, has commenced and convulsions are controlled (Corman 2007 **Level IV**). Guidelines have been established to facilitate management of local anaesthetic toxicity, which now include reference to lipid emulsion therapy (AAGBI 2010 **GL**; Neal 2010 **GL**). It should be noted that local anaesthetic toxicity might recur following successful initial resuscitation, suggesting a need for continued intensive observation if a large dose of local anaesthetic has been administered (Marwick 2009 **GL**).

Key messages

1. Lignocaine intrathecal is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**U**) (**Level I** [Cochrane Review]).
2. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level I**).
3. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blocks (**S**) (**Level I**).
4. Continuous perineural infusions of lignocaine (lidocaine) result in less effective analgesia and more motor block than long-acting local anaesthetic agents (**U**) (**Level II**).
5. There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine in terms of quality of analgesia or motor block, when given in low doses for regional analgesia (epidural and peripheral nerve block) (**U**) (**Level II**).
6. Cardiovascular and central nervous system toxicity of the stereospecific isomers ropivacaine and levobupivacaine is less severe than with racemic bupivacaine (**U**) (**Level II**).
7. Local anaesthetic systemic toxicity is reduced by the use of ultrasound guidance for regional anaesthesia (**N**) (**Level IV**).
8. Local anaesthetic systemic toxicity is increased in paravertebral and upper limb blocks, with the use of lignocaine and higher doses of local anaesthetics (**N**) (**Level IV**).
9. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity (**S**) (**Level IV**); however uncertainties relating to dosage, efficacy and adverse effects still remain; therefore it is appropriate to administer lipid emulsion only once advanced cardiac life support has begun and convulsions are controlled (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Case reports following accidental overdose with ropivacaine, levobupivacaine and bupivacaine suggest that resuscitation is less likely to be successful with bupivacaine (**Q**).

4.5 Inhalational agents

4.5.1 Nitrous oxide

N_2O has been used since the inception of anaesthesia for its modest analgesic and sedative properties. It has minimal respiratory and cardiovascular depression. In many countries it is available as a 50% N_2O /50% oxygen mixture called Entonox®. While it has a long history of use, there is a paucity of good studies examining its effectiveness in comparison with other analgesics.

In a meta-analysis of inhaled analgesics in labour, subgroup analysis of N_2O shows minimal analgesic difference compared with placebo (RR 0.06; 95%CI 0.01 to 0.34) (MD 3.5/100; 95%CI -3.75 to -3.25) (Klomp 2012 (**Level I** [Cochrane], 3 RCTs [N_2O], n=819). A systematic review

shows that N_2O in oxygen has some analgesic efficacy in labour (Likis 2014 **Level IV SR**, 58 studies, n=20,266). Only two studies were of good quality. N_2O provides less analgesia than epidural analgesia but more than pethidine, or bath and shower. Maternal satisfaction with the birth experience using N_2O for analgesia is higher than for pethidine or epidural analgesia. The reports of maternal adverse effects in this review are nausea, vomiting, dizziness and drowsiness. Apgar scores are no different for N_2O when compared with no analgesia. (See also Section 10.1.2.)

For lower gastrointestinal endoscopy, there is no difference in pain scores between N_2O and IV opioid/midazolam, or the ability to successfully complete the procedure (Welchman 2010, **Level I**, 11 RCTs, n=623). The N_2O group has a shorter time to achieve fitness for discharge.

N_2O was effective during painful procedures such as bone marrow aspiration (Gudgin 2008 **Level III-3**), venous cannulation (Gerhardt 2001 **Level II**, n=10, JS 5), sigmoidoscopy (Harding 2000 **Level II**, n=77, JS 5) and liver biopsy (Castera 2001 **Level II**, n=100, JS 5) and in relieving acute ischaemic chest pain (O'Leary 1987 **Level II**, n=12, JS 2) and in trauma patients in the prehospital setting (Ducasse 2013 **Level II,** n=60, JS 4). In elderly patients (median age 84 y), N_2O provided better analgesia than morphine during bed sore and ulcer care (Paris 2008b **Level II**, n=34, JS 3).

In children, N_2O was effective in reducing pain associated with IV cannulation (Henderson 1990 **Level II**, n=165, JS 2; Hee 2003 **Level III-2**; Ekbom 2005 **Level III-2**), urethral catheterisation (Zier 2007 **Level III-2**) and laceration repair (Burton 1998 **Level II**, n=30, JS 5; Luhmann 2006 **Level II**, n=102, JS 3). It has been reported to provide analgesia for the pain associated with fracture manipulation in children (Gregory 1996 **Level III-1**; Evans 1995 **Level III-1**), although its efficacy as an analgesic during very painful procedures may be limited (Babl 2008 **Level IV**).

In the experimental setting, a study measuring changes in detection and pain thresholds to electrical tooth stimulation, reported the development of acute and chronic tolerance in response to single and repeated administration of N_2O (38% or 35%) for 30 min (Ramsay 2005 **EH**). The significance of this finding in the clinical setting is unknown.

A *post-hoc* analysis of an RCT using telephone interviews at a median of 4.5 y following (mostly abdominal) surgery found that the intraoperative use of N_2O reduced the risk of chronic postsurgical pain in an Asian population (OR 0.48; 95%CI 0.33 to 0.93) (Chan 2011 **Level II**, n=423, JS 5); factors increasing risk included severity of acute postoperative pain, wound length, wound infection and anxiety.

N_2O diffuses more rapidly than nitrogen and can expand enclosed air-containing spaces within the body. Its use is therefore contraindicated in the presence of a pneumothorax, obstruction of middle ear and sinus cavities, recent vitreoretinal surgery, pneumocephalus, bowel obstruction and gas embolism (Shaw 1998 **NR**).

4.5.1.1 Toxicity

N_2O oxidises the cobalt ion of cobalamin (vitamin B_{12}) preventing it from acting as a coenzyme for methionine synthetase; methionine synthetase also requires 5-methyltetrahydrofolate as a coenzyme (Sanders 2008 **NR**). Methionine synthetase is required for the synthesis of deoxyribonucleic acid and ribonucleic acid and therefore the production of cells in rapidly dividing tissues such as bone marrow and gastrointestinal mucosa, as well as the synthesis of myelin (Sanders 2008 **NR**). Exposure of young children (median age 11 mth) to N_2O anaesthesia for more than 2 h leads to a statistically significant but small increase in total homocysteine plasma concentrations on the first postoperative morning with unclear clinical relevance (Pichardo 2012 **Level IV**).

Bone marrow and neurological complications have been reported in patients exposed to N_2O. The risk may be greater in critically ill patients with increased metabolic demands or poor nutrition (Amos 1982 **Level IV**).

N_2O-induced bone marrow toxicity leading to megaloblastic anaemia is usually progressive but reversible. The bone marrow changes are almost completely prevented by administration of folinic acid (Amos 1982 **Level IV**).

Neurotoxicity associated with N_2O use is rare but can be rapid and may be irreversible. Patients deficient in vitamin B_{12}, including those with a subclinical deficiency (ie without an associated anaemia), may develop a severe and progressive myeloneuropathy even after brief exposure to N_2O. There are many examples of such in case reports (Schilling 1986 **Level IV**; Holloway 1990 **Level IV**; Flippo 1993 **Level IV**; Kinsella 1995 **CR**; Nestor 1996 **CR**; Rosener 1996 **CR**; Sesso 1999 **CR**; Marie 2000 **CR**; Waters 2005 **CR**; Cartner 2007 **CR**; Wu 2007 **CR**; Meyers 2008 **CR**; Singer 2008 **CR**; Somyreddy 2008 **CR**; Safari 2013 **CR**). Those at risk of vitamin B_{12} deficiency include some vegetarians (in particular vegans) (Rosener 1996 **CR**), the newborns of vegetarian mothers (McNeely 2000 **CR**), patients with gastrointestinal pathology (Schilling 1986 **Level IV**) or phenylketonuria (Walter 2011 **NR**), elderly people (Nilsson-Ehle 1998 **NR**), patients taking PPIs (Schenk 1999 **Level IV**) or H2 blockers and alcoholics (Carmel 2000 **NR**); Sanders 2008 **NR**). In individuals who are not vitamin B_{12} deficient, larger quantities or more prolonged use of N_2O seems to be required before neurotoxicity is seen. Cases have also been reported in those abusing the drug (eg obtained from whipped cream containers) or being exposed to N_2O for medical purposes after longer periods of abuse (Sanders 2008 **NR**; Lin 2011 **Level IV**; Ghobrial 2012 **CR**; Chiang 2013 **CR**; Cheng 2013 **CR**; Hu 2014 **CR**; Rheinboldt 2014 **CR**).

The neuropathy appears to be the result of decreased methionine and subsequent defective myelin formation. The clinical and radiological (magnetic resonance imaging [MRI]) picture is that of a vitamin B_{12} deficiency, where subacute combined degeneration (SACD) of the spinal cord causes numbness, tingling, paresthesiae, ataxia and spasticity (Weimann 2003 **NR**). Involvement of peripheral, autonomic and central nervous systems may also lead to incontinence, diplopia, confusion or impaired cognitive function (Weimann 2003 **NR**). In patients with pernicious anaemia, SACD usually responds well to treatment with vitamin B_{12}, although it may take many months and response to treatment may be incomplete (Toh 1997 **NR**). Patients with SACD related to N_2O exposure may sometimes show improvement after administration of vitamin B_{12} +/- methionine (Wu 2007 **CR**; Meyers 2008 **CR**; Singer 2008 **CR**), although this is not always the case. Early diagnosis and treatment with daily parenteral vitamin B_{12} improves outcomes (Gursoy 2013 **Level IV**).

Despite the lack of any good data assessing efficacy in humans, and even though the bone marrow changes are usually reversible, it may be reasonable to give patients repeatedly exposed to N_2O, vitamin B_{12} and folic or folinic acid supplements (Weimann 2003 **NR**).

Another consequence of N_2O-induced inactivation of methionine synthetase is elevation of plasma homocysteine (a known risk factor for coronary artery and cerebrovascular disease), the levels of which rise after anaesthesia using N_2O (Badner 1998 **Level II**, n=20, JS 2; Myles 2008 **Level II**, n=59, JS 3; Nagele 2008 **Level III-3**). Patients who are homozygous for polymorphisms in the gene encoding the enzyme that is an antecedent to methionine synthetase are at a higher risk of developing abnormal plasma homocysteine concentrations after N_2O anaesthesia (Nagele 2008 **Level III-3**). However, the large ENIGMA II study, comparing oxygen 30% with or without N_2O (70%) in patients with known or risk factors for ischaemic heart disease, found no difference in serious adverse effects in the N_2O group compared with the non-N_2O group (Myles 2014 **Level II**, n=7112, JS 3). However, as this study examined patients who were undergoing major surgery that lasted for at least 2 h, the applicability to the setting of analgesia may be limited.

Methionine given preoperatively to patients undergoing N_2O anaesthesia improved the rate of recovery of methionine synthetase and prevented the prolonged postoperative rise in plasma homocysteine concentrations (Christensen 1994 **Level IV**). Preoperative administration of oral B vitamins (folate, B_6 and B_{12}) (Badner 2001 **Level II**, n=53, JS 3) and of vitamin B_{12} infusions (Kiasari 2014 **Level II**, n=60, JS 5) also prevented the postoperative increase in homocysteine following N_2O anaesthesia.

The information about the complications of N_2O derives from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to N_2O in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to N_2O. Nevertheless, the severity of the potential problems requires highlighting. The suggestions for the use of N_2O outlined below are extrapolations only from the information above.

4.5.1.2 Suggestions for the use of nitrous oxide as an analgesic

When N_2O is to be used repeatedly for painful short procedures, it may be reasonable to:

- exclude patients with a known vitamin B_{12} deficiency;
- screen patients at risk of vitamin B_{12} deficiency by examination of the blood picture and serum B_{12} concentrations before using N_2O;
- exclude asymptomatic patients with macrocytic anaemia or hypersegmentation of neutrophils until it is established that vitamin B_{12} or folate deficiency is not the cause;
- exclude females who may be in the early stages of pregnancy, although this will depend on the relative harm of any alternative methods;
- limit exposure to N_2O to the briefest possible time — restricting the duration of exposure may require strict supervision and limited access to the gas;
- administer methionine, vitamin B_{12} (both cheap with a good safety profile) and possibly folic or folinic acid to patients repeatedly exposed to N_2O (doses that may prevent the complications of exposure to N_2O have not been established); and
- monitor for clinical signs and symptoms of neuropathy on a regular basis.

4.5.2 Methoxyflurane

Methoxyflurane is a volatile anaesthetic agent with analgesic properties. It was first marketed in 1962 and later withdrawn from sale in 2001. The FDA withdrew the medicine because of the risk of nephrotoxicity and hepatotoxicity and stated that it would not consider reintroduction into the market until new clinical trials were undertaken (FDA 2005a). Methoxyflurane is no longer licensed for anaesthesia in humans..

Although no longer used as an anaesthetic, methoxyflurane has been registered in Australia and New Zealand (as well as now a number of other countries) for use as an analgesic in low doses since 1975 for relief of trauma-associated acute pain as well as procedural pain. (Medical Devices International 2009). It is available as a self-administered "Penthrox®" inhaler, which dispenses 0.2–0.4% methoxyflurane (Medical Devices International 2009).

As an analgesic in prehospital and ED settings methoxyflurane has been reported as effective (Grindlay 2009 **Level IV SR,** 48 studies, n unspecified). In ED patients aged ≥12 y it was significantly more analgesic than placebo, with only mild transient adverse effects such as dizziness and headache (Coffey 2014 **Level II**, n=300, JS 4). The median time to onset of analgesia was rapid at 4 min and time to peak analgesia was 15 min. Safety was assessed over 14 d following administration and no significant adverse effects were found, including no renal impairment. Use of the Penthrox® inhaler in children reduced pain associated with extremity injuries (Babl 2006 **Level IV**) but did not provide adequate analgesia for subsequent fracture manipulation (Babl 2007 **Level IV**). It also provided effective pain relief for adult patients in the prehospital setting, as shown in 83 adults travelling by ambulance to an urban teaching hospital (Buntine 2007 **Level IV**). Adverse effects included hallucinations, vomiting, confusion and dizziness, and sedation/drowsiness was common (26%) in children (Babl 2006 **Level IV**; Buntine 2007 **Level IV**).

As an analgesic for painful procedures outside of the ED, methoxyflurane was first described for obstetric analgesia in 1966 (Bodley 1966 **Level IV**) and then used as an analgesic for burns dressings (Packer 1969 **Level IV**; Calverley 1972 **Level IV**; Marshall 1972 **Level IV**; Firn 1972 **Level IV**). Methoxyflurane was effective for prostate biopsies (n=42) achieving a low pain score (median 3), mild adverse effects and high patient acceptance (Grummet 2012 **Level IV**). In patients having colonoscopies, methoxyflurane compared with IV fentanyl plus midazolam resulted in similar pain scores but shorter recovery and fitness for discharge times, no respiratory depression, and high degree of patient satisfaction (Nguyen 2013 **Level II** n=250, JS 3). Ten patients in the methoxyflurane group required supplementation with IV sedation.

In patients having bone-marrow biopsies, local anaesthetic infiltration plus methoxyflurane vs placebo inhaler resulted in lower worst pain scores (4.9 vs 6.0; p=0.011) (Spruyt 2014 **Level II**, n=97, JS 4). Adverse effects were mild and of short duration.

4.5.2.1 Toxicity

Methoxyflurane causes a dose-dependent renal toxicity and, as noted above, renal failure was a key reason behind the withdrawal of the medicine from use. Use of an analgesic device delivering higher concentrations of methoxyflurane was reported to have led to two fatalities from renal toxicity (Toomath 1987 **Level IV**). However, the amount of methoxyflurane delivered using the Penthrox® inhaler is said to be significantly less than the dose that has been associated with subclinical nephrotoxicity (Grindlay 2009 **NR**). There have been no reports of toxicity (Grindlay 2009 **NR**) with dosing limited to 6 mL/d or 15 mL/wk (Medical Devices International 2009). A large population database study (n=17,629) found no long-term (up to 14 y) adverse effects (heart disease, renal disease, hepatic disease, diabetes, or cancer) in patients who had been given methoxyflurane by an ambulance service (Jacobs 2010 **Level IV**).

There has been one documented case report of acute hepatitis following three administrations of methoxyflurane in an otherwise healthy woman for procedural analgesia (O'Rourke 2011 **CR**).

Methoxyflurane is contraindicated in patients with known or at genetic risk of malignant hyperpyrexia (Medical Devices International 2009).

Key messages

1. Nitrous oxide has some analgesic efficacy in labour pain (**S**), increases maternal adverse effects (nausea, vomiting, dizziness) (**N**), with no adverse effects on the newborn (**S**) (**Level I** [Cochrane Review]) and increases maternal satisfaction compared to pethidine and epidural analgesia (**N**) (**Level IV SR**).
2. Nitrous oxide has equivalent effectiveness and more rapid recovery compared with intravenous sedation in patients having lower gastrointestinal endoscopy (**N**) (**Level I**).
3. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations (**U**) (**Level II**).
4. Methoxyflurane, in low doses, is an effective analgesic with rapid onset in the prehospital setting, and a range of procedures in the hospital setting with good safety data (**S**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Neuropathy and bone marrow suppression are rare but potentially serious complications of nitrous oxide use, particularly in at-risk patients, including those abusing nitrous oxide (**S**).
- ☑ The information about the complications of nitrous oxide for procedural pain is from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to nitrous oxide in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to nitrous oxide. The suggestions for the use of nitrous oxide are extrapolations only from the information above. Consideration should be given to the duration of exposure and supplementation with vitamin B_{12}, methionine, and folic or folinic acid (**U**).
- ☑ If nitrous oxide is used with other sedative or analgesic agents, appropriate clinical monitoring should be used (**U**).

4.6 NMDA-receptor antagonists

NMDA-receptor/ion-channel complexes are located peripherally and centrally within the nervous system (Gonda 2012 **NR**). These ionotropic receptors are an important component of glutamergic neurotransmission and thereby involved in multiple functions within the nervous system including learning and memory, cognitive functions, neural development, neuroplasticity, excitotoxicity, addiction, psychiatric disorders and nociception.

At the spinal level, NMDA-receptor activation results in the development of central sensitisation manifested clinically as hyperalgesia and allodynia (Hocking 2007 **NR**, Petrenko 2014 **NR**). Activation of NMDA receptors via glutamate release from excitatory synapses augments the propagation of nociceptive information and is therefore linked to acute and chronic pain states as well as opioid-induced tolerance and hyperalgesia.

The NMDA-receptor antagonists ketamine, dextromethorphan, amantadine, memantine and magnesium have been investigated for the management of acute pain (Suzuki 2009 **NR**).

4.6.1 Systemic NMDA-receptor antagonists

4.6.1.1 Ketamine

In low (subanaesthetic) doses, ketamine acts primarily as a noncompetitive antagonist of the NMDA receptor, although it also binds to many other sites in the peripheral and central nervous systems (Mion 2013 **NR**, Petrenko 2014 **NR**, Sleigh **NR**). In more detail it is a "high-trapping" antagonist with a slow off-rate, causing a prolonged tonic block; therefore it has higher adverse effect rates than "low-trapping" antagonists with a fast off-rate such as memantine (Sleigh **NR**). Consequently, ketamine's main role is as an adjuvant in the treatment of pain associated with central sensitisation (Persson 2013 **NR**), such as in severe acute pain, neuropathic pain (Zhou 2011 **NR**) (see Section 8.1.4) and "opioid-resistant" pain (Tawfic 2013 **NR**) (see Section 10.6). (See also Section 9.4.5 for use in children for acute pain.)

Perioperative use

Perioperative IV ketamine reduces opioid consumption, time to first analgesic request and PONV when compared to placebo (Laskowski 2011 **Level I** [PRISMA], 70 RCTS, n=4,701). Furthermore, analgesia is better in 78% of ketamine-treated groups. Neuropsychiatric effects (hallucinations and nightmares) increase with ketamine use but sedation is not increased. A dose-dependent analgesic effect is not apparent. The benefits are seen in particular in patients with severe pain (VAS >7/10) and are not seen in patients with mild pain (VAS <4/10). By site of surgery, ketamine is particularly effective after thoracic, upper abdominal and major orthopedic surgery, while there is no benefit after tonsillectomy, dental or head and neck surgery. When ketamine is added to the opioid in the PCA solution, analgesic benefits are found following thoracic surgery but not orthopaedic and abdominal surgery due in part to the heterogeneity of these studies and small sample sizes (Carstensen 2010 **Level I**, 11 RCTs, n=811). In line with these findings, specifically after thoracotomy, addition of ketamine to IV morphine PCA was opioid-sparing and improved analgesia in all RCTs and increased patient satisfaction in one (Mathews 2012 **Level I**, 5 RCTs, n=243). Improved respiratory outcomes (oxygen saturations and $PaCO_2$) were found in the RCTs assessing these parameters (2 RCTs, n=89).

Subsequent to these meta-analyses, multiple further RCTs studying the same issue have been performed; overall the outcomes from these studies do not affect the existing conclusions and they are therefore not referenced here.

Subanaesthetic doses of IM ketamine (escalating from 5–25 mg) injected two to three times 17–4 h before cancer surgery reduced postoperative pain and morphine consumption in comparison to a single injection 4 h before surgery and placebo (Rakhman 2011 **Level II**, n=120, JS 5).

Morphine/ketamine vs higher doses of morphine alone improves analgesia (MD 2.19/10; 95%CI 1.24 to 3.13) and wakefulness (MD -1.53/10; 95%CI -2.67 to -0.40) and reduces PONV (OR 3.71; 95%CI 2.37 to 5.80) and need for nonopioid rescue analgesia (Ding 2014

Level I, 7 RCTS, n=492). For multilevel lumbar arthrodesis, a ketamine bolus at induction and a postoperative combination of methadone/ketamine via IV PCA vs methadone alone reduced opioid requirements by 70% over 24 h (Pacreu 2012 **Level II**, n=22, JS 5).

Low-dose parenteral ketamine may also improve analgesia in patients with opioid-induced tolerance or hyperalgesia. After spinal fusion in opioid-tolerant patients, use of a continuous ketamine infusion resulted in significantly less pain but did not reduce PCA opioid requirements (Urban 2008 **Level II**, n=24, JS 4). Similar results were found after noncancer surgery (Barreveld 2013b **Level II**, n=64, JS 5). A preoperative ketamine bolus for extracorporeal shock-wave lithotripsy reduced opioid requirements in chronic opioid users on low and high doses (Gharaei 2013 **Level II**, n=190, JS 4). However, when opioid-tolerant patients had epidural analgesia and IV PCA after spinal surgery, the addition of ketamine bolus and 24 h infusion conveyed no further benefit vs placebo (Subramaniam 2011 **Level II**, n=30, JS 5); the patients in this study also received gabapentin and antidepressants.

NMDA-receptor antagonists (mainly ketamine [8 RCTs] but also magnesium [5 RCTs] and amantadine [1 RCT]) reduce the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 14 RCTs, n=729). This assessment is based on reduced postoperative pain scores and opioid requirements and increased time to first analgesic request and satisfaction scores in the NMDA-receptor antagonist vs the placebo groups but not on QST. These results negate a preceding meta-analysis with eight RCT overlap (5 RCTs [ketamine], 3 RCTs [magnesium]) and poorer methodology, which found only limited benefits (Liu 2012b **Level I**, 14 RCTs (10 ketamine and 4 magnesium), n=623).

After laparoscopic gastric banding in obese patients, intraoperative ketamine infusion reduced pain and PCA opioid requirements (Andersen 2014b **Level I**, 1 RCT, n=60).

Use of a low-dose (0.05 mg/kg/h) IV ketamine infusion 24 h postoperatively significantly reduced pain scores (over 48 h) in patients receiving epidural ropivacaine and morphine analgesia following thoracotomy (Suzuki 2006 **Level II**, n=49, JS 5). However, this was contradicted by a subsequent study, where the addition of IV infusion of ketamine 0.09 mg/kg/h for 48 h to epidural analgesia added no benefit (Joseph 2012 **Level II**, n=60, JS 5).

Perioperative ketamine compared to placebo significantly reduces the incidence of CPSP at 3 mth (5 RCTs, n unspecified) but only when administered for >24 h (OR 0.37; 95%CI 0.14 to 0.98) (Chaparro 2013 **Level I** [Cochrane] 14 RCTs [ketamine], n=1,388). At 6 mth (10 RCTs, n=516), perioperative ketamine reduces CPSP (OR 0.63; 95%CI 0.47 to 0.83), which remains significant when infused for <24 h (OR 0.45; 95 %CI 0.26 to 0.78). These effects were predominantly in abdominal surgery. Another meta-analysis (overlapping by 11 RCTs) found a benefit of perioperative IV ketamine vs placebo in reducing the incidence of CPSP at 3 mth (NNT 12) (RR 0.74; 95%CI 0.60 to 0.93), 6 mth (NNT 14) (RR 0.70; 95%CI 0.50 to 0.98) but not at 12 mth postoperatively (McNicol 2014 **Level I**, 14 RCTs [IV route], n=1,586); such beneficial effects were not found with epidural administration of ketamine (3 RCTs, n=302).

Ketamine has an effect on the regulation of inflammation by inhibiting inflammatory cell recruitment, cytokine production and downregulating inflammatory mediators (Loix 2011 **NR**). Intraoperative administration of ketamine has an inhibitory effect on the early postoperative IL-6 inflammatory response (MD -71 pg/mL; 95%CI -101 to -41) (Dale 2012 **Level I** [PRISMA], 6 RCTs, n=331).

Other acute pain indications

IV ketamine pretreatment reduces pain from propofol injection vs no pretreatment (OR 0.52; 95%CI 0.46 to 0.57) (Jalota 2011 **Level I**, 7 RCTs, n=910).

Ketamine has also some analgesic efficacy in burns patients (McGuinness 2011 **Level I**, 4 RCTs, n=67).

Ketamine may be a useful adjunct in the treatment of pain associated with sickle cell crisis (Zempsky 2010 **Level IV**; Neri 2013 **NR**; Uprety 2014 **NR**).

Ketamine is also a safe and effective analgesic for pain due to trauma in the prehospital setting (Jennings 2011 **Level IV SR**, 2 RCTs, 4 other studies, n=340). (See also Section 8.10.2.3.)

Ketamine 50 mg IN reduced pain scores compared to placebo for NGT insertion (Nejati 2010 **Level II**, n=72, JS 5).

For use in the ED, see Section 8.9.1.5.

Adverse effects with short-term systemic administration of ketamine

Neuropsychiatric effects (hallucinations and nightmares) are increased with various ketamine regimens (7.3 vs 5% with placebo) (Laskowski 2011 **Level I** [PRISMA], 70 RCTS, n=4,701). The incidence can be reduced with a gradual dose increase (Okamoto 2013 **Level IV**).

Contrary to common beliefs, IV ketamine does not increase intracranial pressure or reduce cranial perfusion pressure compared to opioids (Wang 2014 **Level I**, 5 RCTs, n=198). This is also true for patients with nontraumatic neurological diseases (Zeiler 2014 **Level IV SR**, 16 studies, n=127 [adult], n=87 [children]).

Chronic neuropathic pain

IV ketamine is superior to placebo and comparable to IV lignocaine and IV alfentanil in the treatment of pain after SCI (Teasell 2010 **Level I**, 2 RCTs [ketamine], n=19).

IV ketamine reduces phantom limb pain short-term with some possible long-term benefit (McCormick 2014 **Level I**, 4 RCTs, n=107).

Ketamine by various routes of administration (IV, oral, topical) is also a successful treatment for Complex Regional Pain Syndrome (CRPS) based on limited evidence (Azari 2012 **Level IV SR**, 3 RCTS, 16 other studies, n unspecified).

In view of the risks described below, current use of ketamine to treat chronic pain should be restricted to therapy-resistant severe neuropathic pain (Tawfic 2013 **NR**; Niesters 2014a **NR**).

Cancer pain

Ketamine is a viable therapeutic option in treating refractory cancer pain despite limitations in the data available (Bredlau 2013 **Level IV SR**, 5 RCTs and 6 studies, n=483); however, the largest RCT included showed no clinical benefit when ketamine was added to opioids for cancer-pain treatment (Hardy 2012 **Level II**, n=187, JS 5). A preceding Cochrane review of ketamine as an adjunct to opioids in cancer pain excluded most of the RCTs considered above and regards the evidence as currently inconclusive, although both small RCTs included show improvement of the effectiveness of morphine by addition of ketamine (Bell 2012b **Level I** [Cochrane] 2 RCTs, n=30).

Adverse effects with long-term systemic administration of ketamine

Ketamine has an abuse potential (Morgan 2012 NR) with highest abuse rates in South-East Asia and China (Kalsi 2011 **NR**). Heavy use of ketamine has consequences on cognitive and emotional function (Morgan 2010 **NR**). Acute toxicity leads to confusion, drowsiness, or transient loss of consciousness, while symptoms of chronic toxicity are "ketamine cystitis" and chronic abdominal pain (Yiu-Cheung 2012 **NR**) as well as hepatotoxicity. The latter issues need to be considered when using ketamine in a chronic setting therapeutically (Bell 2012a **NR**) and may limit its indications (Niesters 2014a **NR**).

Routes of systemic administration and bioavailability

Ketamine is most commonly administered as a continuous low-dose IV infusion, however SC infusion is also used, especially in palliative care, with a bioavailability (similar to IM) of approximately 90% (Clements 1982 **PK**). Sublingual (SL), IN and TD routes have also been used for acute pain management (see Chapter 5).

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, SL 30% and IN 45%; the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara 2003 **PK**). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both SL and oral routes; peak plasma levels were seen at 30 min and 120 min respectively and terminal half-lives were similar at around 5 h (Chong 2009 **PK**). For both routes, norketamine concentrations exceeded the concentrations of ketamine and, given its pharmacological activity profile, norketamine is

therefore likely to be a major contributor to the overall analgesic effect. A SL ketamine wafer resulted in rapid absorption with a bioavailability of 29% (Rolan 2014 **PK**).

4.6.1.2 Dextromethorphan

Dextromethorphan does not reduce postoperative pain but prolongs time to rescue analgesia (Duedahl 2006 **Level I**, 28 RCTs, n=1,629). Parenteral more than oral dextromethorphan has an opioid-sparing effect of limited clinical relevance but with related reduction of opioid adverse effects in some studies.

A later study looking at the effect of four doses of oral dextromethorphan 30 mg given over 24 h to patients after abdominal hysterectomy showed better pain relief immediately after surgery but not at 6 and 24 h (Chau-In 2007 **Level II**, n=100, JS 5). Similarly, premedication with 30 or 45 mg oral dextromethorphan and a further three postoperative doses over 32 h only reduced pain the first 4 h after surgery without altering morphine metabolism in adolescent patients for scoliosis surgery (Suski 2010 **Level II**, n=60, JS 5). Preoperative administration of 45 and 90 mg oral dextromethorphan alone had no effect on postoperative pain and analgesic requirements after cholecystectomy (Mahmoodzadeh 2010 **Level II**, n=72, JS 5).

As dextromethorphan is metabolised by CYP2D6 to the inactive metabolite dextrorphan, the effect of the CYP2D6 inhibitor quinidine before dextromethorphan 50 mg oral administration has been assessed in knee ligament surgery (Ehret 2013 **Level II**, n=48, JS 4). Dextromethorphan concentrations were higher after quinidine than after placebo and resulted in lower rescue analgesia requirements. Oral dextromethorphan/quinidine was also superior to placebo in diabetic polyneuropathy (Shaibani 2012 **Level II**, n=379, JS 3).

Dextromethorphan oral therapy (titrated to 480 mg/d) for 5 wk was not effective in reversing methadone-induced hyperalgesia (Compton 2008 **Level III-1**).

4.6.1.3 Magnesium

Magnesium is regarded as an NMDA-receptor antagonist but has also anti-inflammatory effects by reducing IL-6 and TNF-alpha plasma levels in the postoperative setting, which might contribute to the effects described here (Aryana 2014 **Level II**, n=90, JS 4).

Magnesium IV as an adjunct to morphine IV analgesia has an opioid-sparing effect (WMD 7.4 mg; 95%CI -9.4 to -5.4) without reducing PONV but with improved pain scores at 4–6 h (Murphy 2013 **Level I**, 22 RCTs, n=1,177). This is in line with a parallel meta-analysis (overlapping by most RCTs), which also describes an opioid-sparing effect (WMD -10.52 mg morphine equivalent; 99%CI -13.50 to -7.54) and reduction of pain at rest (4 and 24 h) and on movement (24 h) (De Oliveira 2013c **Level I** [PRISMA], 20 RCTs, n=1,257). Another meta-analysis published in the same year (overlapping by most RCTs) comes to similar conclusions and found no significant adverse effects (Albrecht 2013 **Level I**, 25 RCTs, n=1,461). These findings contradict a preceding meta-analysis (Lysakowski 2007 **Level I**, 14 RCTs, n=1,128).

Note: reversal of conclusion

This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no effect of IV magnesium on postoperative pain scores or opioid requirements.

Subsequent to these three meta-analyses, multiple further RCTs studying the same issue have been performed; these RCTs are not referenced in this document.

IV magnesium prolonged the duration of sensory block from spinal anaesthesia for abdominal hysterectomy and reduced postoperative pain scores in the first 4 h after surgery (Kahraman 2014 **Level II**, n=40, JS 5). Similarly, after spinal anaesthesia for umbilical hernia repair, IV magnesium prolonged time to first rescue analgesia and was opioid-sparing in the first 24 h after surgery (Kumar 2013 **Level II**, n=60, JS 5). This was also found after spinal anaesthesia for hip arthroplasty, where IV magnesium reduced postoperative pain scores and opioid requirements for 48 h, while increasing serum magnesium concentrations (Hwang 2010 **Level II**, n=40, JS 5). However, IV magnesium did not change magnesium concentrations in the CSF (Mercieri 2012 **Level II**, n=45, JS 3)

Combining ketamine with IV magnesium reduced 48 h morphine consumption by 30% compared to ketamine alone after scoliosis surgery (Jabbour 2014 **Level II**, n=50, JS 5). While pain scores were not different, sleep quality and patient satisfaction were improved with the combination treatment.

IV magnesium prevented remifentanil-induced hyperalgesia after thyroidectomy, without any resulting clinical benefit (Song 2011 **Level II**, n=90, JS 5).

IV magnesium may also have other beneficial effects on postoperative recovery; after segmental mastectomy in an outpatient setting, patients receiving IV magnesium had better quality of recovery (QoR) scores at 24 h compared with the saline group (MD 24/40; 99%CI 3 to 33; P<0.001) and reduced opioid requirements after discharge (De Oliveira 2013a **Level II**, n=50, JS 5). There were significant linear relationships between the postoperative systemic magnesium concentrations and 24 h postoperative QoR scores as well as with pain burden (inverse).

IV magnesium sulphate 4 g attenuated tourniquet pain in healthy volunteers (Satsumae 2013 **Level II EH**, n=24, JS 5).

Oral magnesium lozenges used 30 min preoperatively reduced incidence (by 34% at 2 h postoperatively) and severity of postoperative sore throat after orotracheal intubation (Borazan 2012 **Level II**, n=70, JS 5).

IV magnesium has no effect in acute migraine treatment compared to placebo for any relevant outcome but causes more adverse effects (Choi 2014a **Level I**, 5 RCTs, n=295). IV magnesium also had no effect on any outcome in children with sickle cell crisis (Goldman 2013 **Level II**, n=106, JS 5). IV magnesium also had no effect on any outcome of Irukandji syndrome, caused by jellyfish sting in Northern Queensland (McCullagh 2012 **Level II**, n=39, JS 5). Oral magnesium daily for 4 wk had no beneficial effect in the treatment of neuropathic pain (Pickering 2011 **Level II**, n=45, JS 5).

See Section 5.7.1.4 for magnesium use via the IT route.

4.6.1.4 Amantadine and memantine

A bolus dose of IV amantadine had no effect on postoperative analgesia after abdominal hysterectomy (Gottschalk 2001 **Level II**, n=30, JS 4). However after radical prostatectomy, perioperative oral amantadine reduced morphine consumption, wound pain on palpation and bladder spasms (Snijdelaar 2004 **Level II**, n=24, JS 4). After spinal surgery, premedication with oral amantadine reduced not only intraoperative fentanyl requirements but also postoperative pain intensity and opioid requirements in the first 48 h by 25% (Bujak-Gizycka 2012 **Level II**, n=60, JS 5).

Oral memantine reduced the number of demands for bolus doses of ropivacaine for analgesia via a brachial plexus catheter and, in combination with a continuous ropivacaine infusion, led to a reduction in the incidence of phantom limb pain at 6 mth but not 12 mth, following traumatic upper limb amputation (Schley 2007 **Level II**, n=19, JS 3). It was not effective in reducing the incidence of postmastectomy pain syndrome (Eisenberg 2007 **Level II**, n=22, JS 5).

Key messages

1. Perioperative ketamine reduces the incidence of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review]).
2. Perioperative IV ketamine reduces opioid consumption, time to first analgesic request and postoperative nausea and vomiting compared to placebo (**S**) (**Level I** [PRISMA]); these benefits are limited to patients after thoracic surgery, when ketamine is added to the opioid in the PCA pump (**N**) (**Level I**).

3. Morphine/ketamine compared with higher doses of morphine alone improves analgesia and reduces sedation and postoperative nausea and vomiting in postoperative patients (**S**) (**Level I).**
4. NMDA-receptor antagonists reduce the development of acute tolerance/opioid-induced hyperalgesia associated with remifentanil use (**N**) (**Level I**).
5. IV ketamine does not increase intracranial pressure or reduce cranial perfusion pressure compared to opioids (**N**) (**Level I**).
6. IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect and improves pain scores (**R**) (**Level I**).
7. Ketamine is a safe and effective analgesic in the prehospital setting (**S**) (**Level II**).
8. Ketamine reduces postoperative pain in opioid-tolerant patients (**U**) (**Level II**).
9. IV magnesium extends the duration of sensory block with spinal anaesthesia and reduces subsequent postoperative pain (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Increasing rates of ketamine abuse are reported, in particular from South-East Asia and China (**N**).

☑ Ketamine toxicity leads to cognitive impairment and abuse to chronic organ toxicity (bladder, liver) (**N**).

4.6.2 Regional NMDA-receptor antagonists

4.6.2.1 Ketamine

Neuraxial

Some commercially available preparations of ketamine have a low pH (3.5–5.5) and contain an untested preservative (benzethonium chloride) and thus cannot be recommended for IT use in humans (Hodgson 1999 **NR**; de Lima 2000 **NR**). Subarachnoid administration of S(+)-ketamine without preservative caused histological lesions on the spinal cord and meninges in dogs (Gomes 2011 **BS**).

The addition of IT racemic ketamine to bupivacaine did not prolong postoperative analgesia or reduce analgesic requirements but led to significantly more nausea and vomiting, sedation, dizziness, nystagmus and "strange feelings" (Kathirvel 2000 **Level II**, n=30, JS 2). IT S(+)- ketamine with bupivacaine for Caesarean delivery decreased time to onset and increased spread of the block but did not prolong duration compared with fentanyl (Unlugenc 2006 **Level II**, n=90, JS 5).

Epidural racemic ketamine improved early postoperative analgesia when used with bupivacaine for lower limb amputations, although pain at 1 y was not different; perioperative opioids were not used (Wilson 2008 **Level II**, n=47, JS 5). The combination of epidural ketamine with epidural opioid-based (+/- local anaesthetic) solutions improved pain relief and may reduce overall opioid requirements without increasing the incidence of adverse effects (Walker 2002 **Level I**, 4 RCTs [epidural], n=211; Subramaniam 2004 **Level I** 8 RCTs [epidural], n=513). Ketamine IV may be as effective as epidural ketamine in reducing hyperalgesia.

Caudal epidural ketamine in children, in combination with local anaesthetic or as the sole medicine, improved and prolonged analgesia with few adverse effects (Ansermino 2003 **Level I**, 4 RCTs (ketamine), n=145; Tsui 2005 **NR**). Caudal ketamine prolonged analgesia when administered with caudal bupivacaine but was less effective than midazolam or neostigmine as caudal adjuvants (Kumar 2005 **Level II**, n=80, JS 5) (see also Section 9.6.2).

Peripheral sites

Most studies on the use of ketamine alone or with local anaesthesia show no analgesic benefit for PNB, such as brachial plexus block for arm surgery (Lee 2002 **Level II**, n=51, JS 4), intra-articular injection (where IV ketamine provided better analgesia) (Rosseland 2003 **Level II**, n=77,

JS 5) or wound infiltration such as following Caesarean delivery (Zohar 2002 **Level II**, n=50, JS 5) or inguinal hernia repair (Clerc 2005 **Level II**, n=36, JS 2), although pain scores were lower with preincisional ketamine vs saline in circumcision (Tan 2007 **Level II**, n=40, JS 4). Adding ketamine to lignocaine IVRA did not result in better pain relief compared with ketamine given IV (Viscomi 2009 **Level II**, n=36, JS 4).

Topical administration

Topical ketamine-amitriptyline did not reduce chemotherapy-induced peripheral neuropathic pain (Gewandter 2014 **Level II**, n=462, JS 5).

4.6.2.2 Magnesium

Magnesium influences neuronal calcium influx and may exert an analgesic effect on NMDA receptors in the spinal cord (Bailard 2014 **NR**). The long-term effects of perineural or neuraxial magnesium have not been clarified.

IT magnesium combined with lipophilic opioid, with or without local anaesthetic, prolonged the duration of spinal analgesia in nonobstetric populations (SMD 1.38; 95%CI 0.6 to 2.11) but not in obstetric patients nor in patients with no opioid (Morrison 2013 **Level I**, 15 RCTs, n=980). There was no increase in adverse effects. There was a high degree of heterogeneity, including magnesium dose, making any firm conclusion difficult. This was supported by another meta-analysis (9 RCTs overlap) (Pascual-Ramirez 2013 **Level I**, 12 RCTs, n=817).

Magnesium added to perineural block prolongs analgesia when used with prilocaine, bupivacaine or levobupivacaine (Lee 2012 **Level II**, n=58, JS 4; Gunduz 2006 **Level II**, n=60, JS 4), although only one study identified a decrease in postoperative opioid requirements (Ekmekci 2013 **Level II**, n=100, JS 4). The mechanism of action of magnesium at perineural sites is uncertain and safety and outcome data are limited suggesting caution should be exercised (Bailard 2014 **NR**).

Magnesium added to lignocaine IVRA improved intra and postoperative analgesia and tourniquet tolerance (Turan 2005 **Level II**, n=30, JS 4; Kashefi 2008 **Level II**, n=40, JS 4).

Intra-articular magnesium combined with bupivacaine resulted in better pain relief than either medicine given alone or placebo (Elsharnouby 2008 **Level II**, n=108, JS 4).

Key messages

1. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing adverse effects (**U**) (**Level I**).
2. Caudal ketamine in children, in combination with local anaesthetic or as the sole medicine, improved and prolonged analgesia with few adverse effects (**N**) (**Level I**).

4.7 Antidepressant medicines

4.7.1 Acute pain

There are limited published data on the use of antidepressants in the management of acute nociceptive and neuropathic pain.

4.7.1.1 Tricyclic antidepressants

Amitriptyline given to patients with acute herpes zoster reduced the incidence of postherpetic neuralgia at 6 mth (Bowsher 1997 **Level II**, n=80, JS 5).

Desipramine, but not amitriptyline, given prior to dental surgery increased and prolonged the analgesic effect of a single dose of morphine but both had no analgesic effect on their own (Levine 1986 **Level II**, n=30, JS 3). When used for a fortnight in experimental pain, desipramine had no effect on pain or hyperalgesia (Wallace 2002 **Level II EH**, n=13, JS 4). Amitriptyline given after orthopaedic surgery did not improve opioid analgesia compared to placebo (Kerrick 1993 **Level II**, n=28, JS 5).

4.7.1.2 Serotonin–norepinephrine-reuptake inhibitors

Duloxetine (60 mg preoperative and on postoperative d 1) had an opioid-sparing effect (35%) after total knee joint replacement (Ho 2010 **Level II**, n=50, JS 5). Venlafaxine (37.5 mg) was as effective as gabapentin (300 mg) in reducing pain at rest and analgesic requirements, when given perioperatively for 10 d in mastectomy (Amr 2010 **Level II**, n=150, JS 4). Venlafaxine was inferior to gabapentin in reducing pain on movement; however, at 6 mth postoperatively, fewer patients in the venlafaxine group reported chronic pain or analgesic use.

4.7.2 Chronic pain

Antidepressants are effective in the treatment of a variety of chronic pain states, in particular those of neuropathic origin (Saarto 2007 **Level I** [Cochrane], 61 RCTs, n=3,293).

4.7.2.1 Tricyclic antidepressants

While TCAs are seen as the first-line therapy in neuropathic pain treatment, supportive data are of disappointing quality. Amitriptyline has analgesic effects in diabetic neuropathy, mixed neuropathic pain and fibromyalgia but none in the treatment of neuropathic pain associated with cancer or HIV (Moore 2012 **Level I** [Cochrane], 8 RCTs, n=687). The quality of the studies analysed was generally low. Imipramine is supported only by very low quality evidence in this indication (Hearn 2014 **Level I** [Cochrane], 5 RCTs, n=168).

In elderly patients, TCAs should possibly be avoided as the use of medications with anticholinergic activity increases risk of cognitive impairment and even mortality in this patient group (Fox 2011 **Level III-2**).

4.7.2.2 Serotonin–norepinephrine-reuptake inhibitors

Duloxetine (60–120 mg/d) provides analgesia for diabetic neuropathy (Lunn 2014 **Level I** [Cochrane], 8 RCTs, n=2,728 patients) and, with lower efficacy, for fibromyalgia (Lunn 2014 **Level I** [Cochrane], 6 RCTs, n=2,249). Duloxetine and milnacipran improve pain and quality of life in fibromyalgia, however not sleep and fatigue (Hauser 2013 **Level I** [Cochrane], 10 RCTs, n=6,038). Duloxetine is more effective than milnacipran in fibromyalgia (Derry 2012 **Level I** [Cochrane], 5 RCTs, n=4,138).

4.7.2.3 Selective serotonin-reuptake inhibitors

There is only limited evidence for the effectiveness of SSRIs in neuropathic pain (Saarto 2007 **Level I** [Cochrane] 61 RCTs, n=3,293).

4.7.3 Specific pain conditions

In postherpetic neuralgia, TCAs are less effective than pregabalin and 5% lignocaine medicated plaster (Snedecor 2014 **Level I**, 28 RCTs, n=4,317). In diabetic polyneuropathy, amitriptyline is the least effective of the medications studied with the worst benefit-risk balance, while venlafaxine and duloxetine were the superior antidepressants here (Rudroju 2013 **Level I**, 21 RCTs, n=4,219).

In fibromyalgia, amitriptyline (NNT 4.9) and the serotonin–norepinephrine-reuptake inhibitors (SNRIs) duloxetine and milnacipran (NNT 10) were the most effective antidepressants (Hauser 2012 **Level I**, 35 RCTs, n=6,766).

In chronic headaches, antidepressants are effective in treatment and prophylaxis with better efficacy of TCAs than SSRIs (Jackson 2010 **Level I** [PRISMA], 37 RCTs, n=3,176).

In chronic low-back pain, antidepressants neither improve pain nor depression (Urquhart 2008 **Level I** [Cochrane], 10 RCTs, n=706); this was confirmed in a subsequent systematic review of pharmacological interventions in this indication (Kuijpers 2011 **Level I**, 5 RCTs, n=303). However, these results are challenged as they did not differentiate between different antidepressants; SNRIs like duloxetine (Williamson 2014 **Level I**, 3 RCTs, n=982) and TCAs may be effective, while SSRIs are not (Staiger 2003 **Level I**, 7 RCTs, n=440).

There is only poor evidence for an analgesic effect of antidepressants in orofacial pain disorders (Martin 2012 **Level I**, 6 RCTs, n=208) and for an analgesic effect of TCAs or SSRIs in rheumatoid arthritis (Richards 2011 **Level I** [Cochrane], 8 RCTs, n=652).

Duloxetine improves WOMAC scores in osteoarthritis to an extent comparable to other first-line treatments for osteoarthritis (eg NSAIDs) (Myers 2014 **Level I**, 3 RCTs, n=775). Therefore duloxetine is a recommended treatment in updated guidelines for osteoarthritis (eg McAlindon 2014 **GL**).

See Table 4.1 below for a compilation of NNTs and NNHs from various sources.

Table 4.1 Antidepressants for the treatment of neuropathic pain and fibromyalgia

Efficacy	**NNT (95% CI)**
Pooled diagnoses	
TCAs	
• Amitryptiline	4.6 (3.6–6.6)
• Imipramine	Only poor evidence of benefit
SNRIs	
• Duloxetine	5.8 (4.5–8.4)
SSRIs	Limited evidence of benefit
Diabetic neuropathy	
Duloxetine	5 (4–7)
Postherpetic neuralgia	2.7 (2.0–4.1)
HIV-related neuropathies	No evidence of benefit
Fibromyalgia	
Duloxetine	8 (5–14)
Milnacipran	8–10
Minor adverse effects	**NNH (95% CI)**
Pooled diagnoses	
Amitriptyline	4.1 (3.2-5.7)
Venlafaxine	9.6 (4.2–13.0)
SSRIs	No dichotomous data available
Major adverse effects (withdrawal from study)	**NNH (95% CI)**
Pooled diagnoses	
Amitriptyline	28.0 (17.6–68.9)
Venlafaxine	16.2 (8–436)
Duloxetine	17 (12–50)
Milnacipran	14 (for 100 mg); 7 (for 200 mg)

Note: *CI=confidence interval; TCAs=tricyclic antidepressants; SNRI=serotonin–norepinephrine-reuptake inhibitor; SSRI=selective serotonin-reuptake inhibitor*

Source: *Adapted from (Saarto 2007; Moore 2012; Derry 2012; Lunn 2014; Hearn 2014)*

Currently the use of antidepressants for acute neuropathic pain is mainly based on extrapolation of the above data. Clinical experience in chronic pain suggests that TCAs should be started at low doses (eg amitriptyline 5–10 mg at night) and subsequent doses increased slowly if needed, in order to minimise the incidence of adverse effects.

Key messages

1. In chronic neuropathic pain and fibromyalgia, tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitor are effective analgesics and more effective than selective serotonin-reuptake inhibitors (**S**) (**Level I** [Cochrane Review]).
2. Tricyclic antidepressants are effective in the treatment of chronic headaches (**S**) (**Level I** [PRISMA]).
3. Duloxetine is as effective as other first-line treatments for pain and disability of osteoarthritis (**N**) (**Level I**).
4. There is evidence that some antidepressants, in particular duloxetine, may be effective in the treatment of chronic low-back pain (**S**) (**Level I**).
5. Perioperative serotonin-noradrenaline reuptake inhibitors reduce acute pain and opioid requirements in a limited number of studies (**N**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use tricyclic antidepressants and serotonin–noradrenaline-reuptake inhibitors in the management of acute neuropathic pain (**S**).

☑ To minimise adverse effects, it is advisable to initiate treatment with tricyclic antidepressants at low doses (**Q**).

4.8 Anticonvulsant medicines

4.8.1 Acute pain

4.8.1.1 Alpha-2-delta ligands (gabapentin/pregabalin)

Gabapentin (250 mg) as the sole analgesic reduces the intensity of postoperative pain (NNT 11; 95%CI 6.4 to 35) and requirements for rescue analgesia (NNT 5.8) compared to placebo (Straube 2010 **Level I** [Cochrane], 4 RCTs, n=387). While this is the first time that an anticonvulsant on its own has been shown to be effective in acute postoperative pain, the high NNT, inferior to most analgesics used in this setting, suggests that gabapentin is clinically not useful as sole analgesic for postoperative analgesia.

Perioperative gabapentin (Tiippana 2007 **Level I** [QUOROM] 21 RCTs [gabapentin], n=1,810) and pregabalin (Zhang 2011 **Level I** [QUOROM] 11 RCTs, n=899) improve analgesia (at rest and with movement) and reduce postoperative opioid consumption but increase the incidence of sedation and visual disturbance compared with placebo. Gabapentin and pregabalin reduce opioid-related adverse effects, in particular PONV (Zhang 2011 **Level I** [QUOROM] 11 RCTs, n=899); the NNT was 25 for nausea, 6 for vomiting and 7 for urinary retention (Tiippana 2007 **Level I** [QUOROM], 22 RCTs, n=1,909). Similar benefits occur in specific surgical settings such as hysterectomy (Alayed 2014 **Level I** [PRISMA], 14 RCTs, n=891) and lumbar spinal surgery (Yu 2013 **Level I** [PRISMA], 7 RCTs, n=434). There is a specific effect of gabapentin on PONV in trials assessing this as a primary outcome (Guttuso 2014 **Level I**, 6 RCTs, n=773).

Trials analysed in these meta-analyses used a wide variety of dosing regimens; it is therefore not possible to recommend a particular regimen. The effects of gabapentin were not dose-dependent in the range of 300–1,200 mg (Tiippana 2007 **Level I** [QUOROM], 21 RCTs [gabapentin], n=1,711).

The effects of alpha-2-delta ligands on the prevention of CPSP are presented in Section 1.4.5.

Used as an adjunct to epidural analgesia, perioperative gabapentin reduced pain scores and epidural analgesic requirements and improved patient satisfaction, despite an increase in dizziness (Turan 2006 **Level II**, n=54, JS 5) but these benefits were not confirmed with thoracic epidural analgesia for thoracotomy (Kinney 2012 **Level II**, n=120, JS 5).

Gabapentin was also effective in the setting of acute burns pain (see Section 8.3), acute herpes zoster pain (see Section 8.6.2) and acute pain due to Guillain-Barre Syndrome (see Section 8.8.4).

4.8.1.2 Sodium valproate

Sodium valproate did not improve acute nociceptive pain after surgery (Martin 1988 **Level II**, n=39, JS 3). There are conflicting results on IV sodium valproate in treating acute migraine; it was ineffective in one study (Tanen 2003 **Level II**, n=40, JS 2) and superior to metoclopramide plus sumatriptan in another (Bakhshayesh 2013 **Level II**, n=60, JS 3).

4.8.2 Chronic pain

Overall, there is good evidence for the use of pregabalin and gabapentin in chronic pain conditions including neuropathic pain states such as diabetic polyneuropathy, postherpetic neuralgia and central neuropathic pain as well as fibromyalgia (Wiffen 2013b **Level I** [Cochrane], 91 RCTs, n=17,995). For most other anticonvulsants, the evidence was nonexistent, so little or of so low quality that conclusions were not permitted or of reasonable quality showing no or very little effect.

4.8.2.1 Alpha-2-delta ligands (gabapentin/pregabalin)

Gabapentin

A review of gabapentin for the treatment of chronic neuropathic pain calculated a NNT of 4.3 (95%CI 3.5 to 5.7) overall; the NNTs for painful diabetic neuropathy and postherpetic neuralgia were 5.9 (95%CI 4.6 to 8.3) and 8 (95%CI 6 to 12) respectively **(**Moore 2014 **Level I** [Cochrane], 37 RCTs, n=5633). The NNH for minor adverse effects (dizziness, sedation, ataxia, peripheral oedema) compared with a placebo was 3.7 (95%CI 2.4 to 5.4); the NNH for a major adverse effect was insignificant.

Gabapentin is also effective in pain due to SCI (see Section 8.2) and phantom limb pain (see Section 8.1.5.1). Gabapentin may decrease phantom limb pain, however the evidence is limited and of poor quality (Abbass 2012 **Level I**, 3 RCTs, n=89). Gabapentin was also effective for the treatment of neuropathic pain caused by traumatic or postsurgical nerve injury (Gordh 2008 **Level II,** n=120, JS 5).

Pregabalin

Pregabalin was effective for neuropathic pain; pregabalin 600 mg/d had NNTs of 3.9 (95%CI 3.1 to 5.1) for postherpetic neuralgia, 5.0 (95%CI 4.0 to 6.6) for painful diabetic neuropathy and 5.6 (95%CI 3.5 to 14) for central neuropathic pain (Moore 2009 **Level I** [Cochrane] 19 RCTs, n=7,003).

Pregabalin was also effective in fibromyalgia for pain relief with NNT 12 (95%CI 9 to 21) and overall subjective improvement with NNT 9 (95%CI 7 to 15) and NNH for discontinuation 3 (95%CI 9 to 23) and for dizziness 4 (95%CI 3 to 5) (Uceyler 2013 **Level I** [Cochrane] 8 RCTs, n=2,480).

In postherpetic neuralgia, pregabalin (> 300 mg/d) was the most effective treatment for pain of all compounds studied (Snedecor 2014 **Level I**, 28 RCTs, n=4,317).

4.8.2.2 Carbamazepine

Carbamazepine for the treatment of chronic neuropathic pain has possibly some analgesic efficacy in some patients but the quality of data is insufficient to draw meaningful conclusions or make comparisons (Wiffen 2014 **Level I** [Cochrane], 10 RCTs, n=480).

4.8.2.3 Oxcarbazepine

There is limited evidence for the analgesic efficacy of oxcarbazepine in diabetic polyneuropathy (3 RCTs, n=634); the NNT was 6 (95%CI 3.3 to 41) and NNH 17.4 (95%CI 11 to 42) (1 RCT, n=146) but not in radiculopathy (1 RCT, n=145) (Zhou 2013 **Level I** [Cochrane], 4 RCTs, n=779).

4.8.2.4 Phenytoin

A meta-analysis could not identify any quality studies to support the use of phenytoin in chronic neuropathic pain or fibromyalgia (Birse 2012 **Level II** [Cochrane], 0 RCTs, n=0).

4.8.2.5 Valproate

Valproate may affect pain in diabetic polyneuropathy based on very small RCTs of poor quality (Gill 2011 **Level I** [Cochrane] 2 RCTs, n=84).

Valproate is effective for the prevention of episodic migraine (Linde 2013 **Level I** [Cochrane], 10 RCTs, n=652).

4.8.2.6 Lamotrigine

Lamotrigine showed no analgesic benefit in neuropathic pain in large, high-quality, long-duration RCTs (Wiffen 2013a **Level I** [Cochrane] 12 RCTs, n=1,511).

4.8.2.7 Lacosamide

Lacosamide was not beneficial for the treatment of neuropathic pain and fibromyalgia (Hearn 2012 **Level I** [Cochrane] 6 RCTs, n=2,022).

Key messages

1. Alpha-2-delta ligands (gabapentin and pregabalin) are the only anticonvulsants with well-proven efficacy in the treatment of chronic neuropathic pain (**S**) (**Level I** [Cochrane Review]).
2. Pregabalin is the only anticonvulsant with proven but limited efficacy in chronic pain due to fibromyalgia (**N**) (**Level I** [Cochrane Review]).
3. Perioperative alpha-2-delta ligands (gabapentin/pregabalin) reduce postoperative pain and opioid requirements (**S**) and reduce the incidence of vomiting (**S**), pruritus (**U**) and urinary retention (**U**) but increase the risk of sedation (**U**) (**Level I** [QUOROM]).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use alpha-2-delta ligands (gabapentin, pregabalin) in the management of acute neuropathic pain (**Q**).

4.9 Alpha-2 agonists

4.9.1 Systemic alpha-2 agonists

Systemic perioperative administration (oral, IM, IV) of the alpha-2 agonists clonidine and dexmedetomidine decreases postoperative pain intensity, opioid consumption and nausea without prolonging recovery times (Blaudszun 2012 **Level I** [PRISMA], 30 RCTs, n=1,792). Common adverse effects include arterial hypotension and bradycardia. The effects on development of chronic pain or hyperalgesia remain unclear due to lack of data.

Key message

1. The perioperative use of systemic alpha-2-agonists (clonidine and dexmedetomidine) reduces postoperative pain intensity, opioid consumption and nausea without prolonging recovery times, but the frequency and severity of adverse effects (bradycardia and hypotension) may limit their clinical usefulness (**S**) (**Level I** [PRISMA]).

4.9.2 Regional alpha-2 agonists

Alpha-2 adrenoceptor agonists act as an analgesic at the level of the dorsal horn of the spinal cord, although there may be peripheral effects as well (Chan 2010a **NR**). Systemic adverse effects are predominantly centrally mediated sedation and hypotension.

4.9.2.1 Neuraxial

Clonidine

Clonidine is a selective alpha-2 agonist with an alpha-2 to alpha-1 ratio of 200:1. There is no human or animal evidence of neurotoxicity when preservative-free clonidine is administered IT (Hodgson 1999 **NR**). Epidural clonidine is approved by the FDA for relief of chronic cancer pain.

In volunteers, significant analgesia to experimental heat pain was detected with IT doses >25 mcg clonidine, with 50 mcg having similar effects on heat threshold to 5 mg bupivacaine (Ginosar 2013 **Level II EH**, n=11, JS 4). IT clonidine given in doses from 15–150 mcg, combined with IT local anaesthetic did not affect the rate of onset of a local anaesthetic block but significantly prolonged the time to two-segment block regression and prolonged the time to first analgesic request (median 101 min, range 35–310 min) (Elia 2008 **Level I**, 22 studies, n=1,445). Treatment effects were noted to be heterogeneous and dose responsiveness could not be demonstrated. IT clonidine also reduced intraoperative pain but hypotension was more frequent (RR 1.8; 95%CI 1.4 to 2.3) (Elia 2008 **Level I**, 22 RCTs, n=1,445). Subsequent studies confirmed these findings in elderly orthopaedic patients and after herniorrhaphy (Agarwal 2014a **Level II**, n=60, JS 4; Thakur 2013 **Level II**, n=75, JS 4).

The addition of clonidine to IT morphine caused a small increase in duration of analgesia by 1.63 h (95%CI 0.93 to 2.33 h) and reduced the amount of systemic morphine consumption over 24 h by 4.45 mg (95%CI 1.40 to 7.49 mg) (Engelman 2013 **Level I**, [PRISMA], 7 RCTs, n=503). Hypotension was also increased (OR 1.78; 95%CI 1.02 to 3.12).

In patients having gynaecological surgery with IT bupivacaine, the addition of IT clonidine (30 mcg) (group BC) was compared with IT fentanyl (15 mcg) (group BF) or the combination of both fentanyl and clonidine (group BCF) (Chopra 2014 **Level II**, n=75, JS 4). The duration of effective analgesia, mean time to two-segment regression and duration of sensory and motor block were significantly longer in group BCF as compared to group BC, and longer in group BC as compared to group BF. The incidence of intraoperative pain and the requirement for postoperative analgesics were significantly less when clonidine was added to IT bupivacaine with or without fentanyl.

IT clonidine 150 mcg combined with bupivacaine had a postoperative antihyperalgesic effect at 48 h after elective Caesarean delivery compared with IT bupivacaine/sufentanil and IT clonidine (75 mcg)/bupivacaine/sufentanil; however no reduction in pain scores nor opioid requirements was observed (Lavand'homme 2008b **Level II,** n=96, JS 5). Also in obstetric patients, IT clonidine (75 mcg) with bupivacaine prolonged the time to first analgesic request compared to fentanyl; however, the total analgesic consumption within the first postoperative 24 h was similar (Khezri 2014 **Level II**, n=90, JS 5). In obstetrics patients, the time to achieve highest sensory and complete motor block was less and duration of analgesia was longer when clonidine and hyperbaric bupivacaine were administered sequentially, compared to the mixing the two medicines in a single syringe (Sachan 2014 **Level II**, n=60, JS 4).

The efficacy of epidural clonidine is unclear, with many conflicting results in the literature (Chan 2010a **Level I,** 13 RCTs [epidural], n unspecified). Low-dose infusion of clonidine alone via thoracic epidural catheters after spinal surgery reduced systemic opioid requirements and nausea without causing significant sedation or hypotension (Farmery 2009 **Level II**, n=65, JS 5). The addition of clonidine to PCEA with ropivacaine and morphine after total knee arthroplasty decreased opioid requirements and improved analgesia without increasing adverse effects (Huang 2007 **Level II**, n=80, JS 3). The addition of clonidine in epidural anaesthesia with ropivacaine after haemorrhoidectomy improved analgesia without causing adverse effects

(Baptista 2014 **Level III-2**). In children, addition of clonidine to bupivacaine caudal injection increases the duration and quality of analgesia without an increase in adverse effects.

(See also Section 5.7.1.4).

Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist with an alpha-2 to alpha1 ratio of 1,620:1 (Chan 2010a **NR**). It is not approved for epidural or IT administration and animal studies suggest a risk of axonal injury via the epidural route (Konakci 2008).

Two meta-analyses, with some overlap of included studies, examined whether dexmedetomidine as adjuvant to local anaesthetic for neuraxial block prolonged the duration of analgesia compared with local anaesthetic alone (Abdallah 2013 **Level I** [PRISMA], 9 RCTs, n=516; Wu 2014 **Level I** [QUOROM], 16 RCTs, n=1,092). Both reviews included IT dexmedetomidine (5 and 8 RCTs respectively) and the latter also included epidural and caudal dexmedetomidine (8 RCTs). Both concluded that dexmedetomidine is an effective local anaesthetic adjuvant as part of neuraxial anaesthesia, and the latter could not separate an effect of the IT from the epidural route. The use of neuraxial dexmedetomidine significantly prolonged analgesia duration compared with a placebo group (WMD 6.93 h; 95%CI 5.23 to 8.62) and also significantly reduced postoperative pain intensity and decreased analgesic requirements (Wu 2014 **Level I** [QUORUM], 16 RCTs, n=1,092). Neuraxial dexmedetomidine increased the incidence of bradycardia (OR 2.68; 95%CI 1.18 to 6.10).

In patients having lower abdominal surgery using spinal 0.5% bupivacaine, IT buprenorphine (60 mcg) was compared with IT dexmedetomidine (5 mcg). IT dexmedetomidine resulted in a significant prolongation of anaesthesia and analgesia with a reduced need for sedation and rescue analgesics (Gupta 2014 **Level II**, n=60, JS 5). Similarly, in patients undergoing lower abdominal surgery, the quality of anaesthesia was superior with low-dose bupivacaine and dexmedetomidine compared to bupivacaine and fentanyl (Nayagam 2014 **Level II**, n=150, JS 4). Dexmedetomidine facilitated the spread of the block and offered longer postoperative analgesic duration.

IV dexmedetomidine (0.5 mcg/kg) but not midazolam prolonged spinal bupivacaine sensory block and also provided sedation and additional analgesia in patients undergoing transurethral resection of the prostate (Kaya 2010 **Level II**, n=75, JS 2). In patients undergoing lower limb surgery, IT dexmedetomidine was associated with prolonged motor and sensory block, haemodynamic stability and reduced demand of rescue analgesics at 24 h compared to IT clonidine, fentanyl, or saline with bupivacaine (Mahendru 2013 **Level II**, n=60, JS 4).

Adrenaline (epinephrine)

IT adrenaline (epinephrine) prolongs IT local anaesthetic sensory block (WMD for two-segment regression 35.0 min; 95%CI 22.8 to 47.3) and motor block (de Oliveira 2012a **Level I** [PRISMA], 24 RCTs, n=1,271). Some effects are dose-dependent, with doses of ≤100 mcg prolonging sensory and motor block duration but also causing more hypotension and PONV than higher doses. IT adrenaline at doses >100 mcg prolongs sensory and motor block more than the lower dose but is not associated with a greater incidence of hypotension and PONV compared with IT local anaesthetic alone. The effect of IT adrenaline in prolonging analgesia duration was not seen when added to IT local anaesthetic/opioid combinations (de Oliveira 2012a **Level I** [PRISMA], 24 RCTs, n=1,271).

The influence of caudal adrenaline and/or clonidine on the absorption characteristics of caudal levobupivacaine were evaluated in a 240 paediatric patients (Chalkiadis 2013 **PK**). Adrenaline (5 mcg/mL) decreased the rate of levobupivacaine systemic absorption, reducing peak concentrations by half. Clonidine (2 mcg/mL) resulted in faster systemic absorption of levobupivacaine and a similar concentration time profile to levobupivacaine alone.

In postoperative thoracic epidural infusion, the addition of adrenaline to fentanyl and ropivacaine or bupivacaine improved analgesia (Sakaguchi 2000 **Level II**, n=77, JS 2; Niemi 2002 **Level II**, n=12, JS 5; Niemi 2003 **Level II**, n=33, JS 5). The efficacy of thoracic epidural pethidine

infusions after thoracotomy was not improved by addition of adrenaline (Bryson 2007 **Level II**, n=50, JS 5).

With lumbar epidural infusions, no analgesic benefit was seen with added adrenaline at 2 mcg/mL or 4 mcg/mL (Forster 2003 **Level II**, n=46, JS 5; Forster 2008 **Level II,** n=63, JS 3).

In labour epidural analgesia, adrenaline (5 mcg/mL) added to low-dose bupivacaine infusions decreased pain scores and resulted in longer redosing intervals with no change in labour duration (Connelly 2011 **Level II**, n=60, JS 4).

4.9.2.2 Peripheral nerve block

Clonidine

A meta-analysis evaluated the benefits of clonidine as an adjuvant to local anaesthetics for peripheral nerve and plexus blocks (Popping 2009 **Level I**, 20 RCTs, n=1,054). Clonidine doses ranged from 30–300 mcg with most patients receiving 150 mcg. Clonidine prolonged the duration of postoperative analgesia (WMD 122 min; 95%CI 74 to 169), sensory block (WMD 74 min; 95%CI 37 to 111) and also prolonged motor block. However clonidine increased the risk of hypotension (OR 3.61; 95%CI 1.52 to 8.55), bradycardia (OR 3.09; 95%CI 1.10 to 8.64) and sedation (OR 2.28; 95%CI 1.15 to 4.51). There was a lack of evidence of dose-responsiveness for beneficial or harmful effects. Subsequent studies in supraclavicular blocks report similar findings (Chakraborty 2010 **Level II**, n=70, JS 4; Singh 2010 **Level II**, n=50, JS 4). However, the addition of 150 mcg clonidine to 20 mL of levobupivacaine 0.5% in posterior gluteal (Labat) sciatic nerve block did not prolong the duration of analgesia and resulted in more hypotension when compared to the control group (Fournier 2012 **Level II**, n=60, JS 4).

Evidence is lacking for the use of clonidine as an adjunct to local anaesthetics for continuous catheter techniques, with no studies showing benefit (McCartney 2007 **Level I**, 3 RCTs [continuous], n=110).

Dexmedetomidine

Perineural dexmedetomidine as part of a brachial plexus block increases time to first analgesic request by 345 min (95%CI 103 to 587 min) and prolongs motor block by 268 min (95%CI 15.5 to 520 min) compared with local anaesthetics alone (Abdallah 2013 **Level I** [PRISMA], 4 RCTs [perineural], n=259). The sensory and motor block onset times were similar. In the setting of supraclavicular brachial plexus block, dexmedetomidine (100 mcg) significantly shortened the onset time and prolonged the duration of sensory and motor blocks and duration of analgesia (Agarwal 2014b **Level II**, n=60, JS 4).

Dexmedetomidine (1 mcg/kg) compared with clonidine (1 mcg/kg) as an adjuvant to local anaesthetic in supraclavicular brachial plexus blocks showed no difference in time to onset and resulted in prolonged duration of sensory (413 vs 227 min) and motor block (472 vs 292 min) and duration of analgesia (456 vs 289 min) (Swami 2012 **Level II**, n=60, JS 4). It should be noted that these doses might not be equivalent.

4.9.2.3 Intravenous regional anaesthesia

Addition of (typically 0.5 mcg/kg) to lignocaine or prilocaine IVRA increased duration and quality of analgesia (Memis 2004 **Level II**, n=30, JS 4; Esmaoglu 2005 **Level II**, n=40, JS 4; Kol 2009 **Level II**, n=75, JS 5; Kumar 2012 **Level II**, n=72, JS 5). These findings were not supported by a dose-finding study with clonidine (0–1.5 mcg/kg) added to IVRA, where no analgesic benefit was found (Ivie 2011 **Level II**, n=52, JS 5).

In patients having carpal tunnel repairs under IVRA, dexmedetomidine IV was compared with dexmedetomidine added to the local anaesthetic for IVRA and with placebo. Both routes of dexmedetomidine had similar effects, with improved postoperative pain scores up to 30 min (Mizrak 2010 **Level II**, n=45, JS 5).

4.9.2.4 Intra-articular

Clonidine

The use of intra-articular clonidine on its own or in addition to local anaesthetic agents improved analgesia after knee joint arthroscopy and decreased opioid consumption (Brill 2004 **Level I**, 7 RCTs, n unspecified). Intra-articular clonidine 1 mcg/kg (n=25) provided superior postoperative analgesia to intra-articular placebo, morphine, or tenoxicam and similar duration to intra-articular neostigmine (Alagol 2005 **Level II**, n=150, JS 5). Combined femoral-sciatic nerve block offered better analgesia with fewer adverse effects than intra-articular infiltration with bupivacaine/clonidine/morphine in children undergoing anterior cruciate ligament reconstruction (Tran 2005 **Level II**, n=36, JS 2).

Dexmedetomidine

Intra-articular dexmedetomidine when added to ropivacaine resulted in a longer time to analgesic request than ropivacaine alone (mean 10.8 h [SD 2.6] vs 5.4 h [SD 1.4]) (Paul 2010 **Level II**, n=30, JS 5). Compared with IV dexmedetomidine, intra-articular dexmedetomidine resulted in a longer time to first analgesia (dexmedetomidine 312.0 min [SD 120.7]; IV group 102.1 min [SD 54.4]; placebo group 71.0 min [SD 50.1]) (Al-Metwalli 2008 **Level II**, n=60, JS 5). When intra-articular dexmedetomidine, fentanyl and ropivacaine each alone were compared following knee arthroscopy, time to first analgesia was longest with ropivacaine, followed by fentanyl and then dexmedetomidine (mean: 380 min [SD 22], 327 min [SD 17] and 244 min [SD 20] respectively) (Manuar 2014 **Level II**, n=99, JS 2).

Key messages

1. Intrathecal clonidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics (**S**) (**Level I)** or morphine (**N**) (**Level I** [PRISMA]).
2. Dexmedetomidine when added to local anaesthetics for brachial plexus block prolongs anaesthesia and analgesia (**N**) (**Level I** [PRISMA]).
3. Intrathecal adrenaline (epinephrine) when combined with local anaesthetic, but not with intrathecal opioids, prolongs analgesia duration (**N**) (**Level I** [PRISMA]).
4. Intrathecal dexmedetomidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics (**S**) (**Level I** [QUOROM]).
5 Clonidine improves duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for peribulbar, peripheral nerve and plexus blocks but is associated with increased hypotension and bradycardia (**Q**) (**Level I**).
6. Dexmedetomidine added to intravenous regional anaesthesia improves and prolongs analgesia (**S**) (**Level II**).
7. Epidural clonidine may reduce postoperative systemic opioid requirements (**W**) (**Level II**).
8. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).

4.10 Salmon calcitonin and bisphosphonates

4.10.1 Calcitonin

Calcitonin is a 32-amino acid peptide hormone that regulates calcium homeostasis in vertebrates. It also has analgesic properties, primarily through receptor-mediated modulation of serotonergic activity in pain pathways of the CNS (Visser 2005 **NR**). Salmon calcitonin has a greater potency than mammalian forms of the hormone and is therefore reproduced as a synthetic medicine for pharmaceutical use. The adverse effects of calcitonin therapy such as sedation, nausea, skin flushing and diarrhoea may reflect increased serotonergic activity. In rodents, the $5HT_3$ antagonist tropisetron reduced its analgesic efficacy, which may be relevant in humans during the treatment of its adverse effects, nausea and vomiting (Visser 2005 **NR**).

In patients with osteoporotic vertebral compression fractures, salmon calcitonin (IV, SC, IM, IN or rectal) administered within <10 d reduces acute pain at rest and on movement within 1 wk and improves mobilisation (in 7–28 d); adverse effects are usually minor and mainly gastrointestinal (Knopp-Sihota 2012 **Level I** [PRISMA], 13 RCTs, n=589). In chronic pain (>3 mth) from pre-existing osteoporotic vertebral compression fractures, the effect was minimal and only statistically significant on movement at 6 mth. In a case series (n=8), IN salmon calcitonin reduced pain due to fracture of the coccyx (Foye 2014 **Level IV**).

In acute phantom limb pain, IV (and likely SC) salmon calcitonin was more effective than placebo (Jaeger 1992 **Level II**, n=21 (cross over), JS 3; Turek 2012 **CR**). However, it was not effective for chronic phantom limb pain (Eichenberger 2008 **Level II**, n=20 [cross over], JS 5).

In CRPS, a meta-analysis concluded that salmon calcitonin is beneficial (Perez 2001 **Level I**, 5 RCTs [calcitonin], n unspecified). However, the only two placebo-controlled trials in this meta-analysis produced conflicting results. A subsequent RCT found that calcitonin was no more effective than paracetamol in improving pain and function in CRPS over a 2 mth period in patients already receiving physical therapy following upper limb trauma (Sahin 2006 **Level II**, n=35, JS 2).

Neuropathic pain after SCI was responsive to salmon calcitonin in a case series (n=3) (Humble 2011 **Level IV**).

In lumbar spinal stenosis, salmon calcitonin had no effect on pain or walking distance (Podichetty 2011 **Level I**, 4 RCTs, n=255). An RCT not included in this meta-analysis confirmed this lack of benefit (Sahin 2009 **Level II**, n=45, JS 3).

The limited evidence available does not support the effectiveness of salmon calcitonin in the treatment of acute and persistent metastatic bone pain (Martinez-Zapata 2006 **Level I** [Cochrane], 2 RCTs, n=90).

With long-term use of salmon calcitonin for treatment of chronic osteoporosis (with unproven efficacy), there is a suggested association with increased cancer incidence; however this is based on studies with poor-quality cancer assessment methodology (Overman 2013 **NR**). A subsequent study found an increase in liver malignancies but reduced breast cancer incidence (Sun 2014 **Level III-2**). The FDA has decided to continue the registration of salmon calcitonin, including for chronic use (FDA 2014b).

4.10.2 Bisphosphonates

IV pamidronate (30 mg daily for 3 d), compared to placebo, rapidly reduced pain associated with acute osteoporotic vertebral compression fractures (<21 d after incident) for up to 30 d post treatment (Armingeat 2006 **Level II**, n=35, JS 5). Pamidronate IV was as effective as IV human synthetic calcitonin for this indication (Laroche 2006 **Level II**, n=27, JS 3).

Bisphosphonates reduced subacute and chronic bone pain associated with metastatic carcinoma of the breast (Wong 2012 **Level I** [Cochrane], 9 RCTs, n=2,806) and in multiple myeloma (Mhaskar 2012 **Level I** [Cochrane], 20 RCTs, n=6,692) but not in advanced prostate cancer (OR 1.54; 95%CI 0.97 to 2.44) (Yuen 2006 **Level I** [Cochrane], 10 RCTs, n=1,955). Bisphosphonates improve pain control in patients with metastatic bone disease from lung cancer (Lopez-Olivo 2012 **Level I**, 12 RCTs, n=1,767). Zoledronate specifically reduces the likelihood of experiencing a bone pain event in metastatic bone disease in comparison to placebo (RR 0.83; 95%CI 0.76 to 0.89) (Zhu 2013 **Level I**, 12 RCTs, n=4,450) (see also Section 8.7.7.7).

Bisphosphonates may be of benefit in achieving pain reduction in patients with CRPS Type 1, in particular in early stages (Varenna 2014 **NR**).

Key messages

1. Bisphosphonates reduce bone pain associated with metastatic breast cancer and multiple myeloma (**Q**) (**Level I** [Cochrane Review]).
2 Salmon calcitonin reduces pain and improves mobilisation in the acute phase after osteoporosis-related vertebral compression fractures (**S**) (**Level I** [PRISMA]).
3. Salmon calcitonin reduced acute, but not chronic, phantom limb pain (**U**) (**Level II**).
4. Pamidronate reduced pain associated with acute osteoporotic vertebral compression fractures (**S**) (**Level II**).

4.11 Cannabis, cannabinoids and cannabimimetics

4.11.1 Pharmacology

Medicinal preparations made from the cannabis plant contain several hundred chemical substances, which occur in varying concentrations in different plant strains and growth environments. Cannabis plants and their extracts are uniquely rich in phytocannabinoids (Russo 2011 **NR**), of which delta^9-tetrahydrocannabinol (Δ^9-THC) is the best characterised substance and induces most of the psychogenic effects attributed to cannabis. Tetrahydrocannabinolic acid is the nonpsychotropic phytochemical precursor of THC and is of therapeutic interest for the prevention of nausea (Rock 2013 **BS**) and the selective inhibition of COX 2 (Takeda 2008 **BS**). Other prominent THC congeners include cannabidiol and cannabinol. Cannabidiol is of interest because it opposes the psychotropic activity of THC and is currently being developed for anticonvulsant therapy (Schubart 2011 **Level IV**; Borgelt 2013 **NR**; Devinsky 2014 **NR**). Cannabinol is of interest for possible antitumour actions (Guindon 2011 **NR**).

As an analgesic, cannabis is generally inadequate for acute pain management and it is not yet considered a first-line therapy for chronic pain management.

"Cannabinoids" refers to both the phytocannabinoid congeners of Δ^9-THC and to a wide range of synthetic substances that act on a family of G-protein coupled receptors, which are presently designated subtypes CB_1 and CB_2. CB_1 receptors are predominantly distributed throughout the central and peripheral nervous system, where they mediate inhibition of neurochemical transmitter release and are associated with analgesic and mood modifying effects. CB_2 receptors predominantly occur on immune cells, are associated with modulation of cytokine release and have an anti-inflammatory effect (Mackie 2006 **NR**).

The endogenous cannabinoid system can be considered complementary to the endogenous opioid system (Wilson-Poe 2013 **BS**). Endogenous cannabinoid ligands (endocannabinoids) are derived from arachidonic acid. It is postulated that some (chemically noncannabinoid) analgesic agents (including paracetamol and various NSAIDs) may act, at least in part, via cannabinoid receptor mediation, either directly or indirectly via modulation of endocannabinoid metabolism (Manzanares 2006 **NR**; Graham 2013a **NR**).

It is difficult to group together cannabis-derived preparations and other cannabinoids. This is because plant-extract formulations comprise a mixture of active ingredients (eg the oral mucosal metered-dose spray nabiximols [Sativex®; containing THC:cannabidiol≈1:1] in comparison to pure single ingredient cannabinoid preparations, such as dronabinol [Marinol®, synthetic THC, oral capsules] and nabilone [Cesamet®, synthetic analogue of THC, oral capsules]).

The acute toxicity of phytocannabinoids is extremely low; nevertheless, clinical studies of the effect-adverse effect profile of cannabis and cannabinoids have demonstrated that desirable actions may be limited in a proportion of patients due to adverse effects, including dysphoria, sedation and impaired psychomotor performance, memory and concentration (Robson 2011 **NR**).

Many patients self-administer cannabis by smoking; the traditional route popularised by nonmedical users (McQuay 2010 **NR**; Wilsey 2013 **Level II**, n=39, JS 4). Transpulmonary

administered phytocannabinoids are rapidly and efficiently absorbed; however, newer vaporising delivery techniques are supplanting smoking with its attendant health risks (Hazekamp 2006 **EH**; Zuurman 2008 **Level II**, n=12, JS 4; Eisenberg 2014 **Level IV**). Oral cannabis and cannabinoid preparations have a poor and highly variable systemic bioavailability (Huestis 2007 **NR**). Likewise the oromucosal spray (of nabiximols) does not achieve a rapid systemic absorption, with a profile resembling oral administration (Hazekamp 2006 **EH**; Zuurman 2008 **Level II EH**, n=12, JS 4; Karschner 2011a **Level II PK**, n=9 JS 3; Karschner 2011b **Level II EH**, n=22, JS 3).

4.11.2 Efficacy

A qualitative systematic review examined the evidence for various cannabinoids as analgesics with oral administration for cancer pain (Campbell 2001 **Level I**, 5 RCTs, n=128), oral administration for chronic noncancer pain (Campbell 2001 **Level I**, 2 "n=1" trials, n=2), and IM administration for postoperative pain (Campbell 2001 **Level I**, 2 RCTs, n=72). There is, overall, evidence for clinically relevant effectiveness of these cannabinoids being no greater than 60–120 mg codeine, with significant and generally similar adverse effects.

In treating acute pain, no analgesic benefit over placebo was found with a single 5 mg oral dose of Δ^9-THC on d 2 following hysterectomy in two groups of patients, as judged by pain scores or time to rescue analgesia (Buggy 2003 **Level II**, n=40, JS 5). A pilot comparative study in patients who mainly underwent major orthopaedic or gynaecological surgery found that those patients, in the presence of PCA morphine, who received 2 mg oral nabilone had higher pain scores at rest than those receiving 1 mg nabilone (11 patients), 50 mg ketoprofen (n=11) or placebo (n=10) but did not consume any greater amount of PCA morphine (Beaulieu 2006 **Level** III-1). A dose-escalating single oral dose multicentre study using 5 mg (n=11), 10 mg (n=30) or 15 mg (n=24) Cannador® (Δ^9-THC:cannabidiol ratio=1:03 for 5 mg, 1:05 for 10 and 15 mg) following cessation of PCA after a range of surgical procedures found that the need for rescue analgesia was reduced with increasing Cannador® dose but that the frequency of adverse effects increased at the higher doses (Holdcroft 2006 **Level III-3**). However, no placebo control group was included. In patients having radical prostatectomy, the addition of oral Δ^9-THC (5 mg, 8 doses over 48 h) in 50 patients did not significantly alter the analgesic requirement for PCA piritramide compared to 50 patients having placebo (Seeling 2006 **Level II**, n=100, JS 5).

A volunteer study considering acute pain used electrical and heat stimuli in healthy young adult female volunteers found 20 mg oral standardised cannabis extract to be no different to 5 mg oral diazepam (active placebo) in a variety of endpoint measures (Kraft 2008 **Level II EH**, n=18, JS 4). The authors concluded that "cannabinoids are not effective analgesics for the treatment of acute nociceptive pain in humans". The authors determined the plasma concentrations of the Δ^9-THC and cannabidiol components and found that they varied more than seven-fold between subjects.

In patients with neuropathic pain, some analgesic efficacy of cannabis has been identified. A meta-analysis shows that nabiximols (Sativex®) decreases neuropathic and multiple sclerosis-related pain with the most common adverse effect being dizziness (35% cannabinoid; 10% placebo-treated patients) (Iskedjian 2007 **Level I**, 7 RCTS, n=222). In a 5-wk placebo-controlled study, the intensity of neuropathic pain of peripheral origin was significantly ameliorated by nabiximols, as compared with placebo (Nurmikko 2007 **Level II**, n=125, JS 5). In patients with multiple sclerosis, a systematic review and expert panel concluded that oral cannabinoid extracts were effective in reducing central pain and that THC or nabiximols were probably effective for treating multiple sclerosis-related pain or painful spasms (Koppel 2014 **Level IV SR**, 34 studies).

In patients with a variety of causes for both peripheral and central neuropathic pain, smoking cannabis (low and high dose) was significantly more effective in reducing neuropathic pain than smoking placebo cigarettes; acute cognitive impairment, particularly of memory, was significantly greater at higher cannabis doses but psychoactive effects ("feeling high", "feeling stoned") with both high and low doses were minimal and well tolerated (Wilsey 2008 **Level II**, n=38, JS 5). Smoked cannabis was also more effective than placebo in HIV-associated neuropathic pain (Phillips 2010 **Level I** [PRISMA], 2 RCTs, n=111). In multiple sclerosis, smoked cannabis was of unclear efficacy for reducing pain (Koppel 2014 **Level IV SR**, 34 studies,

n unspecified). Compared with placebo, oromucosal administration of cannabinoids was well tolerated and moderately effective as adjunctive treatment for the relief of intractable central neuropathic pain resulting from brachial plexus avulsion (Berman 2004 **Level II**, n=48, JS 5).

4.11.3 Adverse effects

Transient adverse effects of cannabis and cannabinoids are variable and include impaired cognition, dizziness and sedation. In short-term exposure (mean treatment duration of 2 wk) medical cannabis was not associated with a higher incidence of serious adverse effects compared with control (RR 1.04; 95%CI 0.78 to 1.39), with dizziness being reported as the most commonly reported nonserious event in cannabinoid-treated patients (15.5%) (Wang 2008a **Level I**, 23 RCTs, n=3,141). Longer-term studies in multiple sclerosis patients have indicated no new safety concerns after several years of administration. Nabiximols (Sativex®) treatment in patients with multiple sclerosis was not associated with psychopathology or impaired cognition (Aragona 2009 **Level II**, n=17, JS 5). Similarly, its adverse effects were assessed in an open-label study following a trial for treating spasticity in 146 patients having multiple sclerosis for a mean duration of 334 d (Serpell 2013 **Level IV**). Adverse effects typically reported as "dizziness", "fatigue" and "headache" caused treatment withdrawal in 14% of patients and were serious (eg psychosis) in 4.3%. A further 9% of these patients withdrew due to lack of efficacy.

There is widespread concern about chronic exposure to cannabis and the development of psychosis in susceptible individuals. For example, one widely cited meta-analysis concluded that cannabis plays a causal role in the development of psychosis in some psychiatric patients (Large 2011 **Level III-2 SR**, 83 studies, n=22,519). Others have argued that there is little evidence that, at a population level, cannabis use is a primary contributing factor in the development of psychiatric illness (Macleod 2010 **NR**; Gage 2013 **NR**; Hamilton 2014 **Level III-3**; Hill 2014 **Level IV**).

Rapidly absorbed cannabis (eg smoking) produces a tachycardia by a beta-adrenergic mechanism (Beaconsfield 1972 **NR**). There is increasing concern from three case reports that cannabis use may trigger acute coronary events (Casier 2014 **Level IV**). However, in 519 patients surviving acute myocardial infarction there was no statistically significant association between cannabis use and mortality (Frost 2013 **Level IV**).

Epidemiological evidence of harms is typically derived from "recreational" users where the "cannabis" is defined neither chemically nor posologically and its relevance to the medical use, particularly of pharmaceutical grade cannabis, in supervised patients, is questionable.

It should be noted that all clinical studies to date have various design limitations, most involving small numbers of patients and most using only nonselective highly lipophilic cannabinoids, often of unknown composition. The possible benefits from more selective agonists have yet to be investigated in the clinical setting, along with more innovative or reliable modes of administration.

At present no cannabinoid preparation or mode of administration would yet appear to be effective for the treatment of acute pain, apart from acute exacerbations of chronic pain.

Key messages

1. Current evidence does not support the use of cannabinoids in acute pain management (**U**) (**Level I**).
2. Cannabinoids appear to be mildly effective when used in the treatment of chronic neuropathic pain, including that associated with multiple sclerosis and HIV (**U**) (**Level I**).
3. Adverse effects including dizziness, cognitive changes and psychosis may limit the usefulness of cannabinoids in pain treatment in some patients (**N**) (**Level I**).

4.12 Corticosteroids

4.12.1 Systemic corticosteroids

Surgical tissue trauma leads to the conversion of arachidonic acid to prostaglandins and leukotrienes. NSAIDs inhibit the formation of prostaglandins, whereas corticosteroids also inhibit the production of leukotrienes and cytokines (Gilron 2004 **NR**; Romundstad 2007 **NR**). The anti-inflammatory effects of corticosteroids account for some, but not all, of the antinociceptive effects of corticosteroids seen in clinical practice. It is likely that the analgesic actions of systemically administered corticosteroids are attributable predominantly to rapid-onset nongenomic mechanisms. However, the well-documented anti-inflammatory actions may contribute to a more delayed analgesic effect and may be due to genomic effects (Czock 2005 **NR**; Stellato 2004 **NR**; Lowenberg 2008 **NR**; Stahn 2008 **NR**).

4.12.1.1 Efficacy

Perioperative administration of corticosteroids reduces the severity of postoperative pain and decreases analgesic requirements as discussed below. However, corticosteroids are not only administered in the perioperative setting for their analgesic effects but also for other reasons. These include (but are not limited to) a reduction of PONV (De Oliveira 2013b **Level I** [PRISMA], 60 RCTs, n=6,696), decreased sore throat in intubated patients (Bagchi 2012 **Level II**, n=95, JS 5; Thomas 2007 **Level II**, n=120, JS 5), decreased swelling in dental and maxillofacial surgery (Dan 2010 **Level I**, 12 RCTs, n=574) and an improvement in quality of recovery and decreased postoperative fatigue (Murphy 2011b **Level II**, n=120, JS 5; Murphy 2011a **Level II**, n=117, JS 5; Murphy 2014 **Level II**, n=200, JS 5) with facilitation of earlier hospital discharge (Murphy 2011b **Level II**, n=120, JS 5).

High-dose (dexamethasone equivalent >10 mg), but not low-dose, systemic perioperative corticosteroid administration improves analgesia in patients undergoing elective knee or hip surgery (Lunn 2013 **Level I** [PRISMA], 17 RCTs, n=1,081). Similarly, after maxillofacial surgery, the perioperative administration of corticosteroids (dexamethasone equivalent >5 mg) results in a significant analgesic effects compared to placebo (Dan 2010 **Level I**, 12 RCTs, n=574). After mixed ambulatory surgery, ketorolac provided better pain relief than either dexamethasone or betamethasone in the immediate postoperative period but there were no differences in pain relief or analgesic use in the 4–72 h period after surgery (Thagaard 2007 **Level II**, n=179, JS 5).

Corticosteroids have also been shown to have antihyperalgesic effects in animals and humans (Romundstad 2007 **NR**; Kehlet 2007 **NR**). In experimental burn injury pain, both methylprednisolone and ketorolac reduced secondary hyperalgesia and increased pain pressure tolerance threshold compared with placebo, although the increase in pain pressure tolerance threshold was greater with ketorolac (Stubhaug 2007 **Level II EH**, n=12, JS 4). In surgical patients, preoperative administration of methylprednisolone resulted in significantly less hyperalgesia compared with parecoxib and placebo but there was no reduction in persistent spontaneous or evoked pain (Romundstad 2006 **Level II**, n=204, JS 4).

Dexamethasone

Dexamethasone administration to surgical patients decreases postoperative pain scores, opioid consumption, time to first analgesia, requirements for rescue analgesia and length of stay in the PACU (Waldron 2013 **Level I** [PRISMA], 45 RCTs, n=5,796). However, the differences are small and, while statistically significant, unlikely to confer clinical relevant analgesic benefit (eg 13% reduction in postoperative opioid consumption equals 3 mg morphine equivalent over the first 24 h). Preoperative dexamethasone administration is superior to later administration.

When steroid doses were classified into three levels, an optimal dose of 0.1–0.2 mg/kg dexamethasone was identified (De Oliveira 2011 **Level I** [PRISMA], 24 RCTs, n=2,751); however, a subsequent metaregression did not identify any dose-response relationship for an opioid-sparing effect (Waldron 2013 **Level I** [PRISMA], 45 RCTs, n=5,796).

Procedure-specific data on perioperative dexamethasone administration are in line with these findings. Dexamethasone in doses >10 mg over 24 h given to adults undergoing tonsillectomy

decreases postoperative pain, an effect further improved by repeated administration in the postoperative period (Diakos 2011 **Level I**, 7 RCTs, n=580). Dexamethasone in adults undergoing thyroidectomy reduces postoperative pain scores and analgesic requirements (Chen 2012 **Level I** [PRISMA], 5 RCTs, n=497). The analgesic effect of dexamethasone lasted up to 72 h following total knee arthroplasty at a dose of 10 mg (Koh 2013 **Level II**, n=269, JS 3), with an additional postoperative dose of 10 mg prolonging the analgesic improvement (Backes 2013 **Level II**, n=120, JS 5).

A combination of gabapentin/dexamethasone provided better pain relief and led to less PONV than either medicine given alone after varicocoele surgery; both the combination and the individual medicines were more effective than placebo (Koç 2007 **Level II**, n=80, JS 5). A similar result was observed in rhinoplasty surgery (Demirhan 2013 **Level II**, n=60, JS 3), where the combination of pregabalin/dexamethasone showed significant analgesic benefits up to 24 h. In contrast, there was no difference in pain scores or PCA-morphine requirements during the first 24 h postoperatively in patients given pregabalin, pregabalin/dexamethasone or placebo after hysterectomy (Mathiesen 2009 **Level II**, n=116, JS 5).

Methylprednisolone and prednisolone

Oral prednisolone (50 mg) preoperatively did not improve pain, fatigue, nausea or vomiting in patients undergoing laparoscopic cholecystectomy compared with placebo (Bisgaard 2008 **Level II**, n=200, JS 3). After orthopaedic surgery, there was no difference in the analgesic effect of IV methylprednisolone 125 mg compared with IV ketorolac 30 mg, ,with both being better than placebo; IV methylprednisolone led to greater opioid-sparing but there was no difference in the incidence of adverse effects (Romundstad 2004 **Level II**, n=75 patients, JS 5). In contrast, 125 mg of methylprednisolone did not confer analgesic benefit in patients undergoing total abdominal hysterectomy (Aabakke 2014 **Level II**, n=49, JS 4).

After breast augmentation, IV methylprednisolone 125 mg and IV parecoxib 40 mg provided comparable analgesia; however, PONV and fatigue scores were lower in the patients given methylprednisolone (Romundstad 2006 **Level II**, n=204, JS 4).

4.12.1.2 Adverse effects

The principal safety concerns of perioperative corticosteroid administration relate to the development of hyperglycaemia, increased infection and bleeding risk and the risk of recurrence of malignancy (Ali Khan 2013 **NR**; Dhatariya 2013 **NR**; Turan 2011 **NR**; Ho 2011 **NR**; Yee 2013a **NR**).

The authors of multiple meta-analyses have asserted the safety of perioperative corticosteroids, even in very large doses. However, the RCTs summarised in these meta-analyses are essentially efficacy studies of the antiemetic and anti-inflammatory effects of dexamethasone. Few examined long-term effects or patient outcomes and none of these RCTs were adequately powered to do so.

Hyperglycaemia

A large dose of dexamethasone (1 mg/kg at induction) in cardiac surgery patients resulted in a higher maximum postoperative blood-glucose concentration (MD of 0.9 mmol/L) compared to placebo (Dieleman 2012 **Level II**, n=4,494, JS 5). As all patients received glucose-lowering therapy in the ICU postoperatively, the dexamethasone effect may have been mitigated. A single 8 mg preoperative dose of dexamethasone in major noncardiac surgery produced a small but significant increase (1.6 mmol/L) in blood-glucose concentrations; however, only in patients without diabetes (Abdelmalak 2013b **Level II**, n=381, JS 5). In noncardiac surgery patients, modest increases in blood-glucose concentrations have occurred (Cowie 2010, Hans 2006 **Level III-2**) as has suppression of plasma-cortisol concentrations at 24 h (Cowie 2010 **Level II**, n=14, JS 5).

Conversely, other volunteer and clinical studies have demonstrated no effect on blood-glucose concentrations; after elective gynaecological surgery there were neither early nor late effects of dexamethasone 4 mg and 8 mg on blood-glucose concentrations compared to placebo (Murphy 2014 **Level II**, n=200, JS 5).

Infection risk

In cardiac surgery, a single intraoperative high dose of dexamethasone (1 mg/kg) did not significantly increase the incidence of postoperative wound infection; there was actually a reduction in total infection complications, due mainly to a reduction in pneumonia (Dieleman 2012 **Level II**, n=4,494, JS 5). This was supported by another study in major noncardiac surgery, where the incidence of healthcare-associated infections in the dexamethasone group (11.5%) was not significantly different from the control group (7.4%) (Abdelmalak 2013a **Level II**, n=381, JS 5). Retrospective observational studies of intraoperative single IV dexamethasone found no difference in the rate of wound complications or time to complete wound healing in a range of procedures (Coloma 2001 **Level III-2**; Corcoran 2010 **Level III-2**; Eberhart 2011 **Level III-2**; Bolac 2013 **Level III-2**), with the exception of one, which found a three-fold increase in the risk of infection (Percival 2010 **Level III-2**).

Bleeding risk

In paediatric tonsillectomy dexamethasone does not increase the overall bleeding risk; however its use increases the need for operative intervention for bleeding (Plante 2012 **Level I**, 29 RCTs, n=2,674).

Malignancy recurrence

There are limited and contradictory results on recurrence of malignancy; after colorectal surgery there was an increase in one small RCT (Singh 2014 **Level II**, n=43, JS 4), while a propensity-matched study failed to confirm such an association in ovarian cancer (De Oliveira 2014 **Level III-2**).

Key messages

1. Dexamethasone reduces postoperative pain and opioid requirements to a limited extent but also reduces nausea and vomiting, fatigue, and improves the quality of recovery compared with placebo (**S**) (**Level I** [PRISMA]).
2. Preoperative administration of dexamethasone appears more effective than intraoperative or postoperative administration (**N**) (**Level I** [PRISMA).
3. Mild hyperglycaemia may follow the perioperative administration of corticosteroids (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ The risks of using corticosteroids in surgical populations remain to be evaluated (**N**).

4.12.2 Regional corticosteroids

4.12.2.1 Neuraxial

Dexamethasone when added to bupivacaine/fentanyl solution in epidural analgesia prolonged duration of analgesia in abdominal or thoracic surgery (372 ± 58.1 min vs 234.6 ± 24.3 min) and decreased opioid requirements in the first 24 h (Naghipour 2013 **Level II**, n=72, JS 5). In patients having lower abdominal surgery, single-dose epidural bupivacaine/dexamethasone mixture had similar prolongation of time to first analgesia, opioid-sparing and antiemetic effects as bupivacaine/fentanyl mixture when compared with epidural bupivacaine alone (Khafagy 2010 **Level II**, n=90, JS 5). Preoperative single-dose epidural administration of dexamethasone, with or without bupivacaine, reduced postoperative pain and morphine consumption following laparoscopic cholecystectomy (Thomas 2006 **Level II**, n=94, JS 5).

Use of epidural methylprednisolone resulted in no difference in morphine requirements or pain scores following thoracotomy compared with epidural saline (Blanloeil 2001 **Level II**, n=24, JS 4). Following lumbar disc surgery, the combination of wound infiltration with bupivacaine and epidural and perineural methylprednisolone improved analgesia and decreased opioid consumption compared with placebo (Mirzai 2002 **Level II**, n=44, JS 4; Jirarattanaphochai 2007

Level II, n=103, JS 5). However, epidural administration of either medicine on its own was not superior to placebo (Lotfinia 2007 **Level II**, n=150, JS 4). Epidural analgesic paste containing methylprednisolone when applied to the epidural space at the site of the removed lamina is effective at reducing postoperative pain and decreasing opioid requirements for up to 3 d following lumbar decompressive surgery (Diaz 2012 **Level II**, n=201, JS 5). There was no long-term benefit in a previous RCT for up to 6 wk (Hurlbert 1999 **Level II**, n=60, JS 5).

Lumbar epidural steroid injections for sciatica provide small but statistically significant short-term relief (≤3 mth) from acute radicular pain (MD 6.2/100; 95%CI 3.0 to 9.4) and reduce disability but do not provide significant longer-term benefits beyond this time (Pinto 2012 **Level I,** 23 RCTs, n=2,334). The same was found for the transforaminal route alone (Quraishi 2012 **Level I,** 3 RCTs, n=368; Pinto 2012 **Level I,** 23 RCTs, n=2,334).

The FDA issued a warning in April 2014 that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse effects, including loss of vision, stroke, paralysis and death (FDA 2014a).

4.12.2.2 Perineural sites

The addition of dexamethasone to local anaesthetic prolongs the duration of sensory and motor block, when compared with local anaesthetic alone, in interscalene, supraclavicular and axillary brachial plexus block (Choi 2014b **Level I** [PRISMA], 9 RCTs, n=801). For long-acting local anaesthetics (ropivacaine, bupivacaine, levobupivacaine), dexamethasone addition (4–10 mg) prolonged the analgesic duration from a mean of 730 min to 1,306 min (MD 576 min; 95%CI 522 to 631). For intermediate-acting local anaesthetics (lignocaine, mepivacaine) sensory analgesia was prolonged with added dexamethasone from 168–343 min (MD 175 min; 95%CI 73 to 277). Overall, motor block was also prolonged from 664–1102 min with added dexamethasone (MD 438 min; 95%CI 89 to 787). These effects were associated with no significant reduction in 72-h opioid requirements.

Whether the effect of dexamethasone in prolonging perineural local anaesthetic block is a systemic or local one has been investigated in only a small number of studies. IV dexamethasone was equivalent to perineural dexamethasone in prolonging the analgesic duration of a single-injection interscalene block with ropivacaine (median block duration: control 757 min, systemic dexamethasone 1,275 min and perineural dexamethasone 1,405 min) (Desmet 2013 **Level II**, n=150, JS 5). Substitution of IM dexamethasone for perineural dexamethasone during bupivacaine sciatic and ankle blocks improved pain scores at 24 h in the sciatic group but conferred no other analgesic benefits in either group (Fredrickson 2013 **Level II**, n=126, JS 5). Preoperative administration of IV vs perineural dexamethasone compared with saline did not improve overall QoR-40 or decrease opioid consumption for patients undergoing elective foot and ankle surgery and receiving sciatic nerve block with bupivacaine (Rahangdale 2014 **Level II**, n=80, JS 5). However analgesic duration was prolonged and pain scores on d 1 on movement were reduced in the perineural dexamethasone group.

Although perineural dexamethasone has been shown to prolong sensory and motor block of perineural local anaesthetics, there is little safety data to support its use. Animal data to date are reassuring, with dexamethasone not increasing ropivacaine-induced sensory nerve toxicity at clinically relevant concentrations (Williams 2011 **BS**) and dexamethasone attenuating bupivacaine-induced neuronal injury (Ma 2010 **BS**). However, given the lack of human safety data, the practice of perineural dexamethasone administration needs to be further evaluated (Rahangdale 2014 **NR**). Furthermore, mixtures of ropivacaine and nonparticulate dexamethasone sodium phosphate demonstrated a pH-dependent crystallisation and the use of such combinations may be not advisable (Watkins 2015 **BS**).

4.12.2.3 Peripheral sites

Periarticular injection of combinations of local anaesthetic, opioid and anti-inflammatory agents including steroids have been studied (LIA), however the range of mixtures makes determination of the effect of individual components difficult. In patients having simultaneous bilateral knee joint arthroplasties, bupivacaine/fentanyl/methylprednisolone were infiltrated by the surgeon around one knee but not the other (Mullaji 2010 **Level II**, n=40, JS 4). Pain

scores on the infiltrated side were significantly lower and the joint had greater active flexion up to 4 wk and superior quadriceps recovery up to 2 wk after surgery when compared with noninfiltrated knee. Periarticular injection of a mixture of bupivacaine/morphine/epinephrine/clonidine showed a reduced the length of hospital stay by 24 h without any significant effect on pain relief, motion or function following total knee arthroplasty, when methylprednisolone was added (Christensen 2009 **Level II**, n=76, JS 4). In comparing ropivacaine/adrenaline in three groups with no added steroid, 40 mg and 80 mg triamcinolone, the addition of corticosteroid to periarticular injection of local anaesthetic did not improve pain relief or range of movement outcomes for up to 12 wk of follow-up (Chia 2013 **Level II**, n=126, JS 5).

Intra-articular corticosteroid injections would be expected to have a direct analgesic effect in inflammatory arthropathies. Following knee joint arthroscopy, intra-articular steroids were more effective than placebo in reducing pain, analgesic consumption and duration of immobilisation either alone (Wang 1998 **Level II**, n=60, JS 4) or in conjunction with opioids (Kizilkaya 2004 **Level II**, n=60, JS 2; Kizilkaya 2005 **Level II**, n=72, JS 4) and/or local anaesthetics (Rasmussen 2002 **Level II**, n=60, JS 3). Dexamethasone on its own was less effective than pethidine or fentanyl (Saryazdi 2006 **Level II**, n=48, JS 3). There may be a higher risk of septic arthritis with intra-articular steroids (Armstrong 1992 **Level IV**).

Subacromial injections of corticosteroids have been shown to be effective in treating rotator cuff tendonitis for up to 9 mth vs placebo (NNT 3.3; 95%CI 1.8 to 7.7) and were superior to oral NSAIDs (NNT 2.5; 95%CI 1 to 9) (Arroll 2005 **Level I** [QUOROM], 7 RCTs, n=347). In patients with tendonitis of the shoulder or elbow, steroid injections showed similar benefits to NSAIDs for early (up to 1 wk) pain relief (Gaujoux-Viala 2009 **Level I**, 20 RCTs, n=1,731).

In patients having hand surgery, IVRA using a combination of lignocaine and dexamethasone resulted in lower pain scores and lower analgesic requirements for 24 h compared with lignocaine alone or lignocaine IVRA with dexamethasone in the nonoperative arm (Bigat 2006 **Level II**, n=75, JS 2). The addition of dexamethasone to lignocaine and ketorolac IVRA for hand surgery improved intraoperative tourniquet tolerance and postoperative analgesia compared with lignocaine IVRA alone (Jankovic 2008 **Level II**, n=45, JS 3).

Key messages

1. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**U**) (**Level I** [QUOROM]).
2. Lumbar epidural (or transforaminal) corticosteroid administration is effective for short-term relief of acute radicular pain (**U**) (**Level I**).
3. Addition of dexamethasone to local anaesthetic prolongs the duration of sensory and motor block in brachial plexus block similar to systemic administration (**N**) (**Level II**).
4. Addition of dexamethasone to intravenous regional anaesthesia with lignocaine improves analgesia for up to 24 hours (**U**) (**Level II**).
5. Addition of corticosteroid to periarticular injection of local anaesthetic does not improve pain relief or range of movement following total knee arthroplasty (**N**) (**Level II**).
6. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**U**) (**Level II**).
7. There is a risk of septic arthritis with intra-articular steroids (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Concerns have been raised regarding the safety of epidural steroids (**N**).

☑ There is little data in humans regarding the neurotoxicity of perineural corticosteroids (**N**).

4.13 Other regional analgesic medicines

4.13.1 Midazolam

Midazolam in the preservative-free preparation has been proposed as a potential spinal analgesic due to its action on $GABA_A$ receptors. It is not approved for this indication and efficacy and safety remain unclear.

Reports of IT midazolam administration have appeared in the literature for many years, despite concerns regarding potential neurotoxicity (Yaksh 2004 **NR**). Although neurotoxic damage was not seen in sheep and pigs given continuous IT midazolam (Johansen 2004 **BS**), in isolated sensory neurones, midazolam at twice estimated clinical concentrations produced neurotoxicity after 24 h exposure but to a lesser extent than ropivacaine (Williams 2011 **BS**).

Early patient series suggested a low risk of clinical toxicity and a 1-mth questionnaire follow-up of patients who had received IT midazolam failed to show any evidence of neurological or urological complications (Tucker 2004a **Level III-2**; Tucker 2004b **Level III-2**). The incidence of neurological symptoms after IT midazolam is uncommon (1.8%) and did not differ from placebo (Ho 2008 **Level I**, 13 RCTS, n=672). There are insufficient data to exclude the possibility of long-term neurological complications from IT midazolam, although none have yet been reported.

IT midazolam added to IT local anaesthetic in perioperative and peripartum patients in comparison with IT local anaesthetic alone showed a reduced incidence of nausea and vomiting and delayed time to request for rescue analgesia (WMD 98.7 min; 95%CI 76.1 to 121.4 min) but did not affect the duration of motor block (Ho 2008 **Level I**, 13 RCTs, n=672). IT midazolam as an adjuvant to IT opioids significantly enhanced analgesia in labour pain with no significant adverse effects (Salimi 2014 **Level II**, n=80, JS 2).

In nonobstetric patients, IT midazolam (2 mg) with IT local anaesthetic significantly increased the duration of analgesia (median 320 min vs 220 min) and motor block (median 255 min vs 195 min) and decreased the incidence of PONV compared with IT local anaesthetic alone (Chattopadhyay 2013 **Level II**, n=90, JS 5). In patients undergoing elective lower abdominal, lower limb and gynaecological procedures, preservative-free IT midazolam (2 mg) added to IT bupivacaine resulted in prolonged postoperative analgesia without increasing motor block compared to IT bupivacaine alone (Shadangi 2011 **Level II**, n=100, JS 4).

A single preoperative epidural dose of midazolam combined with ketamine In patients having a gastrectomy improved analgesia and prolonged the time to rescue analgesia compared with epidural ketamine or placebo, with no significant adverse effects (Wang 2006 **Level II**, n=44, JS 4). Midazolam added to bupivacaine for epidural infusion improved analgesia but increased sedation (Nishiyama 2002 **Level II**, n=100, JS 1).

Midazolam has been added to caudal epidural analgesia in paediatric surgery although age-related toxicity issues have not been addressed. In combination with bupivacaine it prolonged postoperative analgesia (Ansermino 2003 **Level I**, 2 RCTs [midazolam], n=60; Kumar 2005 **Level II**, n=80, JS 5). In infants having hernia repairs, neither midazolam nor fentanyl added to bupivacaine for caudal anaesthesia improved postoperative analgesia or recovery (Baris 2003 **Level II**, n=75, JS 4).

4.13.2 Neostigmine

Neostigmine acts as a spinal analgesic by potentiation of muscarinic cholinergic activity. In a literature review of animal and human studies there was no evidence of neurotoxicity with spinal neostigmine (Hodgson 1999 **NR**).

IT neostigmine for perioperative and peripartum analgesia prolongs the time to first analgesia request (168 min; 95%CI 125 to 211 min) and results in a slight improvement in pain scores and a reduced need for rescue medication; however, it increases nausea and vomiting (OR 5.0; 95%CI 3.4 to 7.3), bradycardia requiring atropine (OR 2.7; 95%CI 1.4 to 5.4) and anxiety, agitation and restlessness (OR 10.3; 95%CI 3.7 to 28.9) (Ho 2005 **Level I**, 19 RCTs, n=1,019). The authors concluded that the significant adverse effects outweighed any clinical benefit,

a conclusion supported by a later review where a lack of a clear dose-response was also identified (Habib 2006 **Level I,** 17 RCTs [IT neostigmine], n unspecified; Hye 2010 **Level II**, n=90, JS 4). In patients having surgery under spinal anaesthesia, 25 mcg IT neostigmine prolonged time to first analgesia by a MD of 169 min but postoperative adverse events were not reported (Akinwale 2012 **Level II**, n=60, JS 4). Very low-dose IT neostigmine (1 mcg) increased the duration of analgesia and decreased the analgesic consumption over 24 h postoperatively in patients undergoing total knee replacement with no increase in the incidence of adverse effects including nausea or vomiting (Jain 2012 **Level II**, n=45, JS 4). In patients having spinal anaesthesia, a comparison of IT clonidine (75 mcg) to IT neostigmine (50 mcg) found the clonidine group to have a longer time to first analgesic request (MD 62 min) but more hypotension during surgery (Yoganarasimha 2014 **Level II**, n=50, JS 3).

Epidural neostigmine in the general surgical and obstetric populations improves postoperative analgesia in most studies without increasing the incidence of adverse effects (Habib 2006 **Level I**, 7 RCTs [epidural neostigmine], n unspecified). Epidural neostigmine combined with an opioid reduces epidural opioid requirements but may not decrease opioid-related adverse effects compared with the opioid alone (Walker 2002 **Level I**, 6 RCTs [neostigmine], n=370). The coadministration of sufentanil or clonidine may be of benefit (Roelants 2006 **NR**). The addition of epidural neostigmine to bupivacaine reduced hourly patient-controlled epidural bupivacaine requirements during labour (Ross 2009 **Level II**, n=40, JS 5).

In paediatric caudal analgesia, the addition of neostigmine increases the duration of analgesia by 9.96 h (95%CI 7.75 to 12.16 h) compared with local anaesthetic alone but with a significant increase in PONV (OR 1.78; 95%CI 1.11 to 2.85) (Engelman 2012 **Level I**, 7 RCTs [neostigmine], n=533) (see Section 9.6.2.1).

Intra-articular administration of neostigmine produced a useful analgesic effect in the postoperative period and was not associated with an increase in the incidence of adverse effects (Habib 2006 **Level I**, 4 RCTs [intra-articular neostigmine], n unspecified).

Studies investigating the efficacy of adding neostigmine to the local anaesthetics used for brachial plexus block and IVRA reported conflicting results (Habib 2006 **Level I,** 4 RCTs [perineural neostigmine], n unspecified).

4.13.3 Botulinum toxin A

Following direct IM injection, botulinum toxin acts to irreversibly bind to the acetylcholine receptor and induce a chemical denervation with resultant muscular paralysis. The extent and duration of paralysis depends on the dose administered. Systemic weakness may follow high cumulative doses. Reinnervation may occur over a period of weeks to months. It may also exert analgesic effects by other mechanisms. The use of botulinum toxin in the treatment of chronic painful conditions is beyond the scope of this section.

In treating pain and related muscle spasm in a range of conditions, botulinum toxin is effective in reducing limb spasm (21 RCTs) but evidence relating to spasticity-related pain remains uncertain (Baker 2013 **Level I**, 10 RCTs [in pain], n=971). Similarly, the quality of current evidence is poor but does not support the use of botulinum toxin injection in trigger points for myofascial pain (Soares 2014 **Level I** [Cochrane], 4 RCTs, n=233). In subacute and chronic neck disorders with or without associated cervicogenic headache, IM botulinum toxin injections provide no clear benefit (Langevin 2011 **Level I** [Cochrane], 9 RCTs, n=503).

Key messages

1. Intrathecal neostigmine improves perioperative and peripartum analgesia in combination with other spinal medications but is associated with significant adverse effects (**U**) (**Level I**).
2. Epidural neostigmine combined with local anaesthetics improves postoperative analgesia without increasing the incidence of adverse effects (**S**) (**Level I**).
3. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).
4. Intrathecal midazolam combined with a local anaesthetic prolongs the time to first analgesia and reduces postoperative nausea and vomiting (**U**) (**Level I**).

4.14 Complementary and alternative medicine

Complementary and alternative medicine (CAM) is defined as healthcare practices outside the conventional dominant "orthodox" health system of Western industrialised society (Belgrade 2008 **NR**). The boundary between CAM and conventional medicine overlaps and changes with time. In some cultures, these therapies may be considered conventional mainstream practices. Currently, acupuncture, aromatherapy, chiropractic, homeopathy, meditation and relaxation therapies, osteopathy, traditional Chinese medicine techniques, herbal preparations and dietary supplements are usually referred to as CAM.

There are limited good data on the use of CAMs in the management of acute pain.

Vitamin C (2 g) given before anaesthesia has been shown to reduce IV PCA morphine consumption by 29% after laparoscopic cholecystectomy (Kanazi 2012 **Level II**, n=84, JS 5).

Two preoperative melatonin doses (5 mg) led to lower pain and anxiety scores in the first 24 h (NNT 2.20 and 2.53) and reduced IV PCA morphine requirements after abdominal hysterectomy (Caumo 2007 **Level II**, n=35, JS 5).

Studies on homeopathic preparations of arnica (*Arnica montana*) and St John's wort (*Hypericum perforatum*) in acute postoperative pain have shown variable but mainly negative results. A systematic review and other studies concluded that homeopathic arnica when compared with placebo is not effective for pain relief after orthopaedic surgery in general (Roberts 2012 **Level I** [PRISMA], 3 studies, n=181), hallux valgus surgery (Karow 2008 **Level II**, n=88, JS 4) and abdominal hysterectomy (Hart 1997 **Level II**, n=93, JS 5). However, homeopathic arnica has been reported to provide a significant reduction in acute pain after tonsillectomy (Robertson 2007 **Level II**, n=190, JS 5); a large number of patients in this study was lost to followup.

Traumeel S (an over-the-counter homeopathic highly diluted preparation of extracts from a combination of plants [including arnica] and minerals) was also ineffective following foot surgery (Singer 2010 **Level II**, n=80, JS 4). Another study using a mixture of homoeopathic preparations including arnica did not show any benefit in postoperative pain relief and morphine consumption after knee ligament reconstruction surgery (Paris 2008a **Level II**, n=158, JS 4).

A meta-analysis on homeopathic *Hypericum perforatum* showed no significant benefit on dental pain; the meta-analysis was limited by marked heterogeneity and poor study quality (Raak 2012 **Level I** [QUOROM], 4 studies, n=325). *Hypericum perforatum* affects the metabolism of oxycodone through induction of cytochrome P450 3A (CYP3A) and leads to a significant reduction of plasma concentration and half-life reducing efficacy (Nieminen 2010 **Level II**, n=12, JS 3).

A systematic review looking at the short-term effectiveness of herbal medicines for low-back pain (a mix of acute, subacute and chronic pain) found that white willow bark (*Salix alba*) provided better analgesia than placebo and was similar to rofecoxib (12.5 mg), presumably due to an anti-inflammatory effect of salicylates (Oltean 2014 **Level I** [Cochrane], 15 RCTs,

n=2,050). Devil's claw (*Harpagophytum procumbens*) was also effective and there was moderate evidence that a plaster containing cayenne (*Capsicum frutescens*) may be better than placebo.

There is much CAM literature on the topic of dysmenorrhoea. In a systematic review, although there is supporting evidence for Chinese herbal medicine for primary dysmenorrhoea, the results are limited by the poor methodological quality (Zhu 2008 **Level I**, 39 RCTs, n=3,475). Vitamin E was reported as either no better than placebo (Kashanian 2013 **Level II**, n=120, JS 4) or as reducing pain severity and duration in primary dysmenorrhoea (Ziaei 2005 **Level II**, n=288, JS 5), while vitamin B_1 100 mg was more effective than placebo (Gokhale 1996 **Level II**, n=556, JS 5). Similar findings were reported for fish oil (omega-3 fatty acids) (Harel 1996 **Level II**, n=42, JS 4), a Japanese herbal combination (Kotani 1997 **Level III-2**), fenugreek (*Trigonella foenum-graecum*) seed powder (Younesy 2014 Level II, n=106, JS 4) and valerian (*Valeriana officinalis*) taken at the beginning of menstruation (Mirabi 2011 **Level II**, n=106, JS 5). Thyme (*Shirazi thymus vulgaris*) was as effective as ibuprofen (Direkvand-Moghadam 2012 **Level II**, n=120, JS 2), while guava leaf extract (*Psidii guaja vae*) at 6 mg/d was effective compared to ibuprofen and placebo (Doubova 2007 **Level II**, n=197, JS 5). Dill (*Anethum graveolens*) was as effective as mefenamic acid in reducing the pain severity in primary dysmenorrhoea (Heidarifar 2014 **Level II**, n=75, JS 4). Ginger (*Zingiber officinale*) was as effective as NSAIDs (mefenamic acid and ibuprofen) in reducing the severity of pain in women with primary dysmenorrhoea (Ozgoli 2009 **Level II**, n=150, JS 5; Rahnama 2012 **Level II**, n=118, JS 5). A Thai herbal remedy, prasaplai, was as effective as mefenamic acid (Sriyakul 2012 **Level II**, n=207, JS 4). An Iranian herbal preparation containing highly purified saffron (*Crocus sativus*), celery (*Apium graveolens*) seed and anise (*Pimpinella anisum*) has also been reported to be comparable to mefenamic acid and provide significant reduction in pain and use of other pain-relief medication when compared with placebo (Nahid 2009 **Level II**, n=180, JS 5).

Adverse effects and interactions with medications have been described with CAMs and must be considered before their use.

Key messages

1. White willow bark (*Salix alba*) and devil's claw (*Harpagophytum procumbens*) are effective in treating acute episodes of low-back pain (**N**) (**Level I** [Cochrane])
2. Homeopathic preparations of arnica (*Arnica montana*) (**N**) (**Level I** [PRISMA]) and St John's wort (*Hypericum perforatum*) (**N**) (**Level I** [QUOROM]) are not effective in treating acute postoperative pain
3. St John's wort (*Hypericum perforatum*) induces metabolism of oxycodone reducing its plasma concentrations and efficacy (**N**)(**Level II**).
4. A variety of complementary medicines show efficacy in prevention and treatment of primary dysmenorrhoea (**N**)(**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ There is some evidence that some complementary and alternative medicines may be effective in some acute pain states. Adverse effects and interactions with medications have been described with complementary and alternative medicines and must be considered before their use (**U**).

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5. ADMINISTRATION OF ANALGESIC MEDICINES

Analgesic medicines can be administered by a number of different routes, either relying on a systemic or local effect or a combination of both. The choice of route may be determined by various factors, including the aetiology, severity, location and type of pain, the patient's overall condition and the characteristics of the chosen administration technique. Additional factors to consider with any route of administration are ease of use, accessibility, speed of analgesic onset, reliability of effect, duration of action, patient acceptability and cost.

The principles of individualisation of dose and dosing intervals apply to the administration of all analgesic agents, particularly opioids, by any route. A lack of flexibility in dose schedules has often meant that intermittent and "prn" (as needed) methods of pain relief have been ineffective when the routes of administration discussed below have been used (Bandolier 2003 **NR**). Frequent assessment of the patient's pain and their response to treatment (including the occurrence of any adverse effects) rather than strict adherence to a given dosing regimen is required if adequate analgesia is to be obtained.

Sections 5.1 to 5.5 below relate to opioids, paracetamol, nsNSAIDs and coxibs. For information relating to oral and parenteral routes of administration of systemically administered adjuvant medicines, refer to Sections 4.6 to 4.12.

Sections 5.6 to 5.9 relate to routes of administration involving techniques of regional and local analgesia.

5.1 Oral route

Oral administration of analgesic agents is simple, noninvasive, has good efficacy in most settings and has high patient acceptability. Other than in the treatment of severe acute pain and providing there are no contraindications to its use, it is the route of choice for the administration of most analgesic medicines.

Limitations to the oral route include vomiting or delayed gastric emptying, when absorption is likely to be impaired. If multiple doses of an oral analgesic medicine are given before return of normal gastric motility, accumulated doses may enter the small intestine at the same time once emptying resumes ("dumping effect"). This could result in an unexpectedly large systemic uptake of the medicine and an increased risk of adverse effects.

Rates of absorption will vary according to the formulation of the oral analgesic agent (eg tablet, suspension, CR preparation). Bioavailability will also vary between medicines because of the effects of first-pass hepatic metabolism following uptake into the portal circulation. Titration of pain relief with oral analgesic medicines is slower compared with some of the other routes of administration discussed below.

Direct comparisons between oral opioid and nonopioid analgesics, or between oral and other routes of administration, are limited. Indirect comparisons, where the individual medicines have been compared with a placebo, have been used to generate a "league table" of analgesic efficacy (see Table 5.1). This table is based on randomised, double-blind, single-dose studies or meta-analyses of such studies in patients with moderate to severe pain and shows the number of patients that need to be given the active medicine (NNT) to achieve at least 50% pain relief in one patient compared with a placebo over a 4–6 h treatment period (Moore 2003 **Level I**, unspecified number of RCTs, n unspecified; Moore 2011 **Level I** [Cochrane], ≈350 RCTs, n≈45,000).

The validity of this approach as a true method of comparison of medicines may be questioned as there is no standardisation of the acute pain model or patient and only single doses of the analgesic agents are used. The effects of the analgesics may vary with different pain models (Gray 2005 reanalysing Barden 2004 **Level I**, 43 RCTs [paracetamol], n unspecified). However, it may be reasonable, in some circumstances, to extrapolate estimates of analgesic efficacy from one pain model to another (Barden 2004 **Level I**, 43 RCTs [paracetamol], n unspecified).

Table 5.1 Table of analgesic efficacy (in all types of surgery)

Analgesic	Number of patients in comparison	NNT 50%	Lower confidence interval	Higher confidence interval
Etoricoxib 180/240	199	1.5	1.3	1.7
Dipyrone 1,000	113	1.6	1.3	2.2
Valdecoxib 40	473	1.6	1.4	1.8
Ibuprofen 600/800	165	1.7	1.4	2.3
Valdecoxib 20	204	1.7	1.4	2.0
Ketorolac 20	69	1.8	1.4	2.5
Ketorolac 60 (IM)	116	1.8	1.5	2.3
Oxycodone IR 10 + Paracetamol 1,000	289	1.8	1.6	2.2
Etoricoxib 120	655	1.9	1.7	2.1
Piroxicam 40	30	1.9	1.2	4.3
Ketoprofen 25	535	2.0	1.8	2.3
Diflunisal 1,000	357	2.1	1.8	2.6
Ketoprofen 100	321	2.1	1.7	2.6
Bromfenac 25	370	2.2	1.9	2.6
Codeine 60 + Paracetamol 800/1,000	192	2.2	1.8	2.9
Oxycodone IR 5 + Paracetamol 500	150	2.2	1.7	3.2
Rofecoxib 50	3,688	2.2	2.0	2.3
Diclofenac 100	787	2.3	2.0	2.5
Dipyrone 500	288	2.3	1.9	3.1
Fenoprofen 200	287	2.3	1.9	3.0
Aspirin 1,200	249	2.4	1.9	3.2
Bromfenac 50	247	2.4	2.0	3.3
Ketoprofen 12.5	274	2.4	1.9	3.1
Lumiracoxib 400	578	2.4	2.1	2.8
Celecoxib 400	620	2.5	2.2	2.9
Flurbiprofen 100	416	2.5	2.0	3.1
Ibuprofen 400	6,475	2.5	2.4	2.6
Bromfenac 100	95	2.6	1.8	4.9
Diclofenac 25	502	2.6	2.2	3.3
Diflunisal 500	391	2.6	2.1	3.3
Ketorolac 10	790	2.6	2.3	3.1
Tramadol 75 + Paracetamol 650	679	2.6	2.3	3.0
Diclofenac 50	1,325	2.7	2.4	3.0
Flurbiprofen 50	692	2.7	2.3	3.3
Ibuprofen 600	203	2.7	2.0	4.2
Ibuprofen 200	2,690	2.7	2.5	3.0
Oxycodone IR 10 + Paracetamol 650	1,043	2.7	2.4	3.1
Naproxen 500/550	784	2.7	2.3	3.3
Naproxen 400/440	334	2.7	2.2	3.5
Piroxicam 20	280	2.7	2.1	3.8

Analgesic	Number of patients in comparison	NNT 50%	Lower confidence interval	Higher confidence interval
Dextropropoxyphene 130	50	2.8	1.8	6.5
Tramadol 112 + Paracetamol 650	201	2.8	2.1	4.4
Bromfenac 10	223	2.9	2.3	4.0
Etodolac 400	222	2.9	2.3	4.0
Lornoxicam 8	578	2.9	2.3	4.0
Morphine 10 (IM)	946	2.9	2.6	3.6
Pethidine 100 (IM)	364	2.9	2.3	3.9
Tramadol 150	561	2.9	2.4	3.6
Dexketoprophen 20/25	523	3.2	2.6	4.1
Diflunisal 250	195	3.3	2.3	5.5
Etodolac 200	670	3.3	2.7	4.2
Flurbiprofen 25	208	3.3	2.5	4.9
Ketoprofen 50	624	3.3	2.7	4.3
Ketorolac 30 (IM)	359	3.4	2.5	4.9
Naproxen 200/220	202	3.4	2.4	5.8
Paracetamol 500	561	3.5	2.2	13.3
Dexketoprofen 10/12.5	452	3.6	2.8	5.0
Paracetamol 975/1,000	3,232	3.6	3.2	4.1
Aspirin 1000	770	3.7	3.0	4.7
Paracetamol 1,500	138	3.7	2.3	9.5
Oxycodone IR 5 + Paracetamol 1,000	78	3.8	2.1	20.0
Codeine 60 + Paracetamol 600/650	1,413	3.9	3.3	4.7
Mefenamic acid 500	256	4.0	2.7	7.1
Celecoxib 200	705	4.2	3.4	5.6
Aspirin 600/650	4,965	4.2	3.8	4.6
Ibuprofen 100	396	4.3	3.2	6.4
Lornoxicam 4	151	4.3	2.7	11.0
Dextropropoxyphene 65 + Paracetamol 650	963	4.4	3.5	5.6
Oxycodone IR 15	228	4.6	2.9	11.0
Paracetamol 600/650	1,886	4.6	3.9	5.5
Ibuprofen 50	316	4.7	3.3	8.0
Etodolac 100	498	4.8	3.5	7.8
Tramadol 100	882	4.8	3.8	6.1
Aspirin 650 + Codeine 60	598	5.3	4.1	7.4
Ketoprofen 50	434	5.3	3.7	9.9
Tramadol 75	563	5.3	3.9	8.2
Oxycodone IR 5 + Paracetamol 325	388	5.4	3.9	8.8
Ketorolac 10 (IM)	142	5.7	3.0	53.0
Paracetamol 300 + Codeine 30	690	6.9	4.8	12.0
Bromfenac 5	138	7.1	3.9	28.0

Analgesic	Number of patients in comparison	NNT 50%	Lower confidence interval	Higher confidence interval
Dextropropoxyphene 65	440	7.7	4.6	22.0
Dihydrocodeine 30	194	8.1	4.1	540
Etodolac 50 (dental only)	360	8.3	4.8	30
Tramadol 50	770	8.3	6.0	13.0
Gabapentin 250	327	11.0	6.4	35.0
Codeine 60	2,411	12.0	8.4	18.0

Source: *Compiled with data from Moore 2003 (***Level I***, unspecified number of RCTs, n unspecified) and Moore 2011 (***Level I** *[Cochrane], ≈350 RCTs, n≈45,000).*

5.1.1 Opioids and tramadol

Oral opioids can be as effective in the treatment of acute pain as opioids given by other more invasive routes, if equianalgesic doses are administered (Macintyre 2015 **NR**). Both IR and CR formulations have been used. In a number of postoperative settings (eg ear, nose and throat, trauma and general surgery) combinations of CR and IR opioids have been used successfully without any parenteral opioids to treat acute pain (Pogatzki-Zahn 2013 **Level IV**). Similarly, in combination with a multimodal regimen, oral IR opioids (oxycodone IR) were sufficient to control pain after spine surgery (Rajpal 2010 **Level IV**).

When opioids are prescribed for the treatment of acute pain, consideration should be given to duration of therapy. In most cases short-term use only of these medicines is warranted. Discharge planning must take into account the duration of use of opioids prescribed for the short-term management of acute pain and the weaning of those medicines and, in a small minority of patients, the potential for prescribed opioids to be abused or misused (see Section 8.11).

5.1.1.1 Immediate-release formulations

The NNTs for various IR opioids are listed in Table 5.1.

Oral doses of morphine and oxycodone have an onset of analgesic effect at around 30 min with a peak at 1–2 h (Hoeben 2012 **EH**).

The effectiveness of the different oral opioids and tramadol may change with the addition of paracetamol and NSAIDs.

- Oral codeine in a single dose of 60 mg is not an effective analgesic agent after a variety of operations (NNT 12) (Derry 2010 **Level I** [Cochrane], 35 RCTs, n=2,475). The effect was even smaller in the subgroup after dental surgery (NNT 21) (15 RCTs, n=1,146). Combined with oral paracetamol a significant dose response was seen with NNTs of 2.2 for 800 to 1,000 mg paracetamol/60 mg codeine, 3.9 for 600 to 650 mg paracetamol/60 mg codeine, and 6.9 for 300 mg paracetamol/30 mg codeine, and the combination extended the duration of analgesia by 1 h compared with paracetamol alone (Toms 2009 **Level I** [Cochrane] 26 RCTs, n=2,295). There are no data on combinations of oral paracetamol with codeine doses <30 mg. An oral combination of 5 mg hydrocodone/500 mg paracetamol did not provide superior analgesia to 30 mg codeine/300 mg paracetamol for extremity pain after ED discharge (Chang 2014 **Level II**, n=240, JS 5). However, 25.6–60 mg codeine barely improves the analgesic efficacy of 400 mg ibuprofen in a number of combinations (Derry 2013b **Level I** [Cochrane], 6 RCTs, n=1,342).
- Oral dextropropoxyphene 65 mg alone is a poorly effective analgesic in postoperative pain (NNT 7.7) (Collins 2000 **Level I** [Cochrane], 6 RCTs [dextropropoxyphene only], n=440); it is more effective when combined with 650 mg paracetamol (NNT 4.4) (5 RCTs [combination], n=963). However, this combination provided inferior postoperative analgesia at 1 h and 4 h to 37.5 mg tramadol/325 mg paracetamol (Lin 2012 **Level II**, n=107 [n=62 completed], JS 3).

- Oral oxycodone IR in a single dose of 5 mg shows no benefit over placebo for the treatment of moderate to severe acute pain (Gaskell 2009 **Level I** [Cochrane], 3 RCTs [oxycodone 5 mg], n=317); doses of 15 mg (NNT 4.6) (2 RCTs [oxycodone 15 mg], n=228), 5 mg oxycodone/325 mg paracetamol (NNT 5.4) (3 RCTs [combination], n=388), 10 mg oxycodone/650 mg paracetamol (NNT 2.7)(10 RCTs [combination], n=1,043) and 10 mg oxycodone/1,000 mg paracetamol (NNT 1.8) (2 RCTs [combination], n=289) are more effective than placebo. Similar benefits are achieved by combining 5 mg oral oxycodone with 400 mg ibuprofen (NNT 2.3) (Derry 2013a **Level I** [Cochrane], 3 RCTs, n=1,303).
- Oral tramadol is an effective analgesic agent for postoperative pain with NNTs of 7.1 for 50 mg, 4.8 for 100 mg and 2.4 for 150 mg (Moore 1997 **Level I**, 18 RCTs, n=3,453). The combination of tramadol 75 mg or 112.5 mg with paracetamol 560 mg or 975 mg is more effective than either of its two components administered alone (McQuay 2003 **Level I**, 7 RCTs, n>1,400).

Morphine (IR, oral) is effective in the treatment of acute pain. Following preloading with IV morphine, morphine liquid 20 mg (initial dose 20 mg; subsequent doses increased by 5 mg if breakthrough doses needed) every 4 h with additional 10 mg doses prn has been shown to provide better pain relief after hip surgery than IM morphine 5–10 mg prn (McCormack 1993 **Level II**, n=47, JS 5).

In comparison with IV PCA morphine alone, administration every 4 h of 20 mg but not 10 mg of oral morphine reduced PCA morphine consumption; however there were no differences in pain relief or adverse effects (Manoir 2006 **Level II**, n=63, JS 5).

IR oral opioids such as oxycodone, morphine and tramadol have also been used as "step-down" analgesia after PCA, with doses based on prior PCA requirements (Macintyre 2015 **NR**) and after epidural analgesia (Lim 2001 **Level II**, n=101, JS 5).

5.1.1.2 Controlled-release formulations

CR formulations (also referred to as slow-release or prolonged-release) may take 3–4 h or more to reach peak effect. In contrast and in most cases, the analgesic effect of the IR opioid preparations will be seen within about 45–60 min. This means that rapid titration to effect is easier and safer with IR formulations.

In general the use of CR opioid preparations as the sole agents for the early management of acute pain is discouraged because of difficulties in short-term dose adjustments needed for titration (Macintyre 2015 **NR**). CR opioid preparations should only be used at set time intervals and IR opioids should be used for acute and breakthrough pain, and for titration of CR opioids.

CR oxycodone is an effective component in the immediate management of acute pain (Sunshine 1996 **Level II**, n=182, JS 5; Kampe 2004 **Level II**, n=40, JS 5). However, IR oxycodone and paracetamol 325 mg given every 6 h led to better pain relief than 10 mg CR oxycodone given every 12 h (Kogan 2007 **Level II**, n=120, JS 5). In comparison with IV morphine PCA alone, CR oxycodone in addition to morphine PCA resulted in improved pain relief and patient satisfaction after lumbar discectomy and a lower incidence of nausea and vomiting, as well as earlier return of bowel function (Blumenthal 2007 **Level II**, n=40, JS 5). CR oral oxycodone was found to be effective as "step-down" analgesia after 12–24 h of PCA morphine (Ginsberg 2003 **Level IV**). However, after total knee and hip replacement, the addition of CR morphine 30 mg twice daily to usual care resulted in only minimally improved analgesia but increased adverse effects (Musclow 2012 **Level II**, n=200, JS 5).

A combined formulation of CR oxycodone and naloxone has been shown to result in less constipation than CR oxycodone in chronic pain (Lowenstein 2010 **Level II** [pooled analysis of 2 RCTs], n=578, JS 5). While it was suggested that these benefits were transferable to acute pain settings (Kuusniemi 2012 **NR**), this could not be confirmed after laparoscopic hysterectomy; here oxycodone/naloxone CR had no beneficial effect on constipation or other opioid adverse effects compared to oxycodone CR (Comelon 2013 **Level II**, n=85, JS 5).

5.1.2 Paracetamol

Single doses of paracetamol are effective in the treatment of postoperative pain. The NNTs for a variety of doses, as well as combinations of paracetamol with other analgesic medicines such as codeine, are listed in Table 5.1.

There is no good evidence for a dose-dependent analgesic effect of oral paracetamol; the effects of 500 mg (NNT 3.5; 95%CI 2.7 to 4.8), 600/650 mg (NNT 4.6; 95%CI 3.9 to 5.5) and 1,000 mg (NNT 3.6; 95%CI 3.2 to 4.1) show no statistically significant difference (Moore 2011 **Level I** [Cochrane], 53 RCTs [paracetamol], n=6,230).

The oral bioavailability of paracetamol is good at between 63 and 89% (Oscier 2009 **NR**). However, early postoperative oral administration can result in plasma concentrations that can vary enormously after the same dose and may remain subtherapeutic in some patients (Holmer Pettersson 2004 **PK**).

In the same doses, orally administered paracetamol is less effective and of slower onset than IV paracetamol but more effective and of faster onset than paracetamol administered by the rectal route; see below.

Paracetamol effervescent tablets are absorbed significantly faster than ordinary paracetamol (Rygnestad 2000 **PK**).

5.1.3 Nonselective NSAIDs and coxibs

A number of nsNSAIDs and coxibs have been shown to be effective as sole therapy in a variety of acute surgical pain settings. The NNTs of each of these medicines is listed in Table 5.1.

In general, there is no good evidence that NSAIDs given parenterally or rectally are more effective, or result in fewer adverse effects, than the same medicine given orally for the treatment of postoperative pain (Tramer 1998 **Level I**, 26 RCTs, n=2,225). Only in the treatment of renal colic do IV NSAIDs result in more rapid analgesia.

Key messages

1. Oral paracetamol combined with codeine is more effective than either medicine alone and shows a dose-response effect (**U**) (**Level I** [Cochrane Review]).
2. Oral paracetamol combined with tramadol is more effective than either medicine alone and shows a dose-response effect (**U**) (**Level I**).
3. NSAIDs given parenterally or rectally are not more effective and do not result in fewer adverse effects than the same medicines given orally (**U**) (**Level I**).
4. Early postoperative oral administration of paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (**U**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Other than in the treatment of severe acute pain, and providing there are no contraindications to its use, the oral route is the route of choice for the administration of most analgesic medicines (**U**).
- ☑ Controlled-release oral opioid preparations should only be given at set time intervals (**U**).
- ☑ Immediate-release oral opioids should be used for breakthrough pain and for titration of controlled-release opioids (**U**).
- ☑ The use of controlled-release opioid preparations as the sole agents for the early management of acute pain is discouraged because of difficulties in short-term dose adjustments needed for titration (**U**).

5.2 Intravenous route

Analgesic medicines given by the IV route have a more rapid onset of action compared with most other routes of administration.

5.2.1 Opioids and tramadol

5.2.1.1 Intermittent intravenous bolus doses

Titration of opioids for severe acute pain is best achieved using intermittent IV bolus doses as it allows more rapid titration of effect and avoids the uncertainty of medicine absorption by other routes. The optimal doses and dose intervals for this technique have not yet been established.

In a postoperative care unit, 2 mg or 3 mg bolus doses of morphine, given at 5-min intervals prn and with no limitation on the number of bolus doses administered, was more effective and resulted in no greater incidence of adverse effects than the same doses given at 10-min intervals or when a maximum of five doses only was allowed (Aubrun 2001 **Level III-3**).

In prehospital care, an initial dose of 0.1 mg/kg IV morphine was more effective than 0.05 mg/kg followed by half the initial dose at 5 min prn (VAS ≤30/100; 40 vs 17% at 10 min) (Bounes 2008 **Level II**, n=106, JS 5). In a comparison of IV fentanyl and morphine bolus doses every 5 min as needed for prehospital analgesia over a period of just 30 min, no difference was found in pain relief or incidence of adverse effects (Galinski 2005 **Level II**, n=54, JS 5).

A single dose of 10 mg IV morphine compared to 1g IV paracetamol in moderate to severe traumatic limb pain had a similar analgesic effect with significantly more adverse effects in the morphine arm; approximately one-third of patients in each group required rescue analgesia of titrated IV morphine (Craig 2012 **Level II**, n=55, JS 4).

Titration of IV bolus doses of an opioid is frequently accomplished using a treatment algorithm to guide management, which includes age-based bolus doses of opioid given at 3 or 5 min intervals prn (Macintyre 2015 **NR**).

Approximately one-third of patients given a 1 mg single bolus dose of hydromorphone (followed by another dose at 15 min if needed) desaturated below 95% (Chang 2009 **Level IV**). As a standardised therapy, a single 2 mg dose of IV hydromorphone in adults (age <65 y) resulted in more patients (11.6%; 95%CI 1.8% to 21.1%) not requiring further pain relief after 30 min compared to a standard care group (any IV opioid in any dose) (Chang 2013 **Level II**, n=350, JS 4). Adverse effects of pruritus and nausea were significantly more common in the hydromorphone group, who received double the morphine equivalent dose; however, all patients received oxygen via nasal prongs to prevent desaturation. Comparing the 2 mg hydromorphone bolus to a "1+1" titration protocol, both showed similar efficacy and safety with an opioid-sparing effect noted in the titration group, where 42.3% required only the first bolus (Chang 2013 **Level II**, n=350, JS 4).

For acute traumatic pain in an ED setting, sufentanil given as an IV bolus of 0.15 mcg/kg followed by 0.075 mcg/kg every 3 min was not more effective than IV morphine 0.15 mg/kg followed by 0.075 mg/kg and less effective at 6 h (Bounes 2010 **Level II**, n=108, JS 5).

Tramadol IV was found to be more effective than the same dose given orally after dental surgery, however it was recognised that the difference in bioavailabilty of a single dose of tramadol may be up to 30% (Ong 2005 **Level II**, n=72, JS 5). Large IV bolus doses of tramadol can result in a high incidence of emetic symptoms. This effect can be reduced by slowing delivery of the medicine or, in the surgical setting, by giving it before the patient emerges from general anaesthesia (Pang 2000 **Level II**, n=60, JS 5).

5.2.1.2 Continuous infusions

A continuous infusion of opioids results in constant blood levels after approximately four to five half-lives of the opioid used. The aim of an infusion is to avoid the problems associated with the peaks and troughs of intermittent administration techniques. However, the variation in patient response, the changing intensity of acute pain with time and the delay between any

alteration of the infusion rate and its subsequent effect, may result in inadequate treatment of incident pain or delayed onset of adverse effects, such as respiratory depression. Very close monitoring is therefore essential with continuous infusions of opioids.

PCA with a continuous background infusion increases the risk of respiratory events in comparison to PCA alone in adults only (OR 10.2; 95%CI 3 to 35) (George 2010 **Level I**, 12 RCTs [adults], n=674). Compared with PCA, continuous IV opioid infusions alone in a general-ward setting resulted in a fivefold increase in the incidence of respiratory depression (Schug 1993 **Level IV**). Furthermore, morphine infusion 0.5 mg/h compared to PCA alone after abdominal hysterectomy resulted in higher opioid requirements, pain intensity and adverse effects including emesis and dizziness (Chen 2011 **Level II**, n=60, JS 4).

5.2.2 Paracetamol

Paracetamol IV is an effective analgesic after surgery with an NNT of 4.0 (95%CI 3.5 to 4.8) over 4 h and an NNT of 5.3 (95%CI 4.2 to 6.7) over 6 h (Tzortzopoulou 2011 **Level I** [Cochrane], 36 RCTs, n=3,896). As an adjunct to opioid analgesia, opioid requirements are reduced by 30% over 4 h after a single IV dose. For orthopaedic surgery specifically, IV paracetamol has similar benefits (Jebaraj 2013 **Level I** [PRISMA], 8 RCTs, n unspecified).

Paracetamol given IV perioperatively reduces PONV (Apfel 2013 **Level I** [PRISMA], 30 RCTs, n=2,364). This effect is correlated to pain relief achieved but not to reduced opioid consumption and was most pronounced when IV paracetamol was given prophylactically before surgery (OR 0.54; 95%CI 0.40 to 0.74).

Due to the good bioavailability and tolerability of oral paracetamol, the use of the IV form should be limited to clinical circumstances where use of the enteral route is not appropriate.

5.2.3 Nonselective NSAIDs and coxibs

There are only a limited number of nsNSAIDs or coxibs available for IV injection at present.

Ketorolac IV/IM is an effective adjunct of multimodal analgesia with more beneficial effect of 60 mg than 30 mg and a greater opioid-sparing effect with IM than IV administration (MD 2.13 mg; 95%CI -4.1 to -0.21 mg) (De Oliveira 2012 **Level I** [PRISMA] 13 RCTs, n=782). Ibuprofen IV in doses of 400 and 800 mg every 6 h postoperatively as an adjunct to IV PCA morphine resulted in improved analgesia, but only the 800 mg dose showed an opioid-sparing effect (Southworth 2009 **Level II**, n=406, JS 3). Similar benefits were found for 800 mg IV ibuprofen every 6 h specifically after orthopaedic surgery (Singla 2010a **Level II**, n=185, JS 3) and after abdominal hysterectomy (Kroll 2011 **Level II**, n=319, JS 3).

In single doses as the sole analgesic agent, the COX-2 selective medicine parecoxib IV/IM has been shown to be effective (Lloyd 2009 **Level I** [Cochrane] 7 RCTs, n=1,446); NNTs compared with placebo are for 10 mg 3.1 (95%CI 2.4 to 4.5), 20 mg 2.4 (95%CI 2.1 to 2.8) and 40 mg 1.8 (95%CI 1.5 to 2.3).

In most cases the route of administration does not seem to alter efficacy. IV NSAIDs or COX-2 selective inhibitors are more expensive than oral or rectal NSAIDs, although their efficacy and likelihood of adverse effects is similar (Tramer 1998 **Level I**, 26 RCTs, n=2,225). A comparison of rectal diclofenac and IV parecoxib showed no difference in pain relief, adverse effects or rescue analgesic requirements (Ng 2008 **Level II**, n=55, JS 5). Efficacy and times to onset of analgesia are similar with IV and IM parecoxib (Daniels 2001 **Level II**, n=304, JS 5).

For renal colic, the onset of action of NSAIDs is faster when given IV compared with IM, oral or rectal administration (Tramer 1998 **Level I**, 26 RCTs, n=2,225).

Key messages

1. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
2. Continuous intravenous infusion of opioids in the general-ward setting is associated with an increased risk of respiratory depression compared with other methods of parenteral opioid administration (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Titration of opioids for severe acute pain is best achieved using intermittent intravenous bolus doses as it allows more rapid titration of effect and avoids the uncertainty of medicine absorption by other routes (**U**).

5.3 Intramuscular and subcutaneous routes

IM and SC injections of analgesic agents (usually opioids) are still commonly employed for the treatment of moderate or severe pain. Absorption may be impaired in conditions of poor perfusion (eg in hypovolaemia, shock, hypothermia or immobility), leading to inadequate early analgesia and late absorption of the medicine depot when perfusion is restored.

5.3.1 Opioids and tramadol

IM injection of opioids has been the traditional mainstay of postoperative pain management despite the fact that surveys have repeatedly shown that pain relief with prn IM opioids is frequently inadequate. Although IM opioids are often perceived to be safer than opioids given by other parenteral routes, the incidence of respiratory depression reported in a review ranged from 0.8% (0.2–2.5) to 37.0% (22.6–45.9) using respiratory rate and oxygen saturation, respectively, as indicators (for comparisons with PCA and epidural analgesia, see Chapter 6; for comments on respiratory rate as an unreliable indicator of respiratory depression, see Section 4.1.1.4) (Cashman 2004 **Level IV**).

Single doses of IM morphine 10 mg (McQuay 1999 **Level I**, 15 RCTs, n=1,046) and IM pethidine (meperidine) 100 mg (Smith 2000 **Level I**, 8 RCTs, n=364) have been shown to be effective in the initial treatment of moderate to severe postoperative pain.

The use of an algorithm allowing administration of IM morphine or pethidine hourly prn and requiring frequent assessments of pain and sedation, led to significant improvements in pain relief compared with longer dose interval prn regimens (Gould 1992, **Level III-3**).

The quality of pain relief is lower with intermittent IM regimens compared with IV PCA (Hudcova 2006 **Level I** [Cochrane], 55 RCTs, n=3,681).

The placement of SC plastic cannulae or "butterfly" needles allows the use of intermittent injections without repeated skin punctures. In healthy volunteers, median time to reach maximum serum concentration (T_{max}) after SC injection of morphine was 15 min (Stuart-Harris 2000). In elderly adults, mean T_{max} after a single SC injection of morphine was 15.9 min and the rate of absorption and the variability in the rate of absorption were similar to those reported after IM injection (Semple 1997 **Level IV**). In patients given a second and same dose of SC morphine 5 h after the first, it was shown that there can also be significant within-patient variations in absorption (Upton 2006). The absorption rate of SC fentanyl was found to be similar to that of SC morphine with a significantly longer terminal half-life for fentanyl (10 h vs 2.1 h) (Capper 2010 **Level IV**).

In children, there was no difference in rate of onset, analgesic effect and adverse effects when morphine SC was compared with morphine IM and there was a significantly higher patient preference for the SC route (Cooper 1996 **Level II**, n=55, JS 4; Lamacraft 1997 **Level IV**). Also, IM and IV administration of morphine (along with IN fentanyl) were found to be equally effective with no significant differences in FLACC scores for postoperative pain in children (Hippard 2012 **Level II**, n=171, JS 5). A comparison of IM and SC morphine in patients after Caesarean delivery

reported no significant differences in adverse effects, patient satisfaction or pain relief at rest, but lower pain scores after SC administration at 12, 16 and 20 h after surgery (Safavi 2007 **Level II**, n=60, JS 3).

A comparison of the same dose of morphine given as either a single SC or IV injection, showed that use of the IV route resulted in more rapid onset of analgesia (5 min IV vs 20 min SC) and better pain relief between 5 and 25 min after injection but also led to higher sedation scores up to 30 min after injection and higher $PaCO_2$ (Tveita 2008 **Level II**, n=40, JS 5). However, a comparison of intermittent IV and SC doses of hydromorphone (the doses adjusted in a similar manner according to the patients' pain scores and given at intervals of no less than 3 h) showed no differences in pain relief or adverse effects over a 48-h period after surgery; pain relief was the same but the incidence of pruritus lower compared with PCA hydromorphone (Bell 2007 **Level II**, n=130, JS 3).

Treatment algorithms for intermittent SC morphine and hydromorphone using age-based dosing are available (Macintyre 2015 **NR**).

Continuous infusions of opioids via the SC route are as effective as continuous IV infusions (Semple 1996 **Level II**, n=30, JS 2).

5.3.2 Nonselective NSAIDs and coxibs

There are only a limited number of NSAIDs or COX-2 selective inhibitors available for IM injection at present and fewer still where Level I evidence for individual efficacy is available. Ketorolac and parecoxib IM are effective analgesic agents (Lloyd 2009 **Level I** [Cochrane] 7 RCTs, n=1,446; De Oliveira 2012 **Level I** [PRISMA] 13 RCTs, n=782).

Key message

1. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance (**U**) (**Level II**).

5.4 Transdermal route

Not all medications applied topically have a local, peripheral action. The term "transdermal" will be used to describe medicines that, while applied to the skin, have predominantly central effects that are the result of systemic absorption of the medicine. The term "topical" will be used in the discussion of medicines – primarily NSAIDs – that are applied topically (including to skin) but have a predominantly peripheral effect (see Sections 5.4.2 and 5.5).

5.4.1 Opioids

The stratum corneum of the epidermis forms a major barrier to the entry of medicines. However, medicines such fentanyl (Sathyan 2005 **PK**) and buprenorphine (Skaer 2006 **NR**) are available as TD preparations. The analgesic effects are a result of systemic effects rather than local peripheral opioid analgesia (Worrich 2007 **Level IV**).

TD fentanyl is commonly used in the management of cancer and chronic pain. Due to the formation of a significant intradermal "reservoir", onset and offset times of this preparation are slow and this makes short-term titration impossible. The time to first analgesic effect is generally between 12 and 24 h after initial patch application and after the patch is removed, serum fentanyl concentrations decline with a mean terminal half-life of 17 h (Lotsch 2013 **NR**).

TD fentanyl patches are currently specifically contraindicated for the management of acute or postoperative pain in many countries (FDA 2007b; emc 2014; MIMS 2014).

Nevertheless, TD fentanyl patches have been trialled in the management of postoperative pain. For example, after hip arthroplasty (Minville 2008 **Level II**, n=30, JS 2) and hysterectomy (Sandler 1994 **Level II**, n=120, JS 4), preoperative use significantly reduced postoperative pain scores and PCA morphine requirements. However, the wide variability of clinical effect (Peng 1999 **NR**) and the high incidence of respiratory depression that can occur in the postoperative setting (Sandler 1994 **Level II**, n=120 [9 patients withdrawn due to severe respiratory compromise], JS 4;

Bulow 1995 **Level II**, n=24 [then terminated for safety concerns], JS 4) make TD fentanyl preparations unsuitable for acute pain management.

Iontophoretic patient-controlled TD delivery systems for fentanyl that can safely be used for the management of acute pain are also available (see Section 6.5.4).

TD buprenorphine patches are available for the management of chronic and cancer pain (Plosker 2011 **NR**). After application of the patch, steady state is achieved by d 3; after removal of the patch, buprenorphine concentrations decrease with a terminal half-life of 12 h (range 10–24 h) (MIMS 2014). Given the slow onset and offset of the medicine, it is unlikely to be of much use in the management of acute pain. However, it showed a dose-dependent analgesic effect with no serious adverse effects in gynaecological postoperative patients (Setti 2012 **Level II**, n=47, JS 4).

5.4.2 Other medicines

TD nicotine patches were applied in six of nine RCTs included in a meta-analysis of nicotine for postoperative pain (Mishriky 2014 **Level I** [PRISMA], 9 RCTs, n=662); the results of a subgroup analysis showed no difference between TD patch and nasal spray. There is an insignificant reduction of opioid consumption (except in nonsmokers) and pain with a significant increase in postoperative nausea.

TD administration of ketamine as a patch delivering 25 mg over 24 h reduced rescue analgesic consumption after gynaecological surgery (Azevedo 2000 **Level II**, n=52, JS 4).

Key messages

1. Transdermal fentanyl (except for Iontophoretic patient-controlled transdermal devices) should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration (**Q**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Transdermal fentanyl preparations should not be used in the management of acute pain in opioid-naïve patients because of safety concerns and, in most countries, the lack of regulatory approval for use in other than opioid-tolerant patients (**S**).

5.5 Transmucosal routes

Medicines administered by transmucosal routes (rectal, IN, SL, buccal and pulmonary) are rapidly absorbed directly into the systemic circulation, thus bypassing hepatic first-pass metabolism. The medicines most commonly administered by transmucosal routes in acute pain management are the more lipid-soluble opioids.

5.5.1 Rectal route

Rectal administration of medicines is useful when other routes are unavailable. It results in uptake into the submucosal venous plexus of the rectum, which drains into the inferior, middle and superior rectal veins. Medicine absorbed from the lower half of the rectum will pass into the inferior and middle rectal veins and then the inferior vena cava, bypassing the portal system. Any portion of the medicine absorbed into the superior rectal vein enters the portal system, subjecting it to hepatic first-pass metabolism.

Potential problems with the administration of medicine by the rectal route relate to the variability of absorption, possible rectal irritation and cultural factors. Some suppositories should not be divided as the medicine may not be evenly distributed in the preparation. Contraindications to the use of this route include pre-existing rectal lesions, recent colorectal surgery, severe thrombocytopaenia and immune suppression. Whether the medicine is administered to a patient who is awake or under anaesthesia, it is important to obtain prior consent from the patient or guardian.

5.5.1.1 Opioids

In most instances similar doses of rectal and oral opioids are administered, although there may be differences in bioavailability and the time to peak analgesic effect for the reasons outlined above; rectal opioids play primarily a role in cancer-pain management (Kestenbaum 2014 **NR**). Here, no differences in either pain relief or adverse effects were found in a comparison of oral and rectally administered tramadol (Mercadante 2005 **Level II**, n=60, JS 5).

5.5.1.2 Paracetamol

Paracetamol is effective when given by the rectal route (Romsing 2002 **Level I**, 8 RCTs, n=640), although absorption is slower and less predictable than after oral administration, with a bioavailability of between 24 and 98% (Oscier 2009 **NR**). In children, it is also less effective than the same dose administered by the oral route (Anderson 1996 **Level II**, n=100, JS 4; Anderson 1999 **Level IV**). However, in children aged 3–36 mth, there were no differences in T_{max}, C_{max} and total medicine exposure between rectal and oral administration, possibly due to slower gastric emptying in this age group (Walson 2013 **Level II**, n=30, JS 2).

Doses of 1 g rectally after cardiac surgery (Holmer Pettersson 2006 **Level II**, n=48, JS 2) and hysterectomy (Kvalsvik 2003 **Level II**, n=60, JS 4) as well as 2 g given rectally to patients undergoing laparoscopic gynaecological surgery (Hahn 2000 **Level IV**) resulted in subtherapeutic blood levels, although levels may increase to within the therapeutic range after repeat administration (Holmer Pettersson 2006 **Level II**, n=48, JS 2). When available, the oral route is therefore preferable.

Higher doses may be more effective. Blood concentrations in the therapeutic range have been reported in adults after doses of 40 mg/kg but not 20 mg/kg (Beck 2000 **Level IV**) and sustained therapeutic levels followed the use of 35 mg/kg and 45 mg/kg, but not 15 mg/kg and 25 mg/kg (Stocker 2001 **Level IV**).

In children, initial doses of 40 mg/kg followed by 20 mg/kg also provided therapeutic blood levels without evidence of accumulation (Birmingham 2001 **Level IV**). In children after ophthalmic surgery, 20 and 40 mg/kg rectally were equally effective and superior to placebo (Gandhi 2012 **Level II**, n=135, JS 4). Rectal administration of paracetamol 30 mg/kg provided equivalent analgesia postoperatively compared to peritonsillar infiltration of bupivacaine (Dahi-Taleghani 2011 **Level III-1**).

5.5.1.3 NSAIDs

Rectal administration of nsNSAIDs provides effective analgesia after a variety of surgical procedures (Tramer 1998 **Level I**, 26 RCTs, n=2,225). Local effects such as rectal irritation and diarrhoea have been reported following use of the rectal route but other commonly reported adverse effects such as nausea, vomiting, dizziness and indigestion are independent of the route of administration (Tramer 1998 **Level I**, 26 RCTs, n=2,225). Consequently, there appears to be no advantage in using NSAID suppositories if the oral route is available.

5.5.2 Intranasal route

A variety of different medicines can be administered by the IN route, including analgesic medicines. The human nasal mucosa contains medicine-metabolising enzymes but the extent and clinical significance of human nasal first-pass metabolism is unknown (Dale 2002 **NR**). It is suggested that the volume of a dose of any medicine given IN should not exceed 150 mcL in order to avoid run-off into the pharynx (Dale 2002 **NR**). Absorption through the nasal mucosa depends on both the lipid solubility and degree of ionisation of the medicine (Shelley 2008 **NR**).

5.5.2.1 Opioids

Single-dose pharmacokinetic data in healthy volunteers for a number of opioids administered by the IN route have been published (Dale 2002 **NR**; Grassin-Delyle 2012 **NR**). The mean bioavailabilities and T_{max} reported were fentanyl 71% and 5 min; sufentanil 78% and 10 min; alfentanil 65% and 9 min; butorphanol 71% and 49 min; oxycodone 46% and 25 min; and buprenorphine 48% and 30 min. An analysis of multiple trials for IN fentanyl showed a

bioavailability of 89% with an onset of analgesia at 2–5 min (Lotsch 2013 **NR**). Hydromorphone, when given to volunteers in doses of 1 mg or 2 mg IN and compared with 2 mg IV, had median T_{max} after the 1 mg and 2 mg IN doses of 20 min and 25 min respectively and an overall bioavailability of only 55% (Coda 2003 **PK**).

Clinical data exist for the effectiveness of several opioids administered via the IN route. IN fentanyl must be provided in a sufficient concentration to deliver an analgesic dose in a volume that does not exceed the nasal capacity. It is an effective treatment for breakthrough pain in cancer patients (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699) and has similar analgesic efficacy to IV administration (Hansen 2012 **Level I** [PRISMA], 3 RCTs, n=301). IN fentanyl spray compared to oral transmucosal fentanyl, fentanyl buccal tablet and oral morphine for the treatment of breakthrough cancer pain provides the greatest and fastest improvement (Vissers 2010 **Level I**, 6 RCTs, n=594). It provides also similar or better analgesia than other opioids or routes of administration in children without compromising safety (Mudd 2011 **Level IV SR**, 12 studies, n=1,743) (see Section 9.4.4). When IN fentanyl was used in the prehospital setting, there was no difference in effectiveness compared to IV morphine (Rickard 2007 **Level II**, n=258, JS 3) (see Section 8.10.2).

Analgesic efficacy has also been shown for IN butorphanol (Abboud 1991 **Level II**, n=186, JS 5; Wermeling 2005 **Level II**, n=60, JS 4), pethidine (Striebel 1993 **Level II**, n=60, JS 5; Striebel 1995 **Level II**, n=44, JS 2), morphine (Stoker 2008 **Level II**, n=187, JS 5), hydromorphone (Wermeling 2010 **Level IV**) and sufentanil ((Mathieu 2006 **Level II**, n=40, JS 4; Stephen 2012 **Level IV**; Steenblik 2012 **Level IV**).

Butorphanol (Abboud 1991 **Level II**, n=186, JS 5) and morphine (Christensen 2008 **Level II**, n=225, JS 5) had similar efficacy when given by IN or IV routes. IN pethidine was more effective than SC injections of pethidine (Striebel 1995 **Level II**, n=44, JS 2).

Patient-controlled IN analgesia (PCINA) using diamorphine (bolus doses of 0.5 mg) was less effective than PCA IV morphine (1 mg bolus doses) after joint replacement surgery (Ward 2002 **Level II**, n=52, JS 2) but provided better pain relief in doses of 0.1 mg/kg than 0.2 mg/kg IM morphine in children with fractures (Kendall 2001 **Level II**, n=404, JS 3).

Adverse effects can be related to the medicine itself or to the route of administration. Systemic effects appear to be no higher for IN administration than for other routes with equivalent efficacy; nasal irritation, congestion and bad taste have been reported (Dale 2002 **NR**; Grassin-Delyle 2012 **NR**).

Technical problems with pumps have been reported in up to 10% of cases and dispensing issues for techniques such as PCINA, which could allow ready and unauthorised access to the medicines, have not been addressed (Dale 2002 **NR**).

5.5.2.2 NSAIDs

IN ketorolac has also been shown to be effective; after major surgery 31.5 mg (Singla 2010b **Level II**, n=321, JS 5) but not 10 mg IN ketorolac resulted in significant opioid-sparing and better pain relief (Moodie 2008 **Level II**, n=127, JS 5). This was also found after oral surgery (Grant 2010 **Level II**, n=80, JS 5).

5.5.2.3 Ketamine

IN ketamine has been shown to provide relatively rapid onset of effective pain relief (within 15 min); any adverse effects were mild and transient (Christensen 2007 **Level II**, n=40, JS 4). It has been used successfully as an analgesic in EDs (Andolfatto 2013 **Level IV**; Yeaman 2013 **Level IV**) and in the prehospital setting (Johansson 2013 **Level IV**). IN ketamine is also used for pain relief and sedation as well as a premedicant in paediatric patients (see Section 9.4.5).

5.5.3 Sublingual and buccal routes

When analgesic medicines are administered by the SL or buccal routes, their efficacy will in part depend on the proportion of medicine swallowed.

5.5.3.1 Opioids

A number of different SL fentanyl preparations are currently on the market world-wide; these include oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablets (FBT), SL fentanyl citrate orally disintegrating tablet (ODT) and fentanyl buccal soluble film (FBSF) (Grape 2010 **NR**). In addition, buccal or SL sprays and a wafer are under development (Paech 2012 **NR**).

The only registered indication of these preparations in all countries is the treatment of break-through pain in opioid-tolerant cancer patients. SL and buccal fentanyl are effective treatments for breakthrough pain in cancer patients (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699). In this indication OTFC, FBT and ODT are providing more efficacious analgesia than oral morphine (Jandhyala 2013 **Level I**, 5 RCTs, n=415). However, as outlined above, IN fentanyl was superior to OTFC and FBT here (Vissers 2010 **Level I**, 6 RCTs, n=594).

In many countries, regulatory authorities have specifically noted that SL preparations must not be used in opioid-naïve patients or in the management of acute and postoperative pain: OTFC has been the suspected primary cause of death in 226 USA fatalities between 2004 and 2011 (Paech 2012 **NR**). Warnings regarding this have been issued for OTFC (FDA 2011; MIMS 2014; emc 2014) as well as FBSF (FDA 2009) and FBT (FDA 2007a).

Oral transmucosal fentanyl citrate

OTFC incorporates fentanyl into a flavoured solid lozenge on a stick and is available in a range of doses from 200–1,600 mcg. Overall, the bioavailability of OTFC is about 50% compared with IV fentanyl, with C_{max} achieved in 23 min (Lotsch 2013 **NR**); the time to onset of analgesia is about 4.2 min. The relative potency compared with IV morphine is 1:8–14 (200 mcg OTFC≈2 mg IV morphine) (Lichtor 1999 **Level II**, n=133, JS 5).

Only a few studies have investigated the postoperative use of OTFC. It was found to be an effective analgesic after orthopaedic surgery (Ashburn 1993 **Level II**, n=38, JS 5), abdominal surgery (Lichtor 1999 **Level II**, n=133, JS 5), retinal photocoagulation (Hillier 2009 **Level II**, n=35, JS 5) and during burns wound care in paediatric patients (Sharar 1998 **Level II**, n=14, JS 3; Sharar 2002 **Level II**, n=22, JS 3). Pain relief at 15 min in children with lower extremity injuries was the same with IV bolus doses of morphine and OTFC, but lower with OTFC after that until the end of the 75-min study period (Mahar 2007 **Level II**, n=87, JS 3). However, because of the risk of achieving high peak plasma levels with unsupervised administration, the limited data available, and the specific lack of approval for use in opioid-naïve patients, OTFC cannot be recommended for the management of acute pain.

Fentanyl buccal tablets

FBTs use an effervescent medicine delivery technology that enables more rapid absorption and delivery of a larger proportion of the fentanyl dose compared with OTFC (Grape 2010 **NR**); bioavailability is 65% with time to onset of effect 10 min (Lotsch 2013 **NR**). FBTs are effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1699; Jandhyala 2013 **Level I**, 5 RCTs, n=415; Vissers 2010 **Level I**, 6 RCTs, n=594). Although only indicated for this usage, FBTs have been studied in the ED. Here, a 100 mcg FBT had faster onset of analgesia (10 vs 35 min) than an oxycodone 5 mg/paracetamol 325 mg combination tablet, with no other advantages (Shear 2010 **Level II**, n=60, JS 4).

Sublingual fentanyl citrate orally disintegrating tablets

SL fentanyl citrate ODTs consist of a mixture of carrier particles coated with fentanyl and a mucoadhesive agent and are left under the tongue to dissolve, leading to rapid fentanyl absorption (Paech 2012 **NR**). This leads to a bioavailability of around 70% and a time to onset of effect of 15 min (Lotsch 2013 **NR**). They were effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699) and one subsequent RCT (Shimoyama 2015 **Level II**, n=37, JS 3). They have also been used with effect in breakthrough noncancer pain (Guitart 2013 **Level IV**).

Fentanyl buccal soluble film

FBSF consists of a small soluble disc-shaped film containing fentanyl in doses of 200–1,200 mcg, proportional to the film surface area (Grape 2010 **NR**); bioavailability is 71% and time to onset of effect 15 min (Lotsch 2013 **NR**). FBSF was effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699).

Other transmucosal fentanyl preparations

Fentanyl buccal spray has a bioavailability of 76% and a time to onset of effect of 5 min (Lotsch 2013 **NR**). It was effective in opioid-tolerant cancer patients for breakthrough pain (Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699).

Fentanyl SL wafers showed a bioavailability of 79% (Lim 2012 **PK**).

Sublingual buprenorphine

SL buprenorphine, given as a tablet, has an overall bioavailability of 30–50% and a long duration of action (mean half-life 28 h) (Mendelson 1997 **NR**; Kuhlman 1996 **NR**). SL buprenorphine 0.4 mg was found to be as effective as 10 mg morphine IM after abdominal surgery (Cuschieri 1984 **Level II**, n=89, JS 2) and 75 mg pethidine IM after gynaecological surgery (Moa 1990 **Level II**, n=96, JS 4). For adults with acute fractures in the ED, buprenorphine 0.4mg SL is as effective and safe as morphine 5 mg IV (Jalili 2012 **Level II**, n=49, JS 4).

5.5.3.2 Ketamine

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, SL 30% and IN 45%: the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara 2003 **PK**). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both SL and oral routes; peak plasma levels were seen at 30 min and 120 min respectively and terminal half-lives were similar at around 5 h (Chong 2009 **PK**). For both routes, norketamine concentrations exceeded the concentrations of ketamine and, given its pharmacological activity profile, norketamine is therefore likely to be a major contributor to the overall analgesic effect. A wafer preparation of ketamine showed an oral bioavailability of 29% (Rolan 2014 **PK**).

5.5.4 Pulmonary

5.5.4.1 Opioids

Opioids are rapidly absorbed after nebulised inhalation, reflecting the high blood flow, surface area and permeability of the lungs.

Clinical data exist for the effectiveness of several opioids administered via the pulmonary route including morphine (Dershwitz 2000 **Level IV**; Thipphawong 2003 **Level II**, n=89, JS 5) and fentanyl (Worsley 1990 **Level II**, n=30, JS 3; Miner 2007 **Level II**, n=41, JS 3).

For post-traumatic thoracic pain, there was no difference in the pain relief obtained from nebulised morphine and PCA morphine (Fulda 2005 **Level II**, n=44, JS 4). However, a single dose of 0.2 mg/kg of nebulised morphine was not effective in managing acute pain in the ED setting (Bounes 2009 **Level IV**). C_{max} following administration of morphine via a standard nebuliser occurred within 10 min but bioavailability was low with a mean of only 5% (Masood 1996 **PK**). Bioavailability may be improved (up to 59–100%) with C_{max} occurring at 2 min using specific pulmonary-medicine delivery systems (Ward 1997 **PK**; Dershwitz 2000 **PK**).

Similarly, bioavailability of inhaled fentanyl may approach 100% (Mather 1998 **PK**). The pharmacokinetic profiles of inhaled and IV fentanyl showed similar peak arterial concentrations and areas under the curve (Macleod 2012 **Level II**, n=10, JS 5). The time to maximum concentration was slightly shorter for the inhaled than IV fentanyl (20.5 vs 31.5 s). In children requiring pain relief in an ED, nebulised fentanyl was as effective as IV fentanyl (Miner 2007 **Level II**, n=41, JS 3) (see Section 9.7.4.2).

These systems await further development and thus these data are insufficient to support the routine use of inhaled opioids in acute pain management

5.5.4.2 Other analgesic medicines

See Section 4.5 for inhaled N_2O and methoxyflurane.

Key messages

1. Intranasal, sublingual and buccal fentanyl preparations are effective treatments for breakthrough pain in cancer patients (**S**) (**Level I** [Cochrane Review]) with similar efficacy to IV administration (**N**) (**Level I** [PRISMA]) and superior to oral morphine (**N**) (**Level I**)
2. Intranasal fentanyl provides faster and better analgesia for breakthrough pain in cancer patients than oral transmucosal fentanyl and fentanyl buccal tablets (**N**) (**Level I**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Neither buccal nor transdermal fentanyl preparations should be used in the management of acute pain in opioid-naïve patients because of safety concerns and, in most countries, the lack of regulatory approval for use in other than opioid-tolerant patients (**S**).

5.6 Epidural analgesia

Epidural analgesia (ie the provision of pain relief by continuous administration of pharmacological agents into the epidural space via an indwelling catheter) has become a widely used technique for the management of acute pain in adults and children, particularly after surgery (Freise 2011 **NR**) and in women in labour (see Section 10.1.2).

5.6.1 Efficacy

The difficulty with interpretation of available data is that epidural analgesia is not a single entity but can be provided by a number of pharmacological agents administered into different levels of the epidural space for a wide variety of operations.

5.6.1.1 Efficacy and outcomes in general

The universal efficacy of epidural analgesia has been well demonstrated. Regardless of analgesic agent used, location of catheter, type of surgery and type or time of pain assessment, epidural analgesia provides better pain relief than parenteral opioid administration (the following meta-analyses have overlap of multiple RCTs) (Werawatganon 2005 **Level I** [Cochrane], 9 RCTs, n=711; Wu 2005 **Level I**, 50 RCTs, n=3,208; Guay 2006 **Level I**, 70 RCTs, n unspecified; Marret 2007 **Level I**, 16 RCTs, n=806; Nishimori 2012 **Level I** [Cochrane], 15 RCTs, n=1,297).

One meta-analysis of epidural analgesia vs systemic opioids via PCA concludes that epidural analgesia provides better pain relief at rest and with movement after all types of surgery; with the exception of epidural analgesia using hydrophilic opioids only (Wu 2005 **Level I**, 50 RCTs, n=3,208). The epidural group has a lower incidence of nausea/vomiting and sedation but a higher incidence of pruritus, urinary retention and motor block than IV PCA. A meta-analysis of epidural analgesia provided with local anaesthetics for at least 24 h compared to systemic analgesia after surgery (performed under general anaesthesia) shows reduced mortality with epidural analgesia (3.1 vs 4.9%) (OR 0.60; 95%CI 0.39 to 0.93) (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044), as did a large (n=144,744) matched-cohort retrospective audit of administrative data (30-d mortality 1.7 vs 2.0%; RR 0.89; 95%CI 0.81 to 0.98) (Wijeysundera 2008 **Level III-2**). The meta-analysis also reports benefits of epidural analgesia on perioperative morbidity with decreased risk of atrial fibrillation, supraventricular tachycardia, deep vein thrombosis, respiratory depression, atelectasis, pneumonia, ileus, and PONV and improved recovery of bowel function. A preceding meta-analysis reported similar results (Guay 2006 **Level I**, 70 RCTs, n unspecified). However, adverse effects of epidural analgesia include hypotension, pruritus, urinary retention and motor block (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044).

With regard to pulmonary outcomes specifically, improved pain relief with epidural local anaesthetics led to increased partial pressure of oxygen in arterial blood (PaO_2) (difference 4.56 mmHg; 95%CI 0.058 to 9.075) and a decreased incidence of pulmonary infections (RR 0.36; 95%CI 0.21 to 0.65) and pulmonary complications overall (RR 0.58; 95%CI 0.42 to 0.80) when compared with systemic opioids (Ballantyne 1998 **Level I**, 48 RCTs, n unspecified). Similar results were confirmed in a subsequent meta-analysis with a reduced rate of pneumonia (OR 0.54; 95%CI 0.43 to 0.68) (Popping 2008 **Level I**, 58 RCTs, n=5,904); however, notably a decrease of relative benefit has occurred over time where from 1971–2006 the baseline risk of pneumonia in the opioid group has decreased from 34–12% but remained 8% in the epidural group.

5.6.1.2 Cancer surgery outcomes

Current data do not support a benefit for cancer recurrence or survival through addition of epidural anaesthesia/analgesia to general anaesthesia/systemic analgesia following cancer surgery; neither overall survival (HR 1.03; 95%CI 0.86 to 1.24) nor progression-free survival (HR 0.88; 95%CI 0.56 to 1.38) are improved (Cakmakkaya 2014 **Level I** [Cochrane], 4 RCTs, n=746). Evidence was graded low to very low and all four studies are secondary data analyses of previously conducted RCTs. In a much larger systematic review including not only RCTs, overall survival was improved by epidural anaesthesia (HR 0.84; 95%CI 0.74 to 0.96), in particular after surgery for colorectal cancer (HR 0.65; 95%CI 0.43 to 0.99) (Chen 2013 **Level III-3 SR**, 14 studies, n≈47,000). However, epidural anaesthesia did not improve recurrence-free survival (HR 0.88; 95%CI 0.64 to 1.22).

5.6.1.3 Procedure-specific efficacy

Open abdominal surgery

After colorectal surgery, thoracic epidural analgesia (TEA) in comparison to systemic opioid analgesia reduces pain scores and duration of ileus, with no effect on hospital stay but increased rates of pruritus, urinary retention and hypotension (Marret 2007 **Level I**, 16 RCTs, n=806). These findings are confirmed in a subsequent meta-analysis that shows after gastrointestinal surgery reduced time to first passage of flatus (-31.3 h; 95%CI -33.2 to -29.4) and stool (-24.1 h; 95%CI -27.2 to -20.9) but an increased rate of postoperative hypotension (RR 7.9; 95%CI 2.4 to 26.5) (Shi 2014 **Level I**, 12 RCTs, n=650).

After open abdominal surgery in the setting of enhanced-recovery programs, TEA compared to other analgesic approaches results in no more complications (OR 1.14; 95%CI 0.49 to 2.64) but better analgesia and earlier recovery of bowel function without reducing length of hospital stay (Hughes 2014 **Level I** [PRISMA], 7 RCTs, n=378). A large retrospective cohort study (n=12,817) after elective colectomy reported that postoperative epidural analgesia significantly reduced 7-d (OR 0.35; 95%CI 0.21 to 0.59) and 30-d (OR 0.54; 95%CI 0.42 to 0.70) mortality (Wu 2006a **Level III-2**). In another cohort study of patients with COPD undergoing major abdominal surgery (n=541), TEA added to general anaesthesia compared with general anaesthesia alone did not reduce the incidence of postoperative pneumonia significantly (11 vs 16%; p=0.08), but was associated with decreased 30-d mortality (5 vs 9%; p=0.03) and with improved outcome for postoperative pneumonia (OR 0.5; 95%CI 0.3 to 0.9) (van Lier 2011 **Level III-2**). The beneficial effect of TEA increased with increasing COPD severity.

After major upper abdominal surgery, TEA in combination with NSAIDs and IV nutritional support prevented protein loss compared with epidural analgesia alone or PCA with and without nutritional support (Barratt 2002 **Level II**, n=57, JS 3). Similarly after colonic surgery, epidural analgesia increased the anabolic effect of amino acid infusions in diabetic patients (Lugli 2008 **Level II**, n=12, JS 3) and reduced whole body protein breakdown (Lattermann 2007 **Level II**, n=20, JS 2). Epidural anaesthesia/analgesia reduced insulin-resistance in comparison to general anaesthesia/systemic analgesia only in patients who were insulin-resistant preoperatively (Donatelli 2007 **Level II**, n=60, JS 2).

After abdominal cancer surgery, continuous TEA compared with continuous IT thoracic analgesia resulted in similar efficacy and adverse effects (Mercadante 2008 **Level II**, n=60, JS 3). After open gastrectomy, TEA (PCEA) was superior to IT morphine combined with IV

PCA opioids for all relevant outcomes including analgesia, mobilisation, bowel recovery and pulmonary complications (Lee 2014 **Level II**, n=64, JS 3) and was superior to IV PCA morphine with regard to pain control, gastrointestinal recovery and duration of hospital stay (Zhu 2013 **Level II**, n=67, JS 2). Compared to continuous wound infiltration with local anaesthetics in fast-track open colectomy, epidural analgesia reduced pain scores on mobilisation until hospital discharge, reduced time to return of bowel function and tolerance of a complete diet, improved sleep quality and reduced length of hospital stay (4 vs 5.5 d; p=0.006) (Jouve 2013 **Level II**, n=50, JS 5). These benefits were not demonstrated in another, similar RCT (Bertoglio 2012 **Level II**, n=106, JS 3).

Laparoscopic colectomy

After laparoscopic colectomy, TEA is rarely used in the USA (2.14% of 191,576 operations) (Halabi 2014 **Level III-2**). The literature is conflicting in the report of benefit of TEA in this setting. Only initial pain scores and PONV are reduced by TEA vs IV PCA without any further improved outcomes (Liu 2014 **Level I** [PRISMA], 7 RCTs, n=370), while another meta-analysis (5 RCTs overlap) reports reduction of pain scores and time to first bowel motion (Khan 2013 **Level I** [PRISMA], 6 RCTs, n=340). However, in a large case-matched analysis, TEA resulted in longer hospital stay by 0.60 d (p=0.003), higher hospital charges by USA$ 3,732.71 (p=0.02) and higher rate of urinary tract infection (OR 1.81; p=0.05) without any positive clinical benefits (Halabi 2014 **Level III-2**). Similarly, outcomes were inferior with epidural than with IT analgesia or IV PCA techniques (Levy 2011 **Level II**, n=99, JS 3). TEA also did not improve long-term survival in this setting (n=424), but increased duration of hospital stay (median length 5 vs 3 d with PCA [p<0.0005]) (Day 2012 **Level III-2**).

Hepatic surgery

For hepatic surgery, there is ongoing debate on the value of epidural analgesia. A large USA survey showed the technique is infrequently used (5.9% of 68,028 operations) (Rosero 2014 **Level IV**). Applying propensity-score matching techniques to a cohort of these patients (n=1,604), there was an association of epidural anaesthesia/analgesia with higher need for blood transfusion and longer hospital stay (Rosero 2014 **Level III-2**). After liver resection for cirrhosis, compared with IV fentanyl PCA epidural analgesia reduced pain scores slightly (only on postoperative d 2 and 3) with no further benefits (Fayed 2014 **Level II**, n=34, JS 2). Two patients required correction of coagulopathy prior to epidural catheter removal.

Compared to IT morphine with subsequent IV PCA fentanyl, TEA was not superior with the exception of pain at 12 h postoperatively and reduced blood loss (Kasivisvanathan 2014 **Level III-2**). However, another RCT found significantly improved analgesia and a 50% opioid-sparing effect (Mondor 2010 **Level II**, n=44, JS 5). While epidural analgesia resulted in lower pain scores than continuous local anaesthetic wound infiltration, this did not translate into any other improvement in outcome (Revie 2012 **Level II**, n=65, JS 3). Similarly after live liver donation, TEA compared to IV PCA opioids improved analgesia but no other outcomes (Clarke 2011 **Level III-2**).

Abdominal aortic surgery

After abdominal aortic surgery in comparison with systemic opioid administration, epidural analgesia reduces pain scores on movement in the first 3 d postoperatively, duration of intubation and ventilation (by 48%), and TEA over lumbar epidural analgesia (LEA) reduces myocardial infarction, acute respiratory failure, gastrointestinal and renal complication rates (Nishimori 2012 **Level I** [Cochrane], 15 RCTs [9 TEA, 3 LEA, 2 mixed, 1 unspecified], n=1,297). However, the reduced morbidity does not translate to a difference in mortality between epidural vs systemic opioids use (OR 0.79; 95%CI 0.48 to 1.41).

Subsequent studies support these results: TEA compared with systemic opioids improved pain, mobility and time to oral intake (Salman 2013 **Level III-1**) and pain and postoperative respiratory function in COPD patients (Panaretou 2012 **Level III-2**). After endoluminal aortic aneurysm repair, TEA provided better analgesia than IV opioids (Sen 2014 **Level III-2**). However in a fast-track setting for abdominal aortic aneurysm repair, TEA was similarly effective compared with continuous local anaesthetic wound infiltration with no effects on overall outcome (Renghi 2013 **Level II**, n=60, JS 3).

Gynaecological surgery

In gynaecological surgery, epidural ropivacaine infusion provided only slightly better analgesia in the first 8 h postoperatively compared to wound infiltration/infusion of ropivacaine with no other clinically relevant improvements (Fassoulaki 2014 **Level II**, n=80, JS 3). After open abdominal hysterectomy (midline incision), epidural analgesia increased duration of postoperative analgesic use, nonserious postoperative complications and length of stay compared to parenteral opioids (Belavy 2013 **Level III-2**). Similarly after uterine artery embolisation for uterine fibroids, epidural analgesia increased complications but reduced pain scores at high costs (179 Euro for 1/10 pain score reduction) (van der Kooij 2013 **NR**).

Urologic surgery

After radical retropubic prostatectomy, TEA compared with patient-controlled local anaesthetic wound infusion reduced pain scores upon coughing and opioid requirements, with better preservation of expiratory muscle strength (Fant 2011 **Level II**, n=50, JS 5). However, a cohort study (n=239) found an increased median hospital stay with use of epidural analgesia for this operation (6 vs 7 d; p< 0.048), which remained significant after adjusting for complications (p<0.0001) (Mir 2013 **Level III-2**). Malignancy recurrence based upon prostate-specific antigen change was more common in the epidural group (14.8 vs 4.8%; p=0.012). TEA had no effect on blood loss or transfusion rates (Baumunk 2014 **Level II**, n=235, JS 2).

Thoracic surgery

After lung resection, postoperative TEA reduced mortality at 7 d (OR 0.39; 95%CI 0.19 to 0.80) and 30 d (OR 0.53; 95%CI 0.35 to 0.78) in a retrospective cohort study (n=3,501) (Wu 2006b **Level III-2**). TEA for Ivor Lewis oesophagectomy (removal via laparotomy/right thoracotomy and intrathoracic anastomosis) compared to IV PCA opioids reduced pain at rest and on movement, opioid requirements and proinflammatory markers (IL-6 and IL-8) (Fares 2014 **Level II**, n=30, JS 3). TEA in patients after lobectomy resulted in better pain relief and pulmonary function compared with IV morphine (Bauer 2007 **Level II**, n=93, JS 5). TEA for thoracotomy reduces the risk of persistent postsurgical pain (OR 0.33; 95%CI 0.20 to 0.56; NNT 4) (Andreae 2012 **Level I** [Cochrane], 3 RCTs [thoracotomy], n=250). See also Section 5.8.1.3.

Cardiac surgery

High TEA used for CABG surgery results in reduced postoperative pain (both at rest and with activity), risk of dysrhythmias, pulmonary complications and time to extubation when compared with IV opioid analgesia; there are no differences in mortality or the rate of myocardial infarction (Liu 2004 **Level I**, 15 RCTs, n=1,178). A subsequent larger meta-analysis of outcomes other than pain after cardiac surgery (including 14 of the 15 RCTs above) shows reduced respiratory complications (RR 0.68; 95%CI 0.54 to 0.86) and supraventricular arrhythmias (RR 0.65; 95%CI 0.50 to 0.86) but confirms no effect on mortality, myocardial infarction or stroke (Svircevic 2013 **Level I** [Cochrane], 31 RCTs, n=3,407). These two meta-analyses are contradicted by a third (overlapping by 20 RCTs) reporting that TEA reduces the composite endpoint mortality and myocardial infarction (OR 0.61; 95%CI 0.40 to 0.95; NNT=40) (Bignami 2010 **Level I** [QUOROM], 33 RCTs, n=2,366). In smaller studies, high TEA improved left ventricular function (Schmidt 2005 **Level III-3**) and increased stroke volume index and central venous oxygenation in elderly cardiac surgery patients, without an increase in heart rate or mean arterial pressure (Jakobsen 2012 **Level II**, n=60, JS 3). Prior to CABG surgery, high TEA improved myocardial oxygen availability in patients with ischaemic heart disease (Lagunilla 2006 **Level II**, n=52, JS 4) and partly normalised myocardial blood flow in response to sympathetic stimulation (Nygard 2005 **Level III-3**). After CABG surgery, high TEA postoperatively reduced insulin requirements and hyperglycaemia (Greisen 2013 **Level II**, n=42, JS 3). After off-pump CABG surgery in patients with COPD, TEA provided better analgesia leading to earlier extubation and faster recovery of pulmonary function than systemic analgesia (Mehta 2010 **Level II**, n=62, JS 3). However, TEA did not reduce the duration of the ICU stay or improve the quality of recovery in the ICU (Nielsen 2012 **Level II**, n=60, JS 3). The discussion on the overall value of epidural analgesia after cardiac surgery continues, with concerns regarding anticoagulation risk being a key factor (Ziyaeifard 2014 **NR**).

Rib fractures

In patients with multiple traumatic rib fractures, provision of TEA with local anaesthetic reduced the duration of ventilation compared with other forms of analgesia (including LEA) (Carrier 2009 **Level I**, 8 RCTs, n=232); however, mortality and length of ICU stay was not different in pooled analysis of all routes of epidural administration vs parenteral opioids and hypotension was more frequent in the epidural groups when TEA with local anaesthetic was used. In one study, the risk of nosocomial pneumonia was reduced by TEA compared with parenteral opioids (Bulger 2004 **Level II**, n=46, JS 3). After blunt chest trauma with three or more rib fractures, the use of TEA was more common in USA trauma centres than in nontrauma centres; the use of TEA reduced adjusted mortality at 30 d (OR 0.08; 95%CI 0.01 to 0.43), 90 d (OR 0.09; 95%CI 0.02 to 0.42) and 365 d (OR 0.12; 95%CI 0.04 to 0.42) (n=836: 100 TEA) (Gage 2014 **Level III-2**).

Orthopaedic surgery

After spinal fusion, epidural analgesia with levobupivacaine reduced pain scores, opioid consumption, nausea, blood loss and time to first stool compared with IV opioid analgesia (Servicl-Kuchler 2014 **Level II**, n=81, JS 5). Similarly after major spinal surgery, epidural analgesia (levobupivacaine/fentanyl/epinephrine) compared to systemic opioids reduced pain and nausea, permitted earlier mobilisation and increased satisfaction (Ezhevskaya 2013 **Level II**, n=85, JS 2). In addition, it resulted in less intraoperative and postoperative blood loss and reduced stress response markers (glucose, cortisol, IL-1beta, IL-6, and IL-10). However, when added to systemic multimodal analgesia, TEA did not provide a significant opioid-sparing effect (Choi 2014 **Level II**, n=39, JS 5).

After hip or knee replacement, LEA provides better pain relief than parenteral opioids, in particular with movement (Choi 2003 **Level I** [Cochrane], 13 RCTs, n unspecified). A subsequent study showed that epidural analgesia compared to systemic opioids reduced inflammatory response measured by a number of parameters after total knee replacement (Chloropoulou 2013 **Level II**, n=56, JS 3). For comparisons with other analgesic techniques see Section 5.8.

Vascular surgery of the lower limbs

Used in vascular surgery of the lower limbs, LEA improved outcome by reducing incidence of graft occlusion (Tuman 1991 **Level II**, n=80, JS 1; Christopherson 1993 **Level II**, n=100, JS 3). However, these findings have not been confirmed by other investigators in retrospective reviews (Pierce 1997 **Level IV**; Schunn 1998 **Level IV**).

5.6.1.4 Level of administration

TEA is widely used for the treatment of pain after major abdominal and thoracic surgery. Administration of local anaesthetics into the thoracic epidural space resulted in improved bowel recovery after abdominal surgery, while these benefits are not consistent with lumbar administration (Jorgensen 2000 **Level I** [Cochrane], 22 RCTs, n=1,023). In a direct comparison between TEA and LEA for thoracotomy, TEA vs LEA reduced pain scores and opioid requirements as well as hypotension, bradycardia, atelectasis and need for ICU treatment (Sagiroglu 2014 **Level II**, n=134, JS 4). If TEA is extended for more than 24 h, a further benefit is a significant reduction in the incidence of postoperative myocardial infarction (Beattie 2001 **Level I**, 11 RCTs, n=1,173). Benefits of epidural analgesia after abdominal aortic surgery were found with impact on nonanalgesic outcomes significant for TEA but not LEA (see above; Nishimori 2012 **Level I** [Cochrane], 15 RCTs, n=1,297). A comparison of TEA and LEA in patients undergoing gynaecological surgery showed that TEA provided better pain relief only when the incision extended above the umbilicus; TEA led to less motor block but more pruritus (Richman 2007 **Level II**, n=103, JS 5). In patients with multiple traumatic rib fractures, provision of TEA with local anaesthetic reduced the duration of ventilation compared with other forms of analgesia including LEA (Carrier 2009 **Level I**, 8 RCTs, n=232).

TEA permits early removal of urinary catheters in many patients compared with LEA; rates of urinary retention are variably reported as 6.6% (n=61) (Tripepi-Bova 2013 **Level IV**), 11.9% (vs 2.2% after TEA was discontinued; n=118) (Stubbs 2013 **Level III-2**) and 26.7% (vs 12.4% in historic controls; n=101) (Hu 2014 **Level III-3**). Post removal of the urinary catheter, effective

bladder emptying took hours to normalise (defined as post-void volumes <200 mL) in patients who received TEA, however without need for recatheterisation; this effect was prolonged when the urinary catheter was removed early on the morning after surgery rather than remaining *in situ* for the duration of TEA therapy (345 +/-169 vs 207 +/-122 min) (Zaouter 2012 **Level II**, n=205, JS 2). TEA for thoracotomy did not change the post-void volume from the preoperative findings in men (p=0.09) and women (p=0.18) (n=26) (Wuethrich 2011b **Level III-3**); only three men >50 y with prostrate hypertrophy had post-void volumes >100 mL. However, in women undergoing nephrectomy (n=13), early removal of the urinary catheter under TEA led to a significant increase in post-void residual volume (median 5 mL vs 220 mL; p<0.001) and negatively affected other parameters of bladder emptying (detrusor pressure, maximum flow rate, voided volume) (Wuethrich 2011a **Level III-3**); the authors suggest that this necessitates indwelling or intermittent catheterisation or monitoring.

5.6.2 Medicines used for epidural analgesia

Differences in analgesic effect, duration and adverse effects depend upon the various local anaesthetic, opioid and adjuvant medicines used in epidural analgesia.

5.6.2.1 Local anaesthetics

For epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott 1995 **Level II**, n=40, JS 3; Schug 1996 **Level II**, n=50, JS 4). Therefore, most investigators compare infusions of bupivacaine or levobupivacaine at 0.1 or 0.125% with ropivacaine 0.2%, which removes any imbalance in comparative potency. For more information on differences in efficacy and adverse effects between the local anaesthetics used for epidural analgesia see Section 4.4.

5.6.2.2 Opioids

Opioids alone via the epidural route appear to be of limited benefit. In particular, when administered via TEA, opioids failed to demonstrate any advantage over parenteral opioids except for a slight reduction in the rate of atelectasis (Ballantyne 1998 **Level I**, 48 RCTs, n unspecified) with no benefit with regard to bowel recovery (Jorgensen 2000 **Level I** [Cochrane], 22 RCTs, n=1,023). On the basis of the available studies, the benefits of administering lipophilic opioids alone by the epidural route appear to be marginal, or unproven in the case of upper abdominal surgery, and in many situations will not outweigh the risks of the more invasive route of administration (for detailed discussion see Wheatley 2001 **NR** and Section 4.1.2).

For information on the epidural use of morphine, ER morphine, pethidine, fentanyl, alfentanil, sufentanil, diamorphine and hydromorphone see Section 4.1.2.

5.6.2.3 Local anaesthetic-opioid combinations

Combinations of low concentrations of local anaesthetic agents and opioids provide consistently superior pain relief compared with either of the medicines alone (Curatolo 1998 **Level I**, 18 RCTs [fentanyl], n unspecified). Addition of fentanyl to a continuous epidural infusion of ropivacaine reduced the rate of regression of sensory block after orthopaedic (n=80) and abdominal gynaecological surgery (n=39) (Kanai 2007 **Level II**, n=119, JS 3) and decreased the discontinuation of postoperative epidural infusion due to lack of efficacy (Scott 1999 **Level II**, n=244, JS 4).

Addition of 4 mcg/mL of fentanyl to levobupivacaine 0.125% improved quality of analgesia and reduced the stress response (ACTH, cortisol and prolactin levels) after total knee joint replacement compared to plain levobupivacaine (Bayazit 2013 **Level II**, n=40, JS 4). Addition of 0.5 mcg/mL sufentanil to 0.1% ropivacaine compared to higher sufentanil concentrations and 4 mcg/mL fentanyl resulted in no difference in quality of analgesia after arthroplasty and had the lowest rate of pruritus (Jeon 2011 **Level II**, n=80, JS 3). The MLAC of epidural lignocaine of 0.785% (95%CI 0.738 to 0.864) was reduced by 2 mcg/mL fentanyl to 0.596% (95%CI 0.537 to 0.660) and by 3 mcg/mL to 0.387% (95%CI 0.329 to 0.446) (up-down sequential titration) (Zhang 2012 **Level IV**).

5.6.2.4 Adjuvant medicines

The efficacy of adding of adjuvant medicines such as adrenaline (epinephrine), clonidine, ketamine, midazolam, neostigmine and magnesium to solutions used for epidural analgesia has also been investigated (see also Chapter 4).

5.6.3 Patient-controlled epidural analgesia

The use of PCEA has become increasingly popular; it is based on similar concepts as for other patient-controlled techniques. It has been shown to be safe and effective in standard ward settings (Liu 2010 **Level IV**; Tan 2011 **Level IV**; Kim 2013 **Level IV**; Golster 2014 **Level IV**).

5.6.3.1 Comparison with continuous epidural infusions

A meta-analysis comparing PCEA, continuous epidural infusions and IV PCA opioids after surgery showed that both forms of epidural analgesia (with the exception of hydrophilic opioid-only epidural regimens) provide better pain relief with rest and with activity than PCA opioids (Wu 2005 **Level I**, 50 RCTs, n=3,208). However, analgesia with a continuous epidural infusion is superior to PCEA, countered by higher incidence of nausea, vomiting and motor block.

For specific procedures, results of PCEA vs continuous infusion are conflicting. After colonic resection, PCEA was superior to continuous epidural infusion with regard to pain control, requirements for top-ups and systemic analgesia as well as patient satisfaction (Nightingale 2007 **Level II**, n=205, JS 5). In contrast, comparisons of PCEA and continuous epidural infusions for pain relief after thoracotomy using both high (0.5%) and low (0.15%) concentrations of levobupivacaine showed no differences in quality of analgesia, morphine consumption or satisfaction; more patients in the high concentration continuous epidural infusion group had significant motor block (Dernedde 2008 **Level II**, n=82, JS 3).

5.6.3.2 Concurrent background (continuous) infusions

The addition of a continuous background infusion to PCEA using bupivacaine and fentanyl following gastrectomy resulted in better dynamic pain scores, with higher total doses and a greater incidence of pruritus than PCEA-bolus dose only (Komatsu 1998 **Level II**, n=40, JS 2). The use of a night-time-only background infusion with PCEA bupivacaine-fentanyl, also post gastrectomy, resulted in better sleep, but total cumulative doses were similar and pain scores were only better in the morning of postoperative d 2 (Komatsu 2001 **Level II**, n=40, JS 2). A Swedish case series (n=4,663) over 7 y (Golster 2014 **Level IV**) and a USA case series (n=3,736) (Liu 2010 **Level IV**) describe successful and safe use of PCEA with a background infusion.

Other studies have found no improvement in pain relief with background infusions. After lower abdominal surgery there was no difference in pain scores but higher total cumulative doses and incidence of adverse effects when a background infusion was added to PCEA with ropivacaine and fentanyl (Wong 2000 **Level II**, n=42, JS 2). The addition of a background infusion to bupivacaine-fentanyl PCEA did not improve pain relief after pelvic reconstruction (Nolan 1992 **Level II**, n=23, JS 5).

Using programmed intermittent epidural boluses compared with a continuous infusion, has been shown to be advantageous in labour analgesia (see Section 10.1.2) and reduced pain scores and rescue analgesia requirements after total knee joint replacement (Kang 2013 **Level II**, n=53, JS 2).

5.6.3.3 Medicines used in postoperative patient-controlled epidural analgesia

The medicines used for PCEA are typically the same as those used for continuous epidural infusions. Conclusions about the efficacy of different medicines and medicine combinations administered via PCEA are difficult to make because of the wide variety of analgesic agents and concentrations used in the various studies.

5.6.4 Adverse effects

5.6.4.1 Neurological injury

Permanent neurological damage is the most feared complication of epidural analgesia.

A retrospective survey from Sweden (n=450,000 epidurals) put the risk of a severe neurological complication after obstetric epidural analgesia at 1 per 25,000 and for all other patients at 1 per 3,600; 67% of events resulted in permanent neurological deficit (Moen 2004 **Level IV**). It also identified osteoporosis as a previously neglected risk factor. A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 240,000 for persistent neurological injury and 1 per 6,700 for transient (resolution within 12 mth) neurological symptoms (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million).

A review of data from published studies of the risk of neurological injury associated with epidural and other regional anaesthesia and analgesia techniques differentiated between the risk of permanent neurological injury (deficit lasting >12 mth) and transient neuropathy (Brull 2007 **Level IV SR**, 32 studies, n unspecified). This review focussed on adverse neurological sequelae associated with the various regional techniques and did not address the overall risk of epidural haematoma or abscess. The incidence of transient neuropathy (radiculopathy) after epidural anaesthesia was estimated to be 2.19 per 10,000 (95%CI 0.88 to 5.44) (Brull 2007 **Level IV SR**, 4 studies [epidural], n unspecified). The risk of permanent neurological injury was lower and the incidences reported in the studies included in this review ranged from 0–7.6 per 10,000. The rates of paraplegia and cauda equina syndrome associated with epidural anaesthesia were estimated to be 0.09 per 10,000 (95%CI 0.04 to 0.22) and 0.23 per 10,000 (95%CI 0.14 to 0.39) respectively.

A project in the UK (NAP3) assessed the incidence of neurological complications in an estimated 97,925 adult patients with perioperative epidural catheters (Cook 2009 **Level IV**). Depending on the inclusion or exclusion of cases with unlikely causation, pessimistic and optimistic assessments were published. The incidence of permanent injury was pessimistically assessed as 17.4 per 100,000 (95%CI 7.2 to 27.8; 1 in 5,800) and optimistically as 8.2 per 100,000 (95%CI 3.5 to 16.1; 1 in 12,200). Laminectomy was performed with an incidence of 12.3 per 100,000 cases (95%CI 6.3 to 21.4; 1 in 8,100). Paraplegia was caused in 6.1 per 100,000 (95%CI 2.2 to 13.3; 1 in 16,400) in the pessimistic and in 1.0 per 100,000 (95%CI 1.0 to 5.7) in the optimistic model.

Audit data from a single (nonobstetric) tertiary institution with 8,210 epidural catheters inserted over a 16-y period for postoperative pain relief found two spinal haematomas and six epidural abscesses; only one patient (with an epidural abscess) required surgical decompression and no patient suffered any long-term neurological deficit (Cameron 2007 **Level IV**). The largest published audit of patients undergoing arthroplasty with epidural analgesia at one institution (n=62,856) described no persistent neurologic deficit despite four patients developing epidural haematoma and two requiring surgical compression (Pumberger 2013 **Level IV**). Another audit at a single institution (n=5,083) reported 1 epidural haematoma, but 57 postoperative neurologic deficits, which resolved within 3 mth except for one being permanent (unilateral lower limb paraesthesia) (Kang 2014 **Level IV**).

The incidence of transient neuropathy after epidural analgesia in a large case series was in the range of 0.013–0.023% (Xie 1991 **Level IV**; Tanaka 1993 **Level IV**; Auroy 1997 **Level IV**).

5.6.4.2 Epidural haematoma

A major concern is the development of an epidural haematoma with subsequent, potentially permanent, SCI. A review including case series involving over 1,335,000 patients with epidural analgesia reported seven cases of haematoma (1 per 191,000) (Wulf 1996 **Level IV**). On the basis of this case series, the possible incidence is in the order of 1 per 100,000 at the upper limit of the 95% confidence interval. The Swedish case series quoted above puts the overall risk of epidural haematoma after epidural blockade at 1 per 10,300 (Moen 2004 **Level IV**). A Finnish closed-claims study calculated a risk of 1 per 26,400 (Pitkanen 2013) **Level IV**). An

even higher incidence of epidural haematoma (1 per 3,100) has been estimated for epidural analgesia in association with inappropriate low molecular weight heparin (LMWH) dose regimens (Horlocker 2003 **GL**) (see Section 5.9).

A systematic review of the risks of epidural haematoma and neurological injury associated with epidural anaesthesia/analgesia in cardiac, vascular and thoracic surgery patients concluded that the maximum risks of epidural haematoma were 1 per 1,700, 1 per 1,700 and 1 per 1,400 respectively (Ruppen 2006b **Level IV SR**, 12 studies, n=14,105). However, this was a calculated risk only; there were actually no cases of epidural haematoma reported in the studies used in this analysis and the maximal calculated expected rate of permanent neurological injury associated with epidural haematoma was 1 per 4,600.

In a large USA case series (n=62,450) of patients having epidural analgesia perioperatively, seven patients developed haematoma requiring surgical evacuation (1 per 8,921; 95%CI 1/4,330 to 1/22,189) (Bateman 2013 **Level IV**). In four of the seven patients, management of anticoagulation was not in line with the guidelines of American Society of Regional Anesthesia and Pain Medicine (ASRAPM) discussed later. In a similarly large case series of patients having arthroplasty with an indwelling epidural catheter at one institution (n=62,856), four epidural haematomas occurred (1 per 15,714), of which two required emergency decompression and none resulted in persisting neurological deficits (complete recovery at 6 wk) (Pumberger 2013 **Level IV**). It is of note that all four patients had combined spinal and epidural anaesthesia, took at least one medication affecting coagulation (aspirin, TCA, NSAIDs, clopidogrel) and had preoperative hypertension. Additional risk factors were clopidogrel only discontinued for 4 d in one, thrombocytopenia (70,000/mcL) at day of insertion and removal in one and excessive alcohol consumption in two.

In a case series after cardiac surgery, the risk of epidural haematoma was calculated at 1 per 12,000 (95%CI 1 per 2,100 to 1 per 68,000); comparable to an obstetric population (Bracco 2007 **Level IV**). It was described as being in the same risk range as receiving a wrong blood product (or the yearly risk of having a fatal traffic accident in a Western country).

A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 168,000 for epidural haematoma (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million). In a large USA series (n=79,837) of obstetric epidural analgesia, no epidural haematoma was found (Bateman 2013 **Level IV**); the haematoma rate in this setting was significantly lower than in the perioperative data from the same series (p=0.003).

Early diagnosis and, if indicated, immediate decompression (<8 h after the onset of neurological signs) increases the likelihood of partial or good neurological recovery (Horlocker 2003 **GL**).

5.6.4.3 Epidural abscess

Serious neuraxial infections following epidural anaesthesia have previously been reported as rare. However, prospective studies have found rates in the range of 0.015–0.05% (Kindler 1996 **Level IV**; Rygnestad 1997 **Level IV**; Wang 1999 **Level IV**). It is of note that in the studies with these high incidences, patients had long durations of epidural catheterisation; the mean duration in patients with an epidural space infection was 11 d; no infection occurred in any patient whose catheter was *in situ* for <2 d and the majority of patients were immunocompromised (Wang 1999 **Level IV**).

Only 5.5% of 915 cases of epidural abscess published between 1954 and 1997 developed following epidural anaesthesia and analgesia; 71% of all patients had back pain as the initial presenting symptom and only 66% were febrile (Reihsaus 2000 **Level IV**). The classic triad of symptoms (back pain, fever and neurological changes) was present in only 13% of patients with an epidural abscess (in a study unrelated to epidural catheterisation); diagnostic delays occurred in 75% of these patients and such delays led to a significantly higher incidence of residual motor weakness (Davis 2004 **Level IV**).

Audit data from the study referred to above (Cameron 2007 **Level IV**) showed that of the 8,210 patients with epidural catheters over the period of 16 y, six developed epidural abscesses. Only one of these required surgical decompression and they did not suffer any long-term

neurological loss. The authors stress the importance of appropriate patient monitoring and early diagnosis using MRI. In five of the six patients diagnosed with an epidural abscess, both fever and epidural insertion site infection were present. They therefore suggested that MRI investigation may be warranted if this combination is present and that urgent investigation is especially indicated if there is a third sign that could indicate an abscess, such as back pain or neurological change (Cameron 2007 **Level IV**). If the diagnosis of epidural abscess can be made before the onset of any neurological deficit, conservative treatment (antibiotics only) may be effective. The presence of severe or increasing back pain, even in the absence of a fever, may indicate epidural space infection and should be investigated promptly.

A review of data from publications reporting adverse effects after obstetric epidural analgesia reported a risk estimate of 1 per 145,000 for epidural space infection (Ruppen 2006a **Level IV SR**, 27 studies, n≈1.37 million).

Bacterial colonisation of epidural catheter tips is reported to occur in 0–28% of patients (Simpson 2000 **Level IV**; Steffen 2004 **Level IV**; Mishra 2006 **Level IV**; Yuan 2008 **Level IV**). The most common organism cultured from the catheter tips was coagulase-negative staphylococcus.

Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo or povidone-iodine-impregnated dressings reduced the incidence of catheter colonisation (Ho 2006 **Level I**, 8 RCTs, n=2,588). Chlorhexidine was also the superior skin disinfectant prior to regional catheter insertion with a positive skin culture immediately after skin disinfection of 10% compared with 35% of povidone-iodine treated (NNT 4) (Krobbuaban 2011 **Level II**, n=100, JS 4). Chlorhexidine is therefore the recommended skin disinfectant before insertion of regional catheters (Campbell 2014 **GL**). However, chlorhexidine is neurotoxic and skin preparation solutions must be allowed to dry before instrumentation of the epidural space. For this reason, chlorhexidine must also be kept clearly identified and separate from all solutions used for injection. As 2% chlorhexidine is not superior to 0.5% for skin disinfection, UK guidelines recommend the use of 0.5% to reduce neurotoxicity (Campbell 2014 **GL**).

Experimental data suggest that after accidental epidural catheter disconnection, cutting the catheter 2 cm distal to the level of contamination left all such treated catheters sterile, while spray-wipe disinfection or employing ropivacaine 0.75% as flushing solution or a combination of these measures were not as effective (Scholle 2014 **BS**). The authors suggest spray-wipe disinfection and cutting as the safest strategy.

An *in vitro* comparison of the antibacterial activity of medicines used in epidural solutions showed that the minimal inhibitory concentration of bupivacaine for *Staphylococcus aureus*, *Enterococcus faecalis* and *Escherichia coli* was between 0.125% and 0.25% (growth of *Pseudomonas aeruginosa* was not affected at any of the concentrations investigated) (Coghlan 2009 **Level III-2**). Levobupivacaine and ropivacaine showed no activity against *S aureus*, *E faecalis* and *P aeruginosa*, even at the highest concentrations tested, and minimal activity against *E coli* (minimum inhibitory concentrations 0.5 and 1% respectively). The addition of fentanyl, clonidine and adrenaline did not improve antibacterial activity

Comprehensive reviews of infectious complications associated with central neuraxial and PNB, including epidemiology, factors affecting bacterial colonisation of the epidural catheter as well as use in febrile, infected and immunocompromised patients are published (Horlocker 2008 **NR**; Hebl 2011 **NR**).

Guidelines for skin antisepsis prior to neuraxial block (Association of Anaesthetists of Great Britain and Ireland, Obstetric Anaesthetists' Association, Regional Anaesthesia UK, Association of Paediatric Anaesthetists of Great Britain and Ireland) recommend thorough handwashing with surgical scrub solution, the use of barrier precautions, including the wearing of a cap, mask, sterile gown and gloves, and of a large sterile drape (Campbell 2014 **GL**). Chlorhexidine in alcohol (0.5%) should be used for skin preparation, but meticulous care must be taken to avoid this reaching epidural space or CSF.

5.6.4.4 Respiratory depression

The incidence of respiratory depression with epidural opioid analgesia depends on the criteria used to define respiratory depression. In a review of published case series and audit data, the reported incidence of respiratory depression ranged from 1.1 (0.6–1.9%) using respiratory rate to 15.1% (5.634.8%) using oxygen saturation (see Section 4.1.1.4 for comments on respiratory rate as an unreliable indicator of respiratory depression); this was very similar to the incidence reported for PCA (Cashman 2004 **Level IV**).

5.6.4.5 Hypotension

The incidence of hypotension depends on the dose of local anaesthetic and criteria used to define hypotension. In the same review as above, the reported incidence of hypotension was 5.6% (3.0–10.2%) (Cashman 2004 **Level IV**). In the large meta-analysis quoted above, incidence of hypotension is increased by epidural analgesia (OR 4.92; 95%CI 3.11 to 7.78) (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044). But while TEA was associated with arterial hypotension after thoracic or abdominal surgery (n=161), this did not predict inability to walk (Gramigni 2013 **Level IV**); early mobilisation may be carefully attempted despite hypotension or orthostatic changes.

5.6.4.6 Treatment failure

Epidural analgesia may not always be successful due to a number of factors including catheter malposition or displacement, or technical and patient factors resulting in an inability to achieve effective analgesia (Hermanides 2012 **NR**). Intolerable adverse effects may also be an indication for premature discontinuation. In a large prospective audit, 22% of patients had premature termination of postoperative epidural infusions (Ballantyne 2003 **Level IV**): the most common causes were dislodgement (10%), inadequate analgesia (3.5%) and sensory or motor deficit (2.2%). Most of these failures occurred on or after postoperative d 2. The rate of technical failures in a meta-analysis of epidural analgesia was 6.1% (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044).

Tunneling and then suturing the epidural catheter subcutaneously vs fixation with adhesive tape without tunneling reduced incidence of clinically relevant dislocation of epidural catheters (>20 mm; 1/60 vs 9/61) (Sellmann 2014 **Level II**, n=121, JS 3). There was also a trend towards lower bacterial contamination (8/59 vs 14/54; p=0.08). Length of the catheter in the epidural space may also influence rate of dislocation; in an RCT of 3, 5 and 7 cm insertion one patient in the 7 cm group had unilateral sensory block and four patients in the 3 cm group had epidural catheter dislodgement (Afshan 2011 **Level II**, n=102, JS 5). The authors suggest that 5 cm is the ideal depth of insertion.

5.6.4.7 Other

There has been concern among surgeons about increased risk of anastomotic leakage after bowel surgery due to the stimulating effects of epidural administration of local anaesthetics; so far there is no evidence to support these claims in colorectal surgery (Holte 2001 **Level I**, 12 RCTs, n=652). A subsequent audit of patients undergoing surgery for colorectal cancer in one centre (n=1,312) showed that epidural analgesia had no influence on occurrence of anastomotic leakage (Lai 2013 **Level III-2**). After oesophagectomy, TEA reduced the risk of anastomotic leakage (OR 0.13; 95%CI 0.02 to 0.71) (Michelet 2005 **Level III-2**).

Key messages

1. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**U**) (**Level I** [Cochrane Review]); except epidural analgesia using a hydrophilic opioid only (**U**) (**Level I**).
2. Thoracic epidural analgesia for open abdominal aortic surgery reduces the duration of tracheal intubation and mechanical ventilation, as well as the incidence of myocardial infarction, acute respiratory failure, gastrointestinal complications and renal insufficiency when compared with IV opioids (**S**) (**Level I** [Cochrane Review]).
3. High thoracic epidural analgesia used for coronary artery bypass graft surgery reduces postoperative pain, risk of dysrhythmias, pulmonary complications and time to extubation when compared with intravenous opioid analgesia (**S**) (**Level I** [Cochrane Review]).
4. Thoracic epidural analgesia for thoracotomy reduces the risk of chronic postsurgical pain (**N**) (**Level I** [Cochrane Review]).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery) (**S**) (L**evel I** [Cochrane Review]).
6. Epidural analgesia provided with local anaesthetics for at least 24 hours compared to systemic opioid analgesia reduces perioperative mortality and multiple morbidities (including ileus, pneumonia, respiratory depression and arrhythmias) but increases hypotension (**N**) (**Level I** [PRISMA]).
7. After laparoscopic colectomy, initial pain scores and postoperative nausea and vomiting are reduced by thoracic epidural analgesia compared to intravenous PCA with reduced time to first bowel motion, without any further improved outcomes (**N**) (**Level I** [PRISMA]) and at the expense of longer hospital stay and increased urinary tract infection rates (**Level III-2**).
8. Combinations of low concentrations of local anaesthetic agents and opioids for epidural analgesia provide consistently superior pain relief compared with either of the medicines alone; epidural opioids alone have no advantage over parenteral opioids (**N**) (**Level I**).
9. Epidural local anaesthetic administration improves oxygenation and reduces pulmonary infections and other pulmonary complications compared with parenteral opioids (**U**) (**Level I**).
10. Thoracic epidural analgesia extended for more than 24 hours reduces the incidence of postoperative myocardial infarction (**U**) (**Level I**).
11. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**S**) (**Level I**).
12. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**U**) (**Level I**).
13. Thoracic epidural analgesia reduces need for ventilation in patients with multiple rib fractures (**U**) (**Level I**) and reduces incidence of pneumonia (**U**) (**Level II**) and mortality (**N**) (**Level III-2**).
14. The combination of thoracic epidural analgesia with local anaesthetics and nutritional support leads to preservation of total body protein after upper abdominal surgery (**U**) (**Level II**).

15. The incidence of permanent neurological damage in association with epidural analgesia is extremely low, especially in the obstetric population, but increases with various comorbidities and risk factors; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV**).
16. Immediate decompression of an epidural haematoma (within 8 hours of the onset of neurological signs) increases the likelihood of partial or good neurological recovery (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ The provision of epidural analgesia by continuous infusion or patient-controlled administration of local anaesthetic-opioid mixtures is safe on general hospital wards, as long as supervised by an anaesthesia-based pain service with 24-hour medical staff cover and monitored by well-trained nursing staff (**U**).
- ☑ Magnetic resonance imaging investigation may be warranted to assess for possible epidural abscess if patients, who have had an epidural catheter inserted, develop a fever and infection at the catheter insertion site; urgent investigation is especially indicated if other signs are present that could indicate an abscess, such as back pain or neurological change (**U**).
- ☑ Prior to insertion of an epidural catheter, thorough handwashing with surgical scrub solution, the use of barrier precautions including the wearing of a cap, mask, sterile gown and gloves and use of chlorhexidine in alcohol (0.5%) for skin preparation are recommended; but meticulous care must be taken to avoid the chlorhexidine solution from reaching epidural space or cerebrospinal fluid (**N**).

5.7 Intrathecal analgesia

5.7.1 Medicines used for intrathecal analgesia

5.7.1.1 Local anaesthetics

IT local anaesthetics provide short-term postoperative analgesia. The use of spinal microcatheters (<24-gauge) for postoperative infusions of local anaesthetics became controversial when multiple cases of cauda equina syndrome were reported (Bevacqua 2003 **NR**). (See also Section 5.1.3.)

5.7.1.2 Opioids

IT opioids have been used for surgical procedures ranging from lower limb orthopaedic surgery to CABG surgery because of their ability to provide prolonged postoperative analgesia following a single dose compared with systemic administration. IT opioids may be given alone or in conjunction with a local anaesthetic. In acute pain, the use of continuous subarachnoid infusions of opioids for postoperative analgesia is uncommon. Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at clinically used IT doses (Hodgson 1999 **Level IV**). Morphine is the most frequently studied IT opioid followed by fentanyl (Meylan 2009 **Level I**, 27 RCTs, n=1,205; Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). Reported IT use of other opioids includes pethidine (meperidine), hydromorphone, diamorphine, pentazocine, sufentanil, tramadol and buprenorphine (Staikou 2014 **Level I**, 105 RCTs, n unspecified). Some clinical studies used very high IT morphine doses (ie 500 mcg or more) without additional benefit. Lower doses (<300 mcg) should be used as there is no clear dose-response relationship with IT morphine for duration of analgesia nor for adverse effects (Meylan 2009 **Level I**, 27 RCTs, n=1,205; Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338).

For major abdominal or thoracic surgery, IT opioids are typically combined with a general anaesthetic technique. In patients having abdominal, cardiothoracic or spinal surgery, IT morphine (100–500 mcg, without local anaesthetic) reduced pain scores at rest and

with movement at 12 h by 1/10 and 2/10 respectively, and also at 24 h by 1/10 and 2/10. Morphine-sparing was evident for up to 48 h postoperatively; being more pronounced at 24 h after abdominal than cardiothoracic surgery (Meylan 2009 **Level I**, 27 RCTs, n=1,205). In other studies, IT morphine 50–200 mcg ± clonidine after prostatic surgery (Brown 2004 **Level II**, n=99, JS 5), and morphine 500 mcg/fentanyl 150 mcg after liver resection (Roy 2006 **Level II**, n=20, JS 3) resulted in better analgesia and lower opioid requirements than morphine PCA up to 18 h postoperatively. Compared to epidural analgesia, IT morphine 200 mcg in liver resections showed comparable pain scores, although there was a reduction in opioid consumption and intubation duration favouring the epidural group (De Pietri 2006 **Level II**, n=50, JS 2). Similarly, in patients for liver resections, IT morphine 500 mcg and fentanyl 15 mcg was inferior to the additional of epidural bupivacaine infusion, with twice as much morphine consumption 123 mg vs 59 mg and more pain (Mondor 2010 **Level II**, n=44, JS 5). In minimally invasive cardiac surgery, IT morphine reduced PCA-opioid requirements and pain scores (Mukherjee 2012 **Level II**, n=62, JS 3). For open thoracotomy procedures, the combination of IT morphine and sufentanil with a continuous PVB offered slightly higher but acceptable pain scores when compared to epidural analgesia (Dango 2013 **Level II**, n=84, JS 4).

For patients having procedures amenable to spinal anaesthesia alone (orthopaedic, urologic, gynaecologic), the addition of IT morphine (50 mcg–2 mg) was found to consistently provide an increase in duration of analgesia (as time to first dose of additional opioid analgesia) (WMD 503 min; 95%CI 315 to 641)) compared to IT local anaesthetic alone (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). IT fentanyl (10–50 mcg) prolonged the duration of analgesia by a WMD of 114 min (95%CI 60 to 168). There was also a reduction in cumulative morphine consumption when IT morphine was used (WMD -12 mg; 95%CI -18 to -5). There was considerable heterogeneity in the study data and no dose-responsiveness could be identified.

In patients having knee joint arthroplasty under spinal anaesthesia, local anaesthetic infiltration analgesia was superior to 100 mcg IT morphine for pain intensity scores on standing at 24 and 48 h (Kuchalik 2013 **Level II**, n=80, JS 5) and resulted in earlier mobilisation and discharge (Essving 2011 **Level II**, n=50, JS 5). In the IT morphine group, analgesia at rest was greater but nausea, vomiting, and pruritus were more frequent in the 4–24-h time period. In hip joint arthroplasty, IT morphine was opioid-sparing in comparison to local anaesthetic infiltration analgesia in the first 24 h but had higher urinary retention and lower early mobilisation rates (Rikalainen-Salmi 2012 **Level II**, n=53, JS 4). IT hydromorphone in addition to spinal anaesthesia for knee arthroscopic surgery significantly reduced pain scores for up to 12 h with a 5 or 10 mcg dose compared with 2.5 mcg or placebo. Nausea was more frequent (46%) in the 10-mcg group (Lee 2012 **Level II**, n=60, JS 3).

IT morphine at three different doses (100, 200 and 300 mcg) for total abdominal hysterectomy was superior to placebo for analgesia up to 24 h, with the 200 mcg dose equivalent to 300 mcg and superior to 100 mcg in rescue analgesia requirements (Hein 2012 **Level II**, n=144, JS 5). For transurethral resection of the prostate under spinal anaesthesia, low-dose IT morphine, 25 and 50 mcg resulted in similar pain scores for up to 24 h but the higher-dose group had more pruritus (15 vs 0%) (Duman 2010 **Level II**, n=70, JS 4).

IT opioids have been used as a component of the spinal anaesthetic for Caesarean delivery for many years. IT fentanyl may improve the quality of spinal anaesthesia but provides only a short duration of postoperative analgesia (median time to first analgesia 4 h [range 2–13 h]) compared with bupivacaine alone (median time to first analgesia 2 h [range 1–4 h]) and hence it is often combined with IT morphine (median time to first analgesia 27 h [range 11–29 h]) (Dahl 1999 **Level I**, 15 RCTs, n=535). In patients having Caesarean delivery under combined spinal-epidural anaesthesia, the addition of IT morphine to bupivacaine at 50 and 100 mcg doses provided better postoperative analgesia for up to 12 h and decreased requests for analgesia for up to 18 h compared to placebo; however the higher dose resulted in a significantly higher rate of pruritus (64 vs 40%) (Mikuni 2010 **Level II**, n=75, JS 3). Spinal bupivacaine with IT morphine (200 mcg) was combined with IT fentanyl (0–25 mcg) for Caesarean delivery to investigate the possible induction of acute opioid tolerance by the fentanyl component (Carvalho 2012 **Level II**, n=40, JS 5). There was no difference in postoperative analgesic requirements in any treatment group, indicating that the added IT fentanyl did not contribute

to the analgesia provided by IT morphine. In patients having Caesarean delivery under spinal anaesthesia, when compared to a transversus abdominus plane (TAP) block, 100 mcg of IT morphine resulted in lower VAS pain scores but only at the 10-h time point and the morphine group also had more PONV and pruritus (Loane 2012 **Level II**, n=66, JS 5). This study failed to achieve full recruitment.

5.7.1.3 Adverse effects

Typical adverse effects of IT opioids include nausea and vomiting, pruritus and delayed respiratory depression (Meylan 2009 **Level I**, 27 RCTs, n=1,205).

Opioid-induced ventilatory impairment

The definition of "respiratory depression" in different investigations often lacks uniformity, with many studies using respiratory rate as the primary marker and others using desaturation to different levels and a few others using the need for opioid antagonists. This significantly compromises interpretation of reported event rates. OIVI is a more appropriate term (Macintyre 2011 **NR**). Patients may be hypoxic or hypercapnic with a normal respiratory rate (Bailey 1993 **Level IV**), while others may be able to maintain normocarbia with a lower respiratory rate (Boezaart 1999 **Level II**, n=60, JS 5). In a volunteer study, clinical signs or symptoms including respiratory rate, sedation and pupil size did not reliably indicate hypoventilation or hypoxaemia, unlike peripheral pulse oximetry (Bailey 1993 **Level IV**); although desaturation itself is a late indicator when supplemental oxygen is being administered (Shapiro 2005 **Level IV**). Very large numbers of patient exposures are needed to adequately quantify risk of infrequent events (eg OIVI) thus most studies and meta-analyses will have a limited capacity to report meaningfully on such adverse effects (see also Section 4.1.1.4).

When measured in opioid-naïve volunteers, respiratory depression peaked at 3.5–7.5 h following IT morphine at 200–600 mcg doses (Bailey 1993 **Level IV EH**). Volunteers given 600 mcg had significant depression of the ventilatory response to CO_2 up to 19.5 h later.

A prospective audit of 5,969 patients given IT morphine (200–800 mcg) for pain relief following a range of surgical procedures reported a high degree of patient satisfaction and effective analgesia in the first 24 h (Gwirtz 1999 **Level IV**). The incidence of pruritus was 37%, nausea and vomiting 25% and respiratory depression 3% ($PaCO_2$ >50 mmHg and/or respiratory rate <8).

A meta-analysis for a range of procedures, comparing IT morphine doses of <300 mcg, ≥300 mcg and placebo reported a greater risk of respiratory depression (respiratory rate <8–12) with the higher dose group of IT morphine (9%) with no increased risk with lower morphine dose (1%) when compared to systemic opioids (2%) (Gehling 2009a **Level I**, 28 RCTs, n=1,414). This difference was not statistically significant but this may reflect the relatively small number of patients in the higher dose group (n=87). The incidence of pruritus was increased for all doses (low dose RR 1.8; 95%CI 1.4 to 2.2 and high dose RR 5.0; 95%CI 2.9 to 8.6); the risk of nausea and vomiting was increased only in those patients given <300 mcg morphine.

In patients following major surgery, a 7.6% incidence of respiratory depression was reported in three RCTs (n=172) for IT morphine vs none in controls (IV PCA morphine) (OR 7.86; 95%CI 1.54 to 40.3) (Meylan 2009 **Level I**, 27 RCTs, n=1,205). In patients having minor surgery, major respiratory depression (endpoint "SpO2 85–90%" in addition to respiratory rate <12) occurred in 3 of 290 (1.0%) patients receiving IT bupivacaine alone and 15 of 410 (3.7%) receiving IT bupivacaine/morphine (OR 3.49 (95%CI 1.25 to 9.73) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). In the same analysis, the incidence of OIVI in patients receiving IT fentanyl (0.4%) was no different to control (0%). Thus, indirect comparisons suggest that the risk of OIVI is more pronounced with IT morphine than with IT fentanyl.

For Caesarean delivery, when IT opioids (all types of opioids and all doses) were combined with local anaesthetic for analgesia, the rate of respiratory depression was low and not significantly different from controls (Dahl 1999 **Level I**, 15 RCTs, n=535). In a large case series (n=1,915), clinically detected respiratory depression in the 24 h following 150 mcg IT morphine was noted in 0.26% of patients (Kato 2008 **Level IV**).

Overall, considering the increased risk of OIVI with IT morphine, the lowest effective dose of IT opioid should be used and surveillance for OIVI should continue for at least 18–24 h following a single dose (Bailey 1993 **Level IV**; Bujedo 2012 **NR**).

Pruritus

Pruritus is a frequent adverse effect of opioids by all routes. The rate following IT morphine is significantly higher than that for patients receiving IV PCA morphine (OR 3.85; 95%CI 2.40 to 6.15) (Meylan 2009 **Level I**, 27 RCTs, n=1,205). The itch is thought to be caused by stimulation of spinal and supraspinal mu-opioid receptors which includes the trigeminal nucleus and explains the frequency of facial itch (Kumar 2013 **NR**). The incidence of pruritus with IT morphine was 29.2% compared to 4.4% with bupivacaine alone (OR 6.92; 95%CI 4.51 to 10.6; NNH 4) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). IT fentanyl had an incidence of pruritus of 27.3% compared to 0% with bupivacaine alone. Pregnant women report greater rates of pruritus of 60–100%, which may be due to an interaction of oestrogen with opioid receptors (Kumar 2013 **NR**). While the incidence of pruritus is consistently high, the number requiring treatment is lower; in post-Caesarean delivery patients receiving 100 mcg IT morphine, 64% of patients reported pruritus with the proportion requiring treatment being 18% (Mikuni 2010 **Level II**, n=75, JS 3). In patients having Caesarean delivery under spinal anaesthesia, IT morphine 100 mcg was compared to oral opioid (oxycontin). The IT morphine group had similar overall pain scores but reported better satisfaction at 24 h and fewer high pain scores but experienced more pruritus (87 vs 56%) (McDonnell 2010 **Level II**, n=111, JS 5).

$5HT_3$-receptor antagonists decrease the incidence of pruritus related to IT opioids (OR 0.44; 95%CI 0.29 to 0.68; NNT=6) (Bonnet 2008 **Level I**, 15 RCTs, n=1,337). This analysis included a high number of Caesarean delivery patients, who reported higher rates of pruritus. In a subgroup analysis, the antipruritic effect was significant in the morphine group but not with fentanyl. A similar analysis based purely on Caesarean delivery patients receiving IT morphine did not identify a decrease in incidence in pruritus overall with prophylactic $5HT_3$ antagonists, but found a reduction in the incidence of severe pruritus and a NNT of 3 for reduction of established pruritus (George 2009 **Level I** [PRISMA], 9 RCTs, n=1,152). There is limited data and conflicting results regarding the use of opioid antagonists in treating pruritus following IT opioids. However, with parenteral opioids, overall IV naloxone reduces the incidence of pruritus (OR 0.40; 95%CI 0.21 to 0.79) and nausea (OR 0.62; 95%CI 0.43 to 0.89) but not vomiting (Murphy 2011 **Level I**, 8 RCTs, n=800). Other methods that have been described for prevention include nalbuphine (Charuluxananan 2003 **Level II**, n=240, JS 5), mirtazapine (an SSRI antidepressant) and dopamine antagonists such as droperidol (Kumar 2013 **NR**).

Other treatments for established pruritus include pentazocine, a mixed opioid agonist-antagonist with kappa receptor effects, which was more effective in treating pruritus post Caesarean delivery than ondansetron 4 mg (Tamdee 2009 **Level II**, n=208, JS 5). Diphenhydramine 25 mg has also been reported to be as effective as ondansetron 4 mg (Siddik-Sayyid 2010 **Level II**, n=113, JS 5).

Nausea and vomiting

Postoperative nausea is common after IT morphine, especially in obstetrics. Consensus guidelines exist for PONV management, however these do not address IT opioids specifically (Gan 2014). Following minor surgical procedures, the addition of IT morphine significantly increased the risk of nausea from 29.4–39.4% (OR 1.66; 95%CI 1.05 to 2.64; NNH 9.8) and vomiting to 26.2% (OR 1.88; 95%CI 1.20 to 2.94; NNH 10) compared to IT local anaesthetic with systemic analgesics (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338). Following major surgery, comparing IT opioids to systemic opioids there was a nonsignificant increase in the incidence of nausea (30.5 vs 24.2%; OR 1.22; 95%CI 0.77 to 1.95) and no difference in the incidence of vomiting (23.8 vs 22.6%; OR 1.05; 95%CI 0.63 to 1.73) (Meylan 2009 **Level I**, 27 RCTs, n=1,205).

Following Caesarean delivery with IT morphine and fentanyl, ondansetron and transdermal scopolamine were equally effective in reducing emesis from 59.3% (control) to 41.8% (ondansetron) and 40% (scopolamine), although scopolamine use was associated with more anticholinergic adverse effects (Harnett 2007 **Level II**, n=240, JS 4). The combination of

ondansetron with either dexamethasone or droperidol had a better antiemetic effect after gynaecological surgery with IT morphine compared with droperidol plus dexamethasone (Sanchez-Ledesma 2002 **Level II,** n=90, JS 4), although this combination was superior to either alone (Wu 2007 **Level II**, n=120, JS 5).

Urinary retention

The incidence of urinary retention was not increased in patients receiving IT morphine for major surgery (Gehling 2009b **Level I**, 28 RCTs, n=1,414; Meylan 2009 **Level I**, 27 RCTs, n=1,205); however, in patients having spinal anaesthesia for minor surgery, IT morphine increased the risk of urinary retention (OR 3.9; 95%CI 1.94 to 7.86; NNH 6.5) (Popping 2012 **Level I** [PRISMA], 65 RCTs, n=3,338).

Other adverse effects

In women in labour, reactivation of oral herpes simplex labialis was more frequent (38%) following IT morphine for labour analgesia than IV PCA morphine (16.6%) (Davies 2005 **Level II**, n=98, JS 4).

Cardiovascular effects of IT opioids have generally not been reported. In a retrospective cohort study, IT hydromorphone used in patients having elective colorectal resection with restricted fluid therapy found an higher rate of hypotension (mean arterial blood pressure <60 mmHg or systolic blood pressure <110 mmHg) in those receiving hydromorphone (4.3%) compared with the control group up to 12 h (Hubner 2013 **Level III-2**). This normalised by 24 h and was not associated with any identified adverse outcomes.

Caution has been advised regarding the use of IT opioids in patients who are at risk of spinal cord ischaemia (eg thoracic aortic stenting/surgery) (Fedorow 2010 **NR**), although its use has been described (Chaney 1996 **Level IV**). Such caution is based primarily on laboratory data although there is also a case report (Kakinohana 2003 **CR**).

5.7.1.4 Adjuvant medicines

A variety of adjuvant medicines have been used with IT analgesia, including clonidine, ketamine, neostigmine and midazolam. Many medicines are not licensed for use as spinal analgesic agents; however adequate evidence from the literature may make their use acceptable (for more detail see Chapter 4).

Clonidine

The addition of clonidine to IT morphine caused a small increase in duration of analgesia by 1.63 h (95%CI 0.93 to 2.33) and reduced the amount of systemic morphine consumption over 24 h by 4.45 mg (95%CI 1.40 to 7.49) (Engelman 2013 **Level I** [PRISMA], 7 RCTs, n=503). Incidence of hypotension was also increased (OR 1.78; 95%CI 1.02 to 3.12).

Magnesium

Magnesium most likely contributes to analgesia by acting as a noncompetitive NMDA-receptor antagonist in the spinal cord. Magnesium with opioid with or without local anaesthetic prolongs the time to first analgesia requirement in nonobstetric populations (SMD 1.38; 95%CI 0.6 to 2.11) but not obstetric patients (Morrison 2013 **Level I**, 15 RCTs, n=980). This may be an effect of fewer studies in the obstetric group. There is no increase in incidence of hypotension. There was a high degree of heterogeneity making any firm conclusion difficult.

Key messages

1. Intrathecal morphine improves analgesia and is opioid-sparing for up to 24 hours with a low risk of major adverse effects, especially following abdominal surgery (**S**) (**Level I** [PRISMA]).
2. After major surgery, the incidence of opioid-induced ventilatory impairment and pruritus is higher with intrathecal morphine compared with intravenous PCA opioids (**S**) (**Level I**).

3. There is an increase in the incidence of urinary retention (**N**) (**Level I**), nausea and vomiting with intrathecal opioids in comparison to systemic opioids for minor but not major surgery (**Q**) (**Level I**).
4. Pruritus with intrathecal opioids can be effectively managed with $5HT_3$ antagonists (**N**) (**Level I**).
5. The addition of intrathecal clonidine to intrathecal morphine results in slightly longer analgesia and reduced opioid requirements (**N**) (**Level I**).
6. The addition of intrathecal magnesium to opioids and/or local anaesthetics results in slightly longer analgesia in nonobstetric patients (**N**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids and the increase in adverse effects with higher doses suggests that the lowest effective dose (less than 300 mcg morphine) should be used (**Q**).

☑ Patients receiving intrathecal opioids should be monitored for opioid-induced ventilatory impairment for the anticipated duration of opioid effects, eg 18 to 24 hours after intrathecal morphine (**N**).

☑ Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**), however caution is recommended in patients who are at risk of spinal cord ischaemia **(N)**.

5.8 Other regional and local analgesic techniques

PNB has evolved with the widespread use of US-guided techniques. Some regional analgesic techniques provide effective postoperative pain relief but are associated with adverse effects not concordant with the requirements of modern perioperative surgical fast-track pathways. This partly explains the increased interest in wound and periarticular infiltration and catheter techniques.

5.8.1 Continuous and single-injection peripheral nerve blocks

CPNB refers to a technique where a catheter is inserted percutaneously adjacent to a peripheral nerve or plexus. Local anaesthetic, most commonly a low concentration of long-acting local anaesthetic, is given through the catheter to prolong the analgesic and other therapeutic effects beyond that of a single-injection technique. Indications for CPNB include treatment of acute postoperative pain, vascular insufficiency, chronic pain conditions and cancer-related pain. CPNB is used in hospital, ambulatory and in trauma settings (Ilfeld 2011a **NR**; Ilfeld 2011b **NR**).

CPNB improves analgesia and reduces opioid-related adverse effects (Richman 2006 **Level I**, 19 RCTs, n=603). Overall, when compared with single-injection PNB, CPNB techniques result in improved pain control, decreased need for opioid analgesics, reduced nausea and improved patient satisfaction during postoperative d 0–2 (Bingham 2012 **Level I**, 21 RCTs, n=702).

5.8.1.1 Upper limb

Interscalene and suprascapular nerve block

Compared with a single-injection interscalene block, a 2-d interscalene infusion at home after shoulder surgery was opioid-sparing, improved pain relief, sleep and patient satisfaction (Mariano 2009 **Level II**, n=32, JS 5). Compared to patients having single-injection interscalene block or general anaesthesia, patients receiving 48-h continuous interscalene block for outpatient rotator cuff repair surgery had improved pain scores at 7 d postoperatively (Salviz 2013 **Level II**, n=71, JS 3). Continuous interscalene block with ropivacaine 0.2% is more effective than ropivacaine 0.1% (Yang 2013 **Level II**, n=56, JS 4). Continuous interscalene nerve block compared with placebo following shoulder arthroplasty also reduced time to discharge

readiness and was associated with a greater degree of shoulder movement (Ilfeld 2006 **Level II**, n=32, JS 3).

Neuraxial or contralateral spread of local anaesthetic are recognised complications of interscalene block. Because of the potential proximity to the neuraxis, a test dose through an interscalene catheter should precede a continuous infusion. Permanent neurological injury has been reported following injection of local anaesthetic into the cervical spinal cord when an interscalene block was performed under general anaesthesia (Benumof 2000 **CR**).

Phrenic nerve block is the most common adverse effect of interscalene block. Strategies to reduce the likelihood or magnitude of phrenic nerve block include reducing the local anaesthetic dosage, injecting at the C7 level or utilising a different analgesic technique (Verelst 2013 **NR**). Suprascapular block can be employed for shoulder surgery without risk of phrenic nerve block and resultant dyspnoea. Suprascapular block resulted in reduced pain compared to placebo or subacromial local anaesthetic infusion (Jeske 2011 **Level II**, n=45, JS 4).

Other brachial plexus blocks

For continuous infraclavicular block, the incidence of insensate limb was higher when smaller volumes of 0.4% ropivacaine were used compared with higher volumes of 0.2%, despite no difference in the total amount (mg) of local anaesthetic used. There was no difference in analgesia but satisfaction scores were higher in patients who received the 0.2% infusion (Ilfeld 2009 **Level II**, n=50, JS 3).

There is no consistent evidence that continuous axillary analgesia (ropivacaine 0.1 or 0.2%) is better than placebo infusion following a single axillary brachial plexus injection of a long-acting local anaesthetic after hand surgery (Salonen 2000 **Level II**, n=60, JS 4). This is also true in comparison with continuous infraclavicular blocks (Mariano 2011 **Level II**, n=20, JS 3).

5.8.1.2 Lower limb

Regional anaesthesia techniques enable effective analgesia following lower limb surgery, however the potential for muscle weakness and the risk of inpatient falls following major lower extremity orthopaedic surgery is a concern. In an analysis of 191,570 total knee arthroplasty patients from over 400 hospitals in the USA, inpatient falls occurred in 1.6% and were associated with increasing age and a higher comorbidity burden, whereas PNB did not increase the risk (OR 0.85; 95%CI 0.71 to 1.03) (Memtsoudis 2014 **Level IV**); neuraxial anaesthesia reduced the risk of inpatient falls compared with general anaesthesia. In total knee arthroplasty, continuous lumbar plexus block was associated with an increased risk of inpatient falls compared with single-injection block or no block (OR 3.85; 95%CI 1.52 to 9.72; NNH 59) (Johnson 2013 **Level III-3**).

Femoral nerve block

Overall, FNB, either continuous or single-injection, following total knee arthroplasty in comparison with IV PCA analgesia alone, is associated with improved analgesia on movement, reduced morphine consumption and decreased incidence of nausea (Paul 2010 **Level I**, 23 RCTs, n=1,016). Compared with periarticular infiltration of local anaesthetic (LIA), continuous FNB for total knee arthroplasty resulted in reduced opioid consumption and improved functional indicators at 6 wk (Carli 2010 **Level II**, n=40, JS 4). A similar study (infiltration vs continuous FNB) noted no difference in opioid consumption; however, 37% of patients who received the FNB experienced quadriceps weakness compared to 0% in the infiltration group (Chaumeron 2013 **Level II**, n=60, JS 5).

For more information on any differences between the local anaesthetics used for FNBs see Section 4.4.2.

Fascia iliaca block

Single-injection fascia iliaca block provided similar postoperative analgesia to FNB following anterior cruciate ligament repair (Farid 2010 **Level II**, n=23, JS 3); likewise, single-injection fascia iliaca block provided similar postoperative analgesia to "3-in-1" nerve block following knee

joint arthroscopy and meniscal repair (Wallace 2012 **Level II**, n=60, JS 3). Continuous fascia iliaca block provided similar postoperative analgesia to continuous FNB over 48 h following total knee arthroplasty (Brisbane 2010 **Level II**, n=98, JS 2).

Adductor canal block

The saphenous nerve and branches of the obturator nerve are located in the adductor canal and block of both likely contributes to analgesia for knee surgery. An adductor canal block (also described as a saphenous nerve block) is utilised as an alternative to FNB because of concerns regarding quadriceps weakness associated with the latter. In volunteer studies, adductor canal block produced 8% loss of quadriceps strength compared with 49% with FNB (Jaeger 2013 **Level II**, n=12, JS 5); another study reported minimal loss of quadriceps strength compared to FNB (Kwofie 2013 **Level II**, n=16, JS 5). However, significant motor block may still infrequently occur following this technique (Chen 2014 **CR**).

Adductor canal block reduced opioid consumption and pain scores compared to placebo in the first 24 h following total knee arthroplasty (Hanson 2014 **Level II**, n=80, JS 5; Jenstrup 2012 **Level II**, n=75, JS 4; Grevstad 2014 **Level II**, n=50, JS 5); although a significant number of patients in the latter study had moderately severe pain. Adductor canal block had a minimal effect on quadriceps strength and was noninferior to FNB for analgesia over 8 h following total knee arthroplasty (Kim 2014 **Level II**, n=93, JS 5).

The combination of a saphenous nerve catheter and intermittent boluses compared with single-dose LIA improved pain relief and mobilisation on the day of surgery compared to local infiltration alone (Andersen 2013 **Level II**, n=40, JS 5); the benefits of the catheter technique did not extend to the day following surgery. The ideal technique including anatomical location and timing of placement of an adductor canal catheter for total knee replacement is not fully elucidated.

Sciatic nerve

After lower extremity surgery (Ilfeld 2002 **Level II**, n=30, JS 4) and foot surgery (White 2003 **Level II**, n=24, JS 5), continuous popliteal sciatic nerve analgesia resulted in better pain relief, lower opioid requirements and fewer adverse effects compared with opioids alone. The benefit of sciatic nerve block in addition to FNB for analgesia following total knee joint arthroplasty remains unclear (Paul 2010 **Level I**, 23 RCTs, n=1,016).

Lumbar plexus

Continuous FNB was compared to continuous posterior lumbar plexus block following total hip arthroplasty. There was no difference in postoperative pain scores, however patients who received FNB had more motor block impairing ambulatory function (Ilfeld 2011c **Level II**, n=50, JS 3). Lumbar plexus block resulted in a modest improvement in pain in the early postoperative period following hip arthroscopy (YaDeau 2012 **Level II**, n=84, JS 5).

5.8.1.3 Thoracic

Paravertebral block

PVB is a technique that is likely to benefit from US guidance because the landmark technique has been associated with a high proportion of misplaced catheters (Luyet 2012 **Level IV**), and US guidance can improve the needle trajectory (Abdallah 2014a **NR**). All forms of PVB combined (single-injection, multi-level injection and continuous infusion) demonstrate superior analgesia for up to 48 h following breast surgery than systemic analgesia, with a lower incidence of PONV (RR 0.26; 95%CI 0.13 to 0.5) and few specific adverse effects (Schnabel 2010 **Level I** [PRISMA], 15 RCTs, n=877). A further study confirmed an improved quality of recovery (Abdallah 2014b **Level II**, n=64, JS 5).

The use of PVBs in mastectomy is associated with reduction of persistent postsurgical pain at 6 mth (NNT 5) (Andreae 2012 **Level I** [Cochrane], 2 RCTs [PVB], n=89). These findings are reinforced by the results of recent studies. In patients receiving a multiday ambulatory continuous PVB there was reduced pain (primary end-point) and pain-related interference with physical and emotional functioning on the day following mastectomy (Ilfeld 2014 **Level II**, n=60, JS 5).

In a follow-up study, there was a reduced incidence of persistent postsurgical pain at 1 y in patients who received the ropivacaine infusion (13%) compared to those who received saline (47%) (Ilfeld 2015 **Level II**, n=60, JS 5); the patients who received the paravertabral infusion also had significantly lower scores on the brief pain inventory at 12 mth. In a similar study, patients receiving no PVB, vs single-injection block or continuous PVB had a similar incidence of persistent postsurgical pain at 3 and 6 mth but decreased intensity of chronic pain at rest 3 mth after mastectomy in the PVB groups (Karmakar 2014 **Level II,** n=177, JS 5); there were no statistically significant differences in outcome between groups who received a single-injection compared to a continuous technique (see also Section 1.4.5).

In thoracotomy patients, when compared to thoracic epidural analgesia, continuous thoracic PVB is as effective for pain relief with a better adverse-effect profile (less urinary retention, hypotension and nausea and vomiting) than epidural analgesia (Davies 2006 **Level I**, 10 RCTs, n=520); there was also a lower incidence of postoperative pulmonary complications. Similarly, in a comparison of different modes of analgesia for thoracotomy, paravertebral and epidural techniques provide superior analgesia to IT, interpleural, IC and systemic opioid techniques; PVBs result in less hypotension than epidural analgesia and reduce the incidence of pulmonary complications compared with systemic analgesia (Joshi 2008 **Level I**, 74 studies, n unspecified).

Intercostal and interpleural block

Following a single IC injection of 0.5% bupivacaine, segmental analgesia can last up to 20 h (Perttunen 1995 **Level II**, n=45, JS 2). Multilevel IC blocks (ICBs) improve analgesia compared with systemic opioids alone, particularly during the postoperative d 1 (Detterbeck 2005 **Level I**, 12 RCTs [ICB vs systemic opioids], n=477); pulmonary function tests are better preserved, although pulmonary complications are not consistently reduced. There are no consistent differences in analgesia outcomes for multilevel ICBs in comparison with epidural analgesia (Detterbeck 2005 **Level I**, 5 RCTs [ICB vs epidural], n=140), although duration of follow-up was not specified and individual studies were small.

Continuous local anaesthetic infusion analgesia can be achieved using a subpleural catheter placed in the space posterior to the parietal pleura alongside the paravertebral area, or more laterally in the IC region. Following posterolateral thoracotomy, patients receiving TEA had superior pain control compared to those receiving continuous subpleural analgesia (Debreceni 2003 **Level II**, n=50, JS 5; Kanazi 2012 **Level II**, n=42, JS 4). However, similar analgesia was achieved for up to 5 d with epidural compared to IC catheter local anaesthetic infusions (Luketich 2005 **Level II**, n=91, JS 3).

Multilevel US-guided IC nerve blocks provided superior pain relief for 24 h compared to systemic analgesics alone after percutaneous nephrolithotomy (Ozkan 2013 **Level II**, n=40, JS 5).

The incidence of pneumothorax following multilevel ICB has been estimated at 0.07% based on data from approximately 100,000 injections (n=10,941) (Moore 1975 **Level IV**).

Interpleural local anaesthetic infusion has not been found to be superior to systemic opioid analgesia in thoracotomy patients (Detterbeck 2005 **Level I**, 11 RCTs [interpleural], n=287). Interpleural analgesia (intermittent bolus injection technique) was compared to continuous TEA following minimally invasive thoracoscopic surgery (Ishikawa 2012 **Level II**, n=40, JS 1); pain scores were not different between the groups. Interpleural analgesia is superior to systemic analgesia following open cholecystectomy but not following laparoscopic cholecystectomy or nephrectomy (Dravid 2007 **NR**).

Pectoralis nerve block

Pectoralis nerve blocks have recently been described and refer to an US-guided block of the medial and lateral pectoral nerves. Pectoralis nerve blocks have been developed as a "less technical" and less invasive alternative to epidural and PVB for postoperative analgesia following breast surgery. Presurgical pectoralis block reduced postoperative pain scores for up to 24 h following modified radical mastectomy surgery, and decreased morphine consumption for up to 12 h (Bashandy 2015 **Level II**, n=120, JS 3).

Abdominal wall block

TAP block is used to provide analgesia following abdominal surgery. Originally described as a landmark technique at the lumbar triangle, TAP blocks are now usually performed with US guidance. In patients following Caesarean delivery, TAP block adds no analgesic benefit to IT morphine but, in the absence of IT morphine, TAP blocks improve analgesia compared to controls (Mishriky 2012 **Level I**, 9 RCTs, n=524). In patients undergoing laparoscopic surgery, US-guided TAP blocks reduce early pain scores (0–4 h) at rest (WMD -2.4/10; 99%CI -3.6 to -1.2) compared with a control group (De Oliveira 2014 **Level I**, 10 RCTs, n=633); late pain scores (24 h) were not significantly different. In paediatric laparoscopic appendectomy, TAP blocks offered no analgesic advantage over local anaesthetic infiltration (Sandeman 2011 **Level II**, n=116, JS 5).

TAP block analgesic outcomes in open abdominal surgery have been mixed. No benefit was found in gynaecological cancer surgery compared to systemic analgesia (Griffiths 2010 **Level II**, n=65, JS 5), inguinal hernia repair compared to local anaesthetic infiltration (Petersen 2013 **Level II**, n=90, JS 5), and gastrectomy (Wu 2013 **Level II**, n=90, JS 3), abdominal surgery (Rao Kadam 2013 **Level** II, n=42, JS 3) and laparoscopic colectomy compared to epidural analgesia (Niraj 2014 **Level II**, n=70, JS 3). However, compared to systemic analgesia alone, analgesia was improved in renal transplant donors (Parikh 2013 **Level II**, n=62, JS 4), renal transplant recipients (Soltani Mohammadi 2014 **Level II**, n=67, JS 5) and gastrectomy patients (Wu 2013 **Level II**, n=90, JS 3). The clinical significance of the results should be evaluated carefully on a surgery-specific basis.

Both landmark and US-guided TAP blocks have been complicated by liver trauma (Farooq 2008 **CR**; Lancaster 2010 **CR**). Landmark TAP block techniques are associated with a high rate of needle misplacement (McDermott 2012 **Level IV**).

Adjuvant agents to perineural blocks

Adjuvant agents to local anaesthetics are considered in other sections: eg alpha-2-agonists in Section 4.9.2 and corticosteroids in Section 4.12.2.

Needle and catheter localising techniques

Techniques used to precisely identify correct needle location and hence local anaesthetic and catheter placement include anatomic landmarks, peripheral nerve stimulation (PNS) and US guidance. Radiologic imaging and direct vision during surgery have also been used.

In comparison with PNS, blocks performed using US guidance are more likely to be successful (RR for block failure 0.41; 95%CI 0.26 to 0.66), faster to perform (mean 1 min less to perform with US), have faster onset (29% shorter onset time; 95%CI 45 to 12%) and longer duration (Abrahams 2009 **Level I**, 13 RCTs, n=941). US guidance vs all non-US techniques is associated with an increase in success rate of nerve blocks (RR 1.11 (95%CI 1.06 to 1.17) and vs PNS alone (RR 1.11, 95%CI 1.05 to 1.17) (Gelfand 2011 **Level I**, 16 RCTs, n=1,264). US-guided techniques, compared with other needle-localisation techniques, are associated with higher success rates, faster onset of block and lower vascular puncture rate (McCartney 2010 **Level I**, 25 RCTs, n=2,187). Duration of analgesia is longer with US-guided blocks than those performed with PNS guidance (SMD 25%; 95%CI 12% to 38%) (Abrahams 2009 **Level I**, 13 RCTs, n=941).

Perineural catheters

Stimulating catheters have been compared with nonstimulating catheter techniques in establishing continuous FNBs for postoperative analgesia following total knee arthroplasty. There was no difference in quality of postoperative analgesia between these two insertion techniques (Morin 2005 **Level II**, n=141, JS 3; Barrington 2008 **Level II**, n=82, JS 5). Stimulating catheters have also been compared with nonstimulating catheter techniques at other anatomical locations with inconclusive results (Rodriguez 2006 **Level II**, n=48, JS 3; Dauri 2007 **Level II**, n=70, JS 3; Stevens 2007 **Level II**, n=43, JS 4).

US guidance has been compared with stimulating and nonstimulating techniques for continuous infraclavicular brachial plexus block. The combination of US and nerve-stimulator guidance (with stimulating catheters) resulted in the highest primary success and reduced secondary catheter failure (Dhir 2008 **Level II**, n=66, JS 3). In the placement of popliteal sciatic nerve catheters, US guidance alone resulted in similar analgesic outcomes for up to 48 h

compared with US and PNS (stimulating catheter) guidance (Robards 2013 **Level II**, n=21, JS 3). In patients having total knee arthroplasty, the combination of US guidance and PNS (needle and/or stimulating catheter) was not different to US guidance alone in analgesic efficacy over 48 h (Farag 2014 **Level II**, n=437, JS 4); stimulating catheter use was associated with a longer procedural time.

Few RCTs have compared US guidance to traditional techniques for thoracic, paravertebral, IC, TAP, rectus sheath and ilioinguinal/iliohypogastric blocks (Abrahams 2010 **NR**).

5.8.2 Periarticular and intra-articular analgesia

The use of intra-articular infusions of bupivacaine with adrenaline has been cautioned against because of reports of glenohumoral chondrolysis following shoulder arthroscopy (Hansen 2007 **Level IV**; Bailie 2009 **Level IV**). The chondrotoxicity of bupivacaine has been supported by animal experiments (Gomoll 2006 **BS**). Intra-articular nsNSAIDs have demonstrated analgesic efficacy over systemic administration in some studies but the overall benefit is less clear (see Section 4.3.3.1).

An analgesic effect for intra-articular morphine following arthroscopy compared with placebo cannot be shown (Rosseland 2005 **Level I**, 46 RCTs, n=3,166).

5.8.2.1 Local infiltration analgesia

LIA refers to the systematic intraoperative injection of local anaesthetics in the periarticular and intra-articular regions. There have been many methodological issues in LIA studies including: lack of blinding, lack of placebo, lack of use of supplemental agents in controls (eg ketorolac), variable use of "top-up" catheters, inferior results with established techniques (peripheral nerve or epidural block) compared to the literature, the use of traditional recovery programs with low activity (limiting the assessment of therapies on early functional recovery) and inadequate pain assessment (Andersen 2014 **Level I**, 27 RCTs, n=1,644). Other limitations of LIA studies have included nonuniform use of both nonopioid and opioid analgesia across treatment groups, poorly defined multimodal analgesia therapies and mobilisation pathways (Kehlet 2011 **NR**). The role of nsNSAIDs introduced via LIA vs systemic administration is also unclear (see Section 4.3.3.3).

Total knee arthroplasty

Compared to placebo or no injection in total knee arthroplasty, LIA (with local anaesthetic in various combinations with NSAID, steroids, opioids, and epinephrine) was associated with reduced pain scores and reduced opioid consumption for up to 32 h (Andersen 2014 **Level I**, 7 RCTs [total knee arthroplasty LIA vs placebo/no injection], n=328); there was a high risk of bias with unbalanced systemic analgesic regimens between groups. In patients having bilateral arthroplasty, LIA improved pain outcomes compared to periarticular saline or placebo in the injected compared to the noninjected side (Andersen 2008 **Level II**, n=12, JS 4; Fajardo 2011 **Level II**, n=30, JS 2; Mullaji 2010 **Level II**, n=40, JS 5).

It is difficult to determine differences in analgesic outcomes when comparing FNB to LIA in total knee arthroplasty, with most studies reporting either equal analgesic efficacy or a short-term benefit of LIA (Andersen 2014 **Level I**, 5 RCTs [total knee arthroplasty LIA vs FNB], n=307; Ng 2012 **Level II**, n=16, JS 4; Ashraf 2013 **Level II**, n=50, JS 3). Once again the interpretation is hindered by the multitude of techniques, leaving the analgesic benefit of LIA *per se* unclear. LIA achieved similar mean readiness for discharge from hospital of 3.2 d compared to combined PCEA/FNB (Yadeau 2013 **Level II**, n=90, JS 3). A single-injection FNB when combined with epidural analgesia resulted in reduced pain compared to LIA during the first 24 h (Reinhardt 2014 **Level II**, n=94, JS 5).

LIA has superior analgesic outcomes compared to epidural analgesia (Andersen 2014 **Level I**, 3 RCTs [total knee arthroplasty LIA vs epidural], n=204); these trials had high risk of bias because of incomplete blinding and high heterogeneity due to different systemic analgesic regimens between groups. In patients receiving epidural analgesia, there was no added analgesic or functional benefit from LIA compared to placebo in the contralateral side for up to 14 d (Joo 2011 **Level II**, n=572, JS 5).

Total hip arthroplasty

In total hip arthroplasty, no additional analgesic benefit of LIA compared with placebo LIA (systemic multimodal analgesia) is identified (Andersen 2014 **Level I**, 10 RCTs [total hip arthroplasty], n=756). Compared with IT morphine and epidural analgesia, LIA was reported to have similar or improved analgesic efficacy. LIA did not reduce pain compared with placebo following bilateral hip arthroplasty (Andersen 2011 **Level II**, n=12, JS 4). Outcomes are inconsistent in comparison to IT morphine; LIA reduced postoperative opioid consumption (Essving 2011 **Level II**, n=50, JS 4), demonstrated no difference in opioid consumption (Kuchalik 2013 **Level II**, n=80, JS 5) and has been associated with similar pain scores but increased opioid consumption over 48 h (Rikalainen-Salmi 2012 **Level II**, n=60, JS 5).

5.8.3 Wound infiltration including wound catheters

Wound catheter local anaesthetic injections provide minor analgesic benefits up to 48 h and reduced hospital length of stay only in patients undergoing obstetric and gynaecological surgery but do not improve analgesic outcomes following abdominal or other nonorthopaedic (urological, plastic or thoracic) surgery (Gupta 2011 **Level I**, 32 RCTs, n unspecified); there was marked heterogeneity between studies. Continuous wound infiltration with ropivacaine compared to placebo leads to a significant reduction in pain scores and opioid consumption (Raines 2014 **Level I**, 14 RCTs, n=756). Abdominal wound catheter local anaesthetic infusions, in comparison to epidural analgesia, demonstrate equal analgesic efficacy for up to 48 h with a lower incidence of urinary retention (Ventham 2013 **Level I** [PRISMA], 9 RCTs, n=505); there was however considerable heterogeneity with variability in analgesic regimens, especially in the epidural arms. Overall, these new meta-analyses qualify a previous key message, which described improved analgesia (reduced pain scores [at rest and with activity], opioid consumption and improved other clinical outcomes) with wound catheter infusions in all surgical groups combined (cardiothoracic, general, gynaecology-urology and orthopaedics) (Liu 2006 **Level I**, 44 RCTs, n=2,141).

Infiltration of local anaesthetic into the scalp is used to treat postoperative pain following craniotomy. Preoperative scalp infiltration provides improved pain scores for up to 8 h postoperatively, with postprocedural infiltration improving analgesia for up to 12 h (Guilfoyle 2013 **Level I** [PRISMA], 7 RCTs, n=325).

Early postoperative abdominal pain is improved after laparoscopic cholecystectomy by the use of intraperitoneal local anaesthetic; the effect is better when given at the start of surgery compared with instillation at the end of surgery (Boddy 2006 **Level I**, 24 RCTs, n=1,256). Preperitoneal infusion of ropivacaine following colorectal surgery resulted in improved pain relief, opioid-sparing and earlier recovery of bowel function (Beaussier 2007 **Level II**, n=49, JS 5).

In laparoscopic gastric surgery, intraperitoneal local anaesthetic reduces postoperative abdominal pain intensity, the incidence of shoulder pain and opioid consumption (Kahokehr 2011 **Level I** [PRISMA], 5 RCTs, n=273).

5.8.4 Topical application of local anaesthetics

Topical EMLA® cream (eutectic mixture of lignocaine and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (Briggs 2003 **Level I** [Cochrane], 6 RCTs, n=343). When compared with EMLA® cream, topical amethocaine provides superior analgesia for superficial procedures in children, especially IV cannulation (Lander 2006 **Level I**, 6 RCTs, n=534).

Topical tetracaine, liposome-encapsulated tetracaine and liposome-encapsulated lignocaine are as effective as EMLA® cream for dermal instrumentation analgesia in the ED (Eidelman 2005 **Level I**, 25 RCTs, n=2,096) (see Sections 9.7.1 and 9.7.2 for use in children and Section 8.9.2 for use in the ED).

Topical local anaesthetic provides no analgesic benefit when performing flexible diagnostic nasoendoscopy, either alone or in combination with a vasoconstrictor (Conlin 2008 **Level I**, 8 RCTs, n=818; Nankivell 2008 **Level I**, 18 RCTs, n=1,356).

Intraurethral instillation of lidocaine gel provides superior analgesia to lubricating gel during flexible cystoscopy (Aaronson 2009 **Level I**, 4 RCTs, n=411).

Following tonsillectomy, local anaesthetics provide a modest reduction in post-tonsillectomy pain; administering the local anaesthetic on swabs appeared to provide a similar level of analgesia to that of infiltration (Grainger 2008 **Level I**, 13 RCTs, n unspecified).

Topical local anaesthetic gel and/or nebulised local anaesthesia of the nose and pharynx reduced pain associated with NGT insertion (OR 0.42; 95%CI 0.20 to 0.88) (Kuo 2010 **Level I**, 5 RCTs, n=212).

The lignocaine 5% patch may reduce acute pain intensity following herpes zoster once lesions have healed (McCarberg 2013 **NR**).

5.8.5 Safety

Regional anaesthesia techniques are widely practiced and when performed with due care carry a high degree of safety (Barrington 2009 **Level IV**; Barrington 2013 **Level IV**; Orebaugh 2012 **Level IV**). Nonetheless, when complications are reported, the consequences may be significant and need to be managed appropriately (Lee 2011 **Level IV**). Simple strategies such as preprocedural checklists, including block "time-out" and a "pause", may help reduce the incidence of these events (Mulroy 2014 **GL**).

5.8.5.1 Anticoagulation

Caution should be used when considering and performing some peripheral nerve or plexus blocks in patients with impaired coagulation (see Section 5.9.2).

5.8.5.2 Nerve injury

A new onset postoperative nerve injury regardless of severity is always of concern to patients and healthcare providers. Methods used to capture, define and report neurologic outcomes vary considerably. A multicentre registry using systematic postoperative contact with all patients reported the incidence of block-related nerve injury as 0.4/1,000 blocks (95%CI 0.08 to 1.1) (Barrington 2009 **Level IV**). A large single-institution database of 14,498 blocks identified four peripheral nerve injuries with sensory loss persisting for 6–12 mth, which were not able to be attributed to nonblock causes (≈0.3/1,000) (Orebaugh 2012 **Level IV**). A single-centre study reported the incidence of postoperative neurologic symptoms >6 mth duration as 0.9/1,000 (95%CI 0.5 to 1.7) (Sites 2012 **Level IV**).

Nerve injury may follow surgery independently of nerve block procedures. The baseline risk of nerve injury risk inherent to common elective orthopaedic surgical procedures is now better understood. After total knee arthroplasty, the all-cause incidence of perioperative nerve injury was 0.79%; however, this outcome was not associated with PNB (Jacob 2011b **Level IV**). Similarly, PNB following total hip (Jacob 2011a **Level IV**) and shoulder arthroplasty (Sviggum 2012 **Level IV**) was not associated with perioperative nerve injury. Observational studies consistently report that postoperative neurologic dysfunction is often related to patient and surgical factors and that the incidence of neuropathy directly related to peripheral regional anaesthesia is infrequent or rare (Barrington 2009 **Level IV**; Jacob 2011a **Level IV**; Jacob 2011b **Level IV**; Sites 2012 **Level IV**; Orebaugh 2012 **Level IV**; Sviggum 2012 **Level IV**).

5.8.5.3 Toxicity

US guidance has been shown to be associated with a reduced incidence of local anaesthetic systemic toxicity following PNB, with an incidence of 0.87/1,000 PNBs and no related deaths (Barrington 2013 **Level IV**). Analysis of 1,994 cases from the Pediatric Regional Anesthesia Network database indicates that TAP block has a low risk from local anaesthetic systemic toxicity in this patient population (Long 2014 **Level IV**).

Caution must be exercised with all regional techniques as case reports of adverse outcomes, including death, continue to occur (Vadi 2014 **Level IV**), even with local anaesthetic infusion catheters placed under direct vision (Calenda 2014 **CR**). This caution also applies to

newer techniques such as TAP block (Hessian 2013 **Level IV**; Griffiths 2013 **Level IV**) (see also Section 4.3.3).

5.8.5.4 Infection

The strongest recommendations for infection-preventive measures are effective hand hygiene and skin preparation with alcohol-based chlorhexidine solution; as per the UK epic2 National Guidelines (Pratt 2007 **GL**). These guidelines recommend full barrier precautions for central venous catheter placement (cap, mask, sterile gown and gloves; and large drape). Although specific data for aseptic technique in CPNB is lacking, advisories have been developed which advocate similar practices (Hebl 2011 **NR**). In a review of infections associated with CPNB, the use of full surgical-type aseptic technique for CPNB procedures was supported (Capdevila 2009 **NR**). Identified risk factors for local CPNB catheter inflammation include ICU stay, duration of catheter use >48 h, lack of antibiotic prophylaxis, axillary or femoral location and frequent dressing changes (Capdevila 2009 **NR**). The use of a chlorhexidine-impregnated patch designed to inhibit bacterial growth for days as a dressing after femoral nerve catheter insertion did not reduce the low rate of bacterial colonisation but showed a trend towards reduced local skin inflammation (2.1 vs 10.6%) in a most likely underpowered RCT (Schroeder 2012 **Level 2**, n=100, JS 3). Chlorhexidine was also the superior skin disinfectant prior to regional catheter insertion compared to povidone iodine (Krobbuaban 2011 **Level II**, n=100, JS); a positive skin culture immediately after skin disinfection occurred in 10 vs 35% resulting in an NNT of 4.

The implications of catheter-related sepsis in patients with implanted prosthetic devices (eg joint arthroplasty) are significant and therefore all reasonable measures should be taken to minimise the risk of infection. The widespread use of US guidance has introduced a potential risk related to contamination of the aseptic field by the US transducer. The use of a sterile disposable sheath over the US probe reduces this risk. Decontaminating US transducers with 70% isopropyl alcohol was effective at removing pathogenic organisms (Chuan 2013 **Level IV**).

Key messages

1. Topical EMLA® cream (eutectic mixture of lignocaine [lidocaine] and prilocaine) is effective in reducing the pain associated with venous ulcer debridement (**U**) (**Level I** [Cochrane Review]).
2. Paravertebral block provides superior analgesia for up to 48 hours following breast surgery when compared to systemic analgesia, with a lower incidence of postoperative nausea and vomiting (**N**) (**Level I** [PRISMA])
3. In thoracic surgery, compared with thoracic epidural analgesia, continuous thoracic paravertebral analgesia results in comparable analgesia but has a better adverse effect profile (less urinary retention, hypotension, nausea and vomiting) than epidural analgesia and leads to a lower incidence of postoperative pulmonary complications (**S**) (**Level I** [PRISMA]).
4. Continuous peripheral nerve block, compared with single-injection peripheral nerve block, results in improved pain control, decreased need for opioid analgesics, reduced nausea and improved patient satisfaction (**N**) (**Level I**).
5. Femoral nerve block, either single-injection or continuous, provides better analgesia and decreased nausea compared with parenteral opioid-based techniques after total knee arthroplasty (**S**) (**Level I**).
6. Compared with opioid analgesia, continuous peripheral nerve block (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**U**) (**Level I**).
7. Transversus abdominis plane blocks improve short-term analgesia compared to controls in Caesarean delivery and in laparoscopic surgery (**N**) (**Level I**).

8. Blocks performed using ultrasound guidance are more likely to be successful, faster to perform, with faster onset and longer duration compared with localisation using a peripheral nerve stimulator (**S**) (**Level I**).
9. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**U**) (**Level I**).
10. Following total knee arthroplasty, local infiltration analgesia reduces postoperative pain for up to 32 hours when compared to systemic analgesics alone (**S**); however, there is limited benefit in comparison to femoral nerve block (**N**) (**Level I**).
11. Following total hip arthroplasty, there is no additional analgesic benefit for local infiltration analgesia over conventional multimodal analgesia (**N**) (**Level I**).
12. Following either knee or hip arthroplasty, there is insufficient evidence to support the use of postoperative administration of local infiltration analgesia via catheter (**N**) (**Level I**).
13. Local anaesthetic injections through wound catheters provide analgesic benefits following gynaecological and obstetric surgery but not other nonorthopaedic surgery (**Q**) (**Level I**).
14. Intraperitonal local anaesthetic after laparoscopic cholecystectomy improves early postoperative pain relief (**N**) (**Level I**).
15. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**N**) (**Level I**).
16. The benefit of routine sciatic nerve block in addition to femoral nerve block for analgesia following total knee joint arthroplasty remains unclear (**N**) (**Level I**).
17. Continuous interscalene analgesia provides better analgesia, reduced opioid-related adverse effects and improved patient satisfaction compared with intravenous PCA or single-injection interscalene block after open shoulder surgery (**Q**) (**Level II**).
18. Adductor canal block provides postoperative analgesia that is noninferior to single-injection femoral nerve block for 8 hours and is associated with reduced quadriceps weakness **(N)** (**Level II**).
19. Lumbar plexus block results in similar pain scores following total hip arthroplasty compared to femoral nerve block; lumbar plexus block results in modest improvements in postoperative pain following hip arthroscopy (**N**) (**Level II**).
20. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**N**) (**Level IV**).
21. Postoperative neurologic dysfunction is often related to patient and surgical factors and the incidence of neuropathy directly related to peripheral regional anaesthesia is rare (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Continuous peripheral nerve blocks carry a risk of infection; skin preparation with alcohol-based chlorhexidine and full barrier precautions (including face masks) are recommended for insertion of peripheral nerve catheters (**N**).

☑ Ultrasound-guided techniques should be practiced with a high degree of skill and care, including aseptic techniques, as they do not eliminate the risks of injury to tissues and structures, local anaesthetic toxicity or site contamination (**N**).

5.9 Regional analgesia and concurrent anticoagulant medications

5.9.1 Neuraxial block and epidural haematoma

The low event rate of epidural haematoma means that evidence cannot be based on RCTs but must rely on data from case reports, case series and large audits. An ASRAPM Practice Advisory publication provides a good overview of and guidance on neurological complications of regional anaesthesia (Neal 2008 **GL**).

The population incidence of epidural haematoma following neuraxial block is possibly smaller than that of spontaneous epidural haematoma, however the rate in patients exposed to epidural anaesthesia is more appropriate for comparison. Between 1962 and 1992, 326 case reports of spontaneous epidural haematoma were published (Schmidt 1992 **Level IV**), while between 1906 and 1996 only 51 cases of epidural haematoma following epidural anaesthesia or analgesia were reported (Wulf 1996 **Level IV**).

Anticoagulation (present in 48% of cases) was the most important risk factor for epidural haematoma following insertion of an epidural needle/catheter, followed by coagulopathy (present in 38% of cases) (Wulf 1996 **Level IV**). This was confirmed by the series of epidural haematomas that followed epidural anaesthesia/analgesia in combination with inappropriate LMWH regimens in the USA, where the incidence was reported to be 1 in 3,000 (Horlocker 2003 **Level IV**).

In view of the increased risk with anticoagulation, the ASRAPM (Horlocker 2010 **GL**) and the European Society of Anaesthesiology (ESA) (Gogarten 2010 **GL**) published a number of consensus statements and recommendations on regional anaesthesia in patients receiving antithrombotic or thrombolytic therapy. Such statements should be viewed as "a panel of experts" best faith efforts to offer reasonable pathways to provide safe and quality patient care while allowing for clinical differences based on individual situations (Bergqvist 2003 **NR**). It is recognised that variances from recommendations outlined in the ASRAPM guidelines "may be acceptable based on the judgement of the responsible anesthesiologist" (Horlocker 2010 **GL**). That is, these guidelines will not substitute for an individual risk/benefit assessment of every patient by the individual anaesthetist.

The ASRAPM (Horlocker 2010 **GL**) and ESA (Gogarten 2010 **GL**) recommendations have not been updated since 2010, despite the fact that new information on both established and newly introduced anticoagulants has become available. Therefore the most relevant statements summarised below are based on these two guidelines and also subsequent guidelines developed for interventional spine and pain procedures jointly by ASRAPM, ESA, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society and the World Institute of Pain (Narouze 2015 **GL**). The guidelines they have formulated for intermediate-risk pain procedures are suggested to be transferable to neuraxial anaesthesia.

A combined summary of these guidelines is presented here (Horlocker 2010 **GL**; Gogarten 2010 **GL**; Narouze 2015 **GL**).

- *Antiplatelet medications* — nsNSAIDs including aspirin alone do not significantly increase the risk of spinal haematoma but should be regarded as a risk factor if combined with other classes of anticoagulants. In such situations, coxibs should be considered. Recommended time intervals between discontinuation of other antiplatelet medications (P2Y12 receptor inhibitors) and neuraxial block are 5-7 d for ticagrelor, 7 d for clopidogrel, 7–10 d for prasugrel and 14 d for ticlopidine. According to a draft version of the next guidelines by ASRAPM, prasugrel and ticagrelor can be restarted 6 h after removal of the epidural catheter (ASRAPM 2015 **GL**).
- *Unfractionated SC heparin* — thromboprophylaxis with SC heparin given twice-daily is not a contraindication to neuraxial block. To identify heparin-induced thrombocytopenia, a platelet count should be done prior to removal of an epidural catheter in patients who have had more than 4 d of heparin therapy. Epidural catheters should be removed a minimum of 8 h after the last heparin dose and not less than 2 h before the next dose.

Safety in patients receiving total daily doses of greater than 10,000 units or if doses are given more often than twice daily has not yet been established.

- *Unfractionated IV heparin* — intraoperative anticoagulation with IV heparin should start no sooner than 2 h after placement of the epidural or spinal needle. A bloody tap may increase the haematoma risk; a 24 h interval to unfractionated heparin commencement is then recommended. Careful patient monitoring should be continued postoperatively. Epidural catheters should be removed no sooner than 4 h after an IV heparin infusion has been stopped; however as higher doses of heparin increase its half-life (1–2 h), with higher doses normalisation of activated partial thromboplastin time should be awaited.
- *Low molecular weight heparin* — Epidural catheter placement should occur at least 12 h after standard prophylactic once-daily LMWH (enoxaparin) doses and at least 24 h after a therapeutic dose (1 mg/kg enoxaparin) or when dalteparin is used. The first postoperative dose of LMWH dose should be given 6–8 h after surgery and subsequent doses every 24 h. The epidural catheter should be removed at least 10–12 h after the last prophylactic dose of LMWH. Current guidelines disagree on time interval between removal and the next LMWH dose; 2 h were initially recommended (Horlocker 2010 **GL**). However, an FDA safety advisory from 2013, updated in 2015 (FDA 2015), increased this time interval to 4 h. The latest guidelines recommend a 12 h interval, based on the identification by the manufacturer of enoxaparin of a time interval of <12 h as one risk factor for epidural haematoma (Narouze 2015 **GL**). Concurrent administration of other medicines that may affect haemostasis (eg antiplatelet medicines) should be avoided. Renal impairment prolongs the effect of LMWH although only one of the guidelines suggests determination of antifactor Xa activity in patients with renal insufficiency (Narouze 2015 **GL**).
- *Oral warfarin* — Established warfarin therapy should be discontinued 5 d prior to neuraxial block and the INR normalised. Preoperative initiation of warfarin therapy requires an INR check prior to neuraxial block if a single dose of warfarin 5 mg was given >24 h preoperatively or a second dose was given. The INR should also be checked prior to removal of indwelling epidural catheters if warfarin was administered >36 h before. An INR <1.5 is estimated to be a safe level for removal, while an INR >3 requires withholding warfarin and waiting for normalisation or actively reversing warfarin to allow earlier catheter removal.
- *Fibrinolytics and thrombolytics* — Patients receiving fibrinolytic or thrombolytic medicines should not undergo neuraxial block except in exceptional circumstances; no data are available on a safe time interval after use of such medicines but at least 48 h is recommended. No definite recommendations are given for the removal of neuraxial catheters after initiation of such therapy, although determination of fibrinogen level might be a useful guide in such situations.
- *New oral anticoagulants (NOACs)* — The situation with regard to the newer anticoagulants remains unclear. Recommendations are to avoid neuraxial techniques while NOACs are taken and to use extreme caution after discontinuation. Discontinuation prior to neuraxial block is recommended for 3 d for rivaroxaban, 3–4 d for fondaparinux, 3–5 d for apixaban and 4–5 d for dabigatran. Intake of all NOACs can be recommenced 24 h after single-injection neuraxial block or removal of an epidural catheter, although a draft version of the next guidelines by ASRAPM suggests that rivaroxaban, apixaban and dabigatran can already be restarted 6 h after removal of the epidural catheter (ASRAPM 2015 **GL**).
- *Glycoprotein IIb/IIIa Inhibitors* — Discontinuation prior to neuraxial block is recommended for 5 d for abciximab and 24 h for eptifibatide and tirofiban. Readministration can occur 8–12 h after single-injection neuraxial block or removal of an epidural catheter.
- *SSRIs* — These antidepressants have an antiplatelet effect due to inhibition of serotonin-mediated platelet aggregation. The risk is regarded as low; however in patients at increased risk of bleeding (old age; advanced liver disease; concomitant use of aspirin, nsNSAIDs, antiplatelet agents or anticoagulants) discontinuation or a switch to other antidepressants may need to be considered according to one guideline (Narouze 2015 **GL**).

- *Herbal therapy* — Although garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), ginseng (*Panax* spp), dong quai (*Angelica sinensis*) and danshen (*Salvia miltiorrhiza*) have effects on haemostasis, there are currently no specific concerns about their use alone with neuraxial block. However, their combination with other anticoagulants or antithrombotics increases the risks. One of the guidelines recommends platelet function testing with high dose garlic alone (>1,000 mg/d) or danshen and ginkgo in combination with aspirin, nsNSAIDs or SSRIs (Narouze 2015 **GL**). Dong quai and danshen combined with warfarin require INR check.

5.9.2 Plexus and other peripheral regional block and anticoagulants

Significant blood loss or haematoma formation, rather than neurological deficit, seems to be the main risk when plexus or other regional blocks are performed in patients taking anticoagulant medications (Horlocker 2010 **GL**).

In a series of peripheral nerve blocks (6,935 blocks) for joint replacement (continuous lumbar plexus, continuous femoral and continuous or single sciatic block), with removal of the catheters at d 2 or 3 postoperatively, no perineural haematoma was found despite use of warfarin (50.0%), fondaparinux (12.8%), dalteparin (11.6%), enoxaparin (1.8%) and aspirin (23.8%) (Chelly 2008a **Level IV**). A case series (n=504) of patients receiving rivaroxaban 10 mg with a femoral catheter for total knee joint replacement *in situ* and removal 20 h after intake reported no cases of haematoma formation (Idestrup 2014 **Level IV**). However, a case series of bleeding complications after removal of femoral and sciatic catheters under LMWH suggests that caution is appropriate (Bickler 2006 **Level IV**; Horlocker 2010 **GL**).

For obvious reasons, deep blocks may be more at risk of bleeding complications than superficial blocks, where external compression is possible. Case reports of retroperitoneal haematoma after lumbar plexus block in conjunction with anticoagulation are published with either no neurological sequelae (Weller 2003 **CR**) or plexopathy (Klein 1997 **CR**). However, in a case series (n=670), where lumbar plexus catheters were removed in warfarinised patients (36.2% with an INR >1.4 [range: 1.5–3.9]), only one superficial bleeding event occurred (INR 3.0) (Chelly 2008b **Level IV**). Nevertheless, the ASRAPM guidelines conclude that recommendations for neuraxial block be followed for patients receiving deep plexus or peripheral blocks (Horlocker 2010 **GL**).

Key messages

1. Anticoagulation and coagulopathy are the two most important risk factors for the development of epidural haematoma after neuraxial block (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Consensus statements of experts guide the timing and choice of regional anaesthesia and analgesia in the context of anticoagulation but do not represent a standard of care and will not substitute the risk/benefit assessment of the individual patient by the individual anaesthetist (**U**).

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6. PATIENT-CONTROLLED ANALGESIA

PCA refers to methods of pain relief that allow a patient to self-administer small doses of an analgesic agent as required. Most often, the term PCA refers to programmable infusion pumps that deliver opioid medications IV, although many other methods and routes of delivery using opioids as well as other analgesic agents have been described (SC, epidural, IT, SL, IN, oral, pulmonary, and TD). In addition to treating postoperative pain, PCA is used for pain following trauma and with cancer.

For epidural PCA see Section 5.6.3; for regional PCA techniques see Section 5.8.1; for PCA use in labour see Section 10.1.2.3 and in children see Sections 9.5.2 to 9.5.4.

6.1 Efficacy of intravenous PCA

6.1.1 Analgesia, patient preference and outcomes

Opioid IV PCA for treatment of postoperative pain provides better analgesia than conventional (IM, SC) opioid regimens, although the magnitude of the difference in analgesia is small (differences: 8/100 for 0–24 h; 9/100 at 25–48 h; 13/100 at 49–72 h) (Hudcova 2006 **Level I** [Cochrane], 55 RCTs, n=3,861). Other findings are increased opioid consumption (7 mg morphine equivalents for 0–24 h; 95%CI 0.50 to 13) and no differences in duration of hospital stay or opioid-related adverse effects other than increased pruritus (RR 1.4; 95%CI 1.0 to 2.0). Patient satisfaction is higher, which may relate to increased autonomy (RR 1.26; 95%CI 1.1 to 1.5). There was heterogeneity of the PCA techniques used, with some studies using small doses and long lockout intervals. Studies were excluded from this review if NSAIDs or paracetamol were coadministered, a continuous background infusion was added or patients had chronic pain or chronic opioid use. In the majority of trials, the comparator was IM opioid, usually morphine.

In women having vaginal reconstructive surgery, IV PCA hydromorphone compared with nurse-administered hydromorphone, achieved lower pain scores on postoperative d 1 (MD 14/100) and used more hydromorphone (mean 1.8 vs 0.7 mg) (Crisp 2012 **Level II,** n=59, JS 3). Satisfaction and adverse effects were the same for both groups. In patients having supratentorial intracranial surgery, IV PCA fentanyl was compared with nurse-administered IV prn fentanyl in an ICU setting. The PCA group received more fentanyl and had lower pain scores (2.53/10 ± 1.96 vs 3.62/10 ± 2.11; p=0.039) than the prn group. There was no difference in adverse effects between groups (Morad 2009 **Level II**, n=64, JS 2).

In an ED setting, IV PCA was as effective as nurse-administered IV bolus doses of opioid in one RCT (Evans 2005 **Level II**, n=86, JS 3). In other RCTs, PCA morphine provided more effective analgesia and with more rapid onset and higher patient satisfaction than nurse-administered IV morphine (Rahman 2012 **Level II**, n=96, JS 3; Birnbaum 2012 **Level II**, n=211, JS 3).

Other information obtained from published RCTs as well as cohort studies, case-controlled studies and audit reports suggests that IV PCA may be appreciably more effective than intermittent IM opioid analgesia in a "real world" clinical setting; patients given IM opioid analgesia were more than twice as likely to experience moderate to severe pain and severe pain than those given PCA (Dolin 2002 **Level IV SR**, 165 studies, n≈20,000).

In settings where there are high nurse:patient ratios and where it might be easier to provide analgesia truly on-demand, conventional forms of opioid administration may be as effective as IV PCA. A comparison of PCA vs nurse-administered analgesia following cardiac surgery found no difference in analgesia at 24 h (a period when nursing attention is likely to be higher) but significantly better pain relief with PCA at 48 h (Bainbridge 2006 **Level I**, 10 RCTs, n=666).

The enormous variability in PCA parameters (bolus doses, lockout intervals and maximum permitted cumulative doses) used in many studies indicates uncertainty as to the ideal PCA program and may limit the flexibility, and thus the efficacy, of the technique. Individual PCA prescriptions may need to be adjusted if patients are to receive maximal benefit (Macintyre 2005 **NR**; Macintyre 2008 **NR**; Macintyre 2015 **NR**).

A number of studies have shown that PCA provides less effective pain relief compared with epidural analgesia (see Section 5.6.1.1).

6.2 Cost of PCA

The use of any analgesic technique, even if it is known to provide more effective pain relief, requires consideration of the cost involved. There is limited data on the economic assessment of PCA compared with conventional opioid analgesic techniques; information that is available often does not include the full scope of costs (eg cost of adverse effects or failure of an analgesic technique as well as the more obvious costs of pumps, disposables and nursing time). However, in general, PCA comes at a higher cost because of the equipment, consumables and medicine preparation; nursing time needed is much less (Jacox 1997 **NR**; Choiniere 1998 **Level II**, n=126, JS 3; Rittenhouse 1999 **Level III-2**; Chang 2004 **Level II**, n=125, JS 3). PCA was more cost-effective than epidural analgesia after major abdominal surgery (length of stay and morbidity excluded) (Bartha 2006 **Level III-2**). In a subsequent assessment, PCA costs were estimated by analysis of a large administrative database covering 500 USA hospitals (Palmer 2014 **Level III-3**, n=11,805,513). The direct and indirect cost estimates (USA$ in 2012) were assessed for the first 48 h after major surgery (knee and hip arthroplasty and open abdominal procedures). The cost estimates range from $196–243 per patient. Further estimates, adding in the costs of adverse effects of PCA programming errors, phlebitis and bacteraemia due to IV access, increased the costs to $342–389 per patient. (See also Section 3.3.)

6.3 Medicines used for parenteral PCA

6.3.1 Opioids

In general, there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of adverse effects between morphine and other opioids commonly used in PCA, although the results of individual studies are inconsistent. Most studies are not powered adequately to make conclusions about comparative safety.

On an individual patient basis, one opioid may be better tolerated than another and a change to an alternative opioid may be beneficial if the patient is experiencing intolerable adverse effects (Woodhouse 1999 **Level II**, n=82 [cross over], JS 4).

6.3.1.1 Morphine

Morphine is still a commonly used opioid for IV PCA (Palmer 2014 **Level III-2**). Compared with other opioids, morphine has a long equilibration half-life between plasma and the CNS effect site (2–3 h) (Lötsch 2005 **NR**; Aubrun 2012 **NR**). Furthermore, morphine has an active metabolite, M6G, which has opioid effects, with an equilibration half-life of 7 h and a long elimination half-life (Lötsch 2005 **NR**). Simulated peak effect site concentration for morphine occurs 8–24 h after commencement of PCA (Sam 2011 **Level III-3 PK**). These pharmacokinetic features may make morphine less suitable for IV PCA use than other opioids. Limited clinical data suggest that morphine may have a higher incidence of sedation and respiratory depression than fentanyl (Hutchison 2006 **Level III-2**).

6.3.1.2 Fentanyl

In general, there is limited evidence to show a difference between morphine and fentanyl in terms of pain relief or the incidence of most adverse effects (Howell 1995 **Level II**, n=37, JS 3; Woodhouse 1996 **Level II**, n=50, JS 5); pruritus was more common with morphine (Woodhouse 1996 **Level II**, n=50, JS 5). A retrospective cohort study of patients (n=241) having hip or knee surgery found those receiving PCA fentanyl, when compared with morphine or hydromorphone, had lower pain scores and fewer opioid-related adverse effects (PONV, sedation, pruritus or urinary retention) (Hutchison 2006 **Level III-2**). Fentanyl PCA compared with morphine PCA after cardiac surgery had a lower incidence of nausea (32 vs 52%) (Gurbet 2004 **Level II**, n=75, JS 3).

6.3.1.3 Tramadol

Tramadol by IV PCA has similar analgesic efficacy to other opioids via IV PCA, mainly compared with morphine (7 RCTs) (Murphy 2010 **Level I**, 12 RCTs, n=782). However, the adverse-effect profile is different with the tramadol group experiencing more PONV (OR 1.52; 95%CI 1.07 to 2.14)

but less pruritus (OR 0.43; 95%CI 0.19 to 0.98). There was no difference in sedation or fatigue. Data was insufficient to assess safety**.** Tramadol also has a lower risk of respiratory depression and less effect on gastrointestinal motor function compared with other opioids (see also Section 4.1.1.2).

6.3.1.4 Hydromorphone

There is limited data examining the use of hydromorphone when delivered by IV PCA. A survey of a large USA inpatient database (n=11,805,513) found that hydromorphone was the second most commonly used opioid (44% of patients) for PCA after morphine (Palmer 2014 **Level IV**). When compared with morphine, in patients having general surgery, there was no difference in adverse effects, pain relief or satisfaction (Hong 2008 **Level II**, n=50, JS 4). Hydromorphone and morphine IV PCA had similar rates of opioid-induced adverse effects, with fentanyl having the lowest in a retrospective comparison (n=254) of patients after hip or knee surgery (Hutchison 2006 **Level III-2**). In a comparison of IV PCA morphine with hydromorphone in patients having open abdominal surgery, analgesia was equivalent with similar adverse effects (Rapp 1996 **Level II**, n=61, JS 3). The morphine group had less cognitive impairment and the hydromorphone group had better mood. A study of patients having IV PCA for oral mucositis pain after bone marrow transplantation found that hydromorphone compared to morphine was equally effective for analgesia but hydromorphone had more frequent adverse effects (Coda 1997 **Level II**, n=119, JS 4). Safety issues have occurred due to confusion about the name of the medicine and its high potency (NSW Health 2011). (See also Section 9.5.5).

6.3.1.5 Oxycodone

Oxycodone IV PCA, when compared to morphine IV PCA, resulted in similar pain relief and adverse effects during the first 24 h after surgery (breast or spinal) (Silvasti 1998 **Level II,** n=50, JS 3). The dose requirements were similar. After laparoscopic hysterectomy, PCA oxycodone dose requirements were lower than with morphine (Lenz 2009 **Level II**, n=91, JS 4) with less sedation in the oxycodone group; pain scores were lower but only in the first hour after surgery and thereafter were similar. Compared to IV PCA tramadol after maxillofacial surgery, IV PCA oxycodone provided equivalent analgesia (Silvasti 1999 **Level II**, n=54, JS 3).

6.3.1.6 Pethidine

Compared with morphine, pethidine (meperidine) may lead to less effective pain relief on movement (Sinatra 1989b **Level II**, n=75, JS 4; Bahar 1985 **Level II**, n=48, JS 1; Plummer 1997 **Level II**, n=102, JS 4), no difference in nausea and vomiting (Bahar 1985 **Level II**, n=48, JS 1; Woodhouse 1996 **Level II**, n=50, JS 5; Stanley 1996 **Level II**, n=40, JS 5; Plummer 1997 **Level II**, n=102, JS 4) and less sedation (Sinatra 1989a **Level II**, n=75, JS 4) and pruritus (Sinatra 1989b **Level II**, n=75, JS 4; Woodhouse 1996 **Level II**, n=50, JS 5). Pethidine may cause more cognitive impairment than morphine (Plummer 1997 **Level II**, n=102, JS 4). Pethidine has a neurotoxic metabolite (norpethidine) that can accumulate during PCA administration and can cause adverse effects (Stone 1993 **Level IV**; McHugh 1999 **NR**; Simopoulos 2002 **Level IV**).

6.3.1.7 Methadone

Methadone by IV PCA, in comparison to morphine, provided more effective pain relief at rest and during movement for the first 24 h after surgery with no difference in adverse effects (Neto 2014 **Level II,** n=34 [trial discontinued prematurely], JS 4). It should be noted, that the pharmacokinetics of methadone are complex (and are not suited to IV PCA use in acute pain management) (Weschules 2008 **NR**). (See also Section 4.1.)

6.3.1.8 Other opioids

Piritramide was equally effective and had similar adverse effects compared to morphine (Dopfmer 2001 **Level II**, n=92, JS 5).

Remifentanil provided at least equivalent analgesia compared with morphine and fentanyl PCA and may be associated with less nausea and vomiting (Gurbet 2004 **Level II**, n=75, JS 3; Kucukemre 2005 **Level II**, n=69, JS 4).

6.3.1.9 Opioid combinations

The combination of two opioids in the PCA syringe has also been investigated.

There was no difference in pain scores and adverse effects between fentanyl/morphine and fentanyl by PCA, apart from slightly less nausea with the combination (Friedman 2008 **Level II**, n=64, JS 5).

Beneficial effects on pain relief and the incidence of pruritus in a comparison of morphine, nalbuphine and varying combinations of the two medicines were dependent on the ratio of medicines used (Yeh 2007 **Level II**, n=311, JS 5). The combination, when compared to morphine alone, provided improved analgesia and reduced nausea.

The combination of alfentanil/morphine resulted in no differences in pain relief or adverse effects compared with morphine alone, although patients who received alfentanil/morphine rated speed of onset and adequacy of analgesia as better (Ngan Kee 1999 **Level II**, n=80, JS 5). There was no improvement in pain-related sleep disturbance with this combination compared to fentanyl alone but analgesia, both at rest and movement, was better in the first 24 h after surgery (Lee 2013 **Level II**, n=212, JS 5).

Compared with tramadol alone, remifentanil added to tramadol improved pain relief but increased total opioid doses used (Unlugenc 2008 **Level II**, n=62, JS 4).

6.3.1.10 Adverse effects of PCA opioids

As noted in Section 6.1.1 above, meta-analyses and individual studies have shown that, in general, the risk of adverse effects is similar for all opioids administered by PCA, regardless of the opioid used. However, individual patients may be intolerant of specific opioids but tolerant of others (Woodhouse 1999 **Level II**, n=82 [cross over], JS 4).

A review of published RCTs as well as cohort studies, case-controlled studies and audit reports only, reported the following incidences associated with the use of PCA: respiratory depression 1.2–11.5% (depending whether respiratory rate or oxygen saturation were used as indicators), nausea 32%, vomiting 20.7% and pruritus 13.8% (Cashman 2004 **Level IV SR**; Dolin 2005 **Level IV SR**). Excessive sedation was not used as an indicator of respiratory depression in any of the studies included in these reviews (see importance of sedation score in Section 4.1).

The incidence of respiratory depression (<10 breaths/min) with PCA morphine was 0.06% (3 patients; n=5,137) and no patient required naloxone (Cheung 2009 **Level IV**). The incidence of nausea was 47.4% and vomiting was 18.5%; these were most common in female patients and those having gynaecological surgery. The incidence of pruritus was 8%.

In 1.86% (13 patients; n=700) of patients who received PCA for postoperative pain relief, respiratory depression (defined as a respiratory rate of <10 breaths/min and/or a sedation score of 2; defined as “asleep but easily roused”) was identified; of these 13 patients all had respiratory rates of <10 breaths/min and 11 also had sedation scores of 2 (Shapiro 2005 **Level IV**).

The combination of NSAIDs with IV PCA morphine reduces adverse effects compared to IV PCA morphine alone. Sedation is reduced by 29% and PONV by 30%, while respiratory depression, pruritus and urinary retention were not reduced (Marret 2005 **Level I**, 22 RCTs, n=2,307). In a more recent review, PONV was reduced significantly by the addition of NSAIDs (OR 0.70; 95%CI 0.53 to 0.88) (Maund 2011 **Level I**, 60 RCTs, n unspecified). These benefits are most likely due to the opioid dose-sparing effect of concurrent NSAIDs rather than a direct effect of NSAIDs themselves. Similar beneficial effects have also been found for the addition of ketamine IV via various regimens (Laskowski 2011 **Level I** [PRISMA], 70 RCTS, n=4,701), pregabalin (Zhang 2011 **Level I** [QUOROM] 11 RCTs, n=899), IV lignocaine (Sun 2012 **Level I** [PRISMA], 21 RCTs, n=1,108) and the alpha-2 agonists clonidine (19 RCTs) and dexmedetomidine (11 RCTs) by various administration regimens (Blaudszun 2012 **Level I** [PRISMA], 30 RCTs, n=1,792).

6.3.2 Adjuvant medicines

Discussion of adjuvant medicines in this section will be confined to those added to the PCA opioid solution. For additional information see Chapter 4.

6.3.2.1 Antiemetics

Droperidol added to the PCA morphine solution is effective in preventing nausea (NNT 2.7; 95%CI 1.8 to 5.2) and vomiting (NNT 3.1; 95%CI 2.3 to 4.8) with no apparent dose-responsiveness (Tramer 1999 **Level I**, 6 RCTs [droperidol], n=642). Adverse effects were not increased when the dose of droperidol was <4 mg/d. However, in a subsequent comparison of 0.5 mg, 1.5 mg and 5 mg droperidol added to 100 mg PCA morphine, the smallest dose had no significant antiemetic effect and the 1.5 mg dose was effective against nausea (NNT 6.3; 95%CI 3.3 to 100) but not vomiting (Culebras 2003 **Level II**, n=340, JS 4). The 5 mg dose significantly reduced both nausea and vomiting but at the cost of unacceptable sedation (NNH 6.4; 95%CI 4.1 to 15), which was not seen at the other doses. The 1.5 mg and 5 mg doses also reduced pruritus. There was no difference in dysphoric effects. In another study, droperidol 5 mg added to morphine 100 mg by PCA resulted in morphine-sparing and, in the first 24 h after surgery, reduced the frequency of PONV (Lo 2005 **Level II**, n=179, JS 5).

Droperidol given as a single dose at the end of surgery was as effective as adding droperidol to PCA morphine (Gan 1995 **Level II**, n=82, JS 3). The cost-benefit and risk-benefit of the routine addition of droperidol to PCA opioids must therefore be considered because all patients receive the medicine when not all will need it and some patients might receive inappropriately high doses of droperidol.

Evidence of benefit from the addition of $5HT_3$ antagonists to PCA is unclear. Ondansetron, given both as a bolus at the end of surgery and mixed with morphine in the PCA solution, reduced the incidence of nausea and the need for additional antiemetics but not the patients' perception of their overall satisfaction with care (Cherian 2001 **Level II**, n=81, JS 4). Adding ondansetron to PCA opioids reduces nausea and/or vomiting (NNT 2.9; 95%CI 2.1 to 4.7) (Tramer 1999 **Level I**, 2 RCTs [ondansetron], n=184). A later study showed that ondansetron given as an initial dose of 4 mg followed by 0.2 mg/1 mg morphine PCA morphine can reduce nausea and vomiting; although pain scores were higher (Boonmak 2007 **Level II**, n=160, JS4). The combination of ondansetron plus prochlorperazine to PCA morphine was more effective than ondansetron alone (Jellish 2009 **Level II**, n=150, JS 4).

Dexamethasone 8 mg given at the start of surgery reduced the incidence of severe nausea and vomiting only vs ondansetron at the end of surgery in patients receiving PCA fentanyl with added ondansetron (12 mg added to 2 mg fentanyl) (Song 2011 **Level II**, n=130, JS 4). The addition of midazolam to PCA morphine had a similar antiemetic effect to that of ondansetron but was associated with an increase in mild sedation (Huh 2010 **Level II**, n=90, JS 3).

6.3.2.2 Ketamine

When ketamine was added to the opioid in the PCA solution, analgesic benefits were found following thoracic surgery but not for orthopaedic and abdominal surgery, due in part to the heterogeneity of these studies and small sample sizes (Carstensen 2010 **Level I**, 11 RCTs, n=811). Increased dysphoric adverse effects were seen in two of eleven RCTs.

6.3.2.3 Naloxone

There was no analgesic benefit of adding naloxone to the PCA morphine solution (Cepeda 2002 **Level II**, n=166, JS 5; Sartain 2003 **Level II**, n=96, JS 5; Cepeda 2004 **Level II**, n=265, JS 5); with "ultra low doses" only (naloxone 0.6 mcg per 1 mg morphine 1 mg), the incidence of nausea and pruritus was decreased (Cepeda 2004 **Level II**, n=265, JS 5).

6.3.2.4 Other adjuvants

Ketorolac added to morphine (Chen 2005b **Level II**, n=79, JS 5; Chen 2009 **Level II**, n=102, JS 5) or tramadol (Lepri 2006 **Level II**, n=60, JS 3) by PCA did not improve pain relief or alter the incidence of adverse effects; however it was opioid-sparing and led to earlier return of bowel function

after colorectal surgery (Chen 2009 **Level II**, n=102, JS 5). The addition of lignocaine to morphine conferred no benefit in terms of pain relief or adverse effects (Cepeda 1996 **Level II**, n=195, JS 5).

The addition of clonidine to IV PCA morphine resulted in significantly better pain relief for the first 12 h only, and less nausea and vomiting compared with morphine alone; there was no reduction in morphine requirements (Jeffs 2002 **Level II**, n=60, JS 5). A combination of dexmedetomidine and morphine by IV PCA resulted in better pain relief (at rest and movement), significant opioid-sparing (29%) and a lower incidence of nausea compared with morphine alone (Lin 2009 **Level II,** n=100, JS 5). Adverse cardiovascular effects, sedation or respiratory depression were not increased in the dexmedetomidine plus morphine group.

Magnesium added to morphine was opioid-sparing and led to better pain relief (Unlugenc 2003 **Level II**, n=90, JS 3); added to tramadol it was opioid-sparing but only provided better pain relief for the first 2 h (Unlugenc 2002 **Level II**, n=66, JS 4).

Midazolam added to morphine PCA, in patients after spinal surgery reduced anxiety and provided a small reduction in the pattern of morphine consumption over time (Day 2014 **Level II,** n=29, JS 4). Sedation scores were not reported.

The addition of nalbuphine to PCA morphine resulted in reduced pruritus without affecting pain relief (Yeh 2008 **Level II,** n=311, JS 5).

6.4 Program parameters for IV PCA

6.4.1 Bolus dose

While the optimally sized bolus dose should provide good pain relief with minimal adverse effects, there are only limited data available concerning the effects of various dose sizes. In patients prescribed 0.5 mg, 1 mg and 2 mg bolus doses of morphine, most of those who were prescribed 0.5 mg were unable to achieve adequate analgesia, while a high incidence of respiratory depression was reported in those who received 2 mg (Owen 1989a **Level II**, n=21, JS 3). It was concluded that the optimal PCA bolus dose for morphine was therefore 1 mg.

Similarly, in patients prescribed 20, 40 or 60 mcg bolus doses of fentanyl, the larger dose was associated with an increased risk of respiratory depression and a conclusion was made that the optimal dose of fentanyl for use in PCA was 40 mcg (Camu 1998 **Level II**, n=150, JS 4). However in this study, each dose was infused over 10 min, which could alter the effect of that dose.

Four different demand doses of fentanyl (10, 20, 30 and 40 mcg) were assessed for the management of pain during changes of burns dressings. Pain relief was significantly better with the 30 mcg and 40 mcg doses; no patient became sedated or experienced nausea and vomiting (Prakash 2004 **Level II**, n=60, JS 2).

Rigid adherence to an "optimal" dose may not, however, lead to the best pain relief for all patients. If the prescribed dose is not "optimal" and not too small, the patient will be able to compensate to some degree by changing their demand rate. However, they will only compensate to a certain degree. Even if uncomfortable, patients may only average four demands/h, even though they could press the PCA button more frequently (Owen 1989a **Level II**, n=21, JS 3).

Initial orders for bolus doses should take into account factors such as a history of prior opioid use (see Section 10.6) and patient age (Macintyre 2008 **NR**; Macintyre 2015 **NR**); PCA morphine requirements are known to decrease as patient age increases (Macintyre 1996 **Level IV**; Gagliese 2008 **Level IV**). Subsequent bolus doses may require adjustment according to patient pain reports or the onset of any adverse effects. Even though the length of the lockout interval could allow it, patients may not increase their demand rate enough to compensate for bolus doses that are too small (Owen 1989a **Level II**, n=21, JS 3).

The number of demands a patient makes, including the number of "unsuccessful" demands, is often used as an indication that the patient is in pain and as a guide to adjusting the size of the bolus dose. However, there may be a number of reasons for a high demand rate other than pain. For example, excessive PCA demands may correlate with anxiety, poor perioperative

adaptation to surgery involving avoidance behaviour and intrusive thoughts, as well as high pain scores (Katz 2008 **Level IV**). See also Section 1.2.2 for additional information on the relationship between pain relief and psychological factors in PCA.

6.4.2 Lockout interval

The lockout interval is a safety mechanism that limits the frequency of doses delivered to the patient. For maximum safety it should be long enough to allow the patient to feel the full effect of one opioid dose before another dose can be delivered. However, if it is too long the effectiveness of PCA could be reduced. There were no differences in pain relief, adverse effects or anxiety when lockout intervals of 7 or 11 min for morphine and 5 or 8 min for fentanyl were used (Ginsberg 1995 **Level II**, n=78, JS 4).

6.4.3 Concurrent background (continuous) infusions

When a background infusion is used, opioid will continue to be delivered regardless of the patient's sedation level or respiratory status. The addition of a continuous background infusion significantly increases the risk of respiratory depression (OR 4.68; 95%CI 1.20 to 18.21) (George 2010 **Level I** [Cochrane], 14 RCTs, n=769); in 12 of the 14 RCTs, morphine was used. The risk was increased in adults in comparison to children (OR 10.2; 95%CI 3 to 35). The definition of respiratory depression in this meta-analysis was either respiratory rate ≤10, saturation ≤90% or $PaCO_2$ ≥50.

There is no good evidence to show that the addition of a background infusion to IV PCA improves pain relief or sleep or reduces the number of demands (Owen 1989b **Level II**, n=22, JS 2; Parker 1991 **Level II**, n=230, JS 3; Parker 1992 **Level II**, n=156, JS 2; Dal 2003 **Level II**, n=35, JS 3). In adults, the routine use of a background infusion is therefore cautioned against, although it may be useful in opioid-tolerant patients (see Section 10.6).

6.4.4 Dose limits

Limits to the maximum amount of opioid that can be delivered over a certain period (commonly 1 or 4 h) can be programmed into most PCA machines. There is no good evidence of any benefit that can be attributed to these limits (Macintyre 2015 **NR**).

6.4.5 Loading dose

There is enormous variation in the amount of opioid a patient may need as a "loading dose" and there is no good evidence of any benefit that can be attributed to the use of the loading dose feature that can be programmed into PCA machines. PCA is essentially a maintenance therapy, therefore a patient's pain should be controlled before PCA is started by administration of individually titrated loading doses (Macintyre 2008 **NR**; Macintyre 2015 **NR**). IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy in the treatment of acute sickle cell pain (Rees 2003 **GL**).

When administering IV loading doses of opioids, lipophilic medicines such as fentanyl are more appropriate than morphine for titrating analgesia because they equilibrate more quickly with the brain. While plasma and CNS fentanyl levels equilibrate within minutes, morphine takes many hours, which can lead to OIVI occurring well after a patient has been deemed "comfortable" and discharged from a high acuity area to a lower level area (eg PACU or ED to the ward) (Lötsch 2005 **NR**; Aubrun 2012 **NR**).

6.5 Efficacy of PCA using other systemic routes of administration

6.5.1 Subcutaneous PCA

Data on the effectiveness of SC PCA compared with IV PCA are variable and inconsistent. Both similar (Urquhart 1988 **Level II**, n=30, JS 1; White 1990 **Level II**, n=24, JS 5; Munro 1998 **Level II**, n=80, JS 3; Bell 2007 **Level II**, n=130, JS 3) and significantly better (Dawson 1999 **Level II**, n=100, JS 2; Keita 2003 **Level II**, n=40, JS 3) pain relief has been reported, as well as the same (Dawson 1999 **Level II**, n=100, JS 2; Urquhart 1988 **Level II**, n=30, JS 1; Munro 1998 **Level II**, n=80, JS 3; Keita 2003 **Level II**, n=40, JS 3) and a higher incidence of nausea and vomiting (White 1990 **Level II**, n=24, JS 5) or pruritus

(Bell 2007 **Level II**, n=130, JS 3). Compared with IV PCA, SC PCA may result in higher opioid use (Dawson 1999 **Level II**, n=100, JS 2; Urquhart 1988 **Level II**, n=30, JS 1; White 1990 **Level II**, n=24, JS 5; Bell 2007 **Level II**, n=130, JS 3) or may not (Munro 1998 **Level II**, n=80, JS 3).

6.5.2 Oral PCA

Oral PCA, using a modified IV PCA system, is as effective as IV PCA (Striebel 1998 **Level II**, n=64, JS 2). An oral PCA device has been developed that uses radiofrequency identification technology to allow patients in an oncology ward access (subject to a lockout interval) to a medication-dispensing system at the bedside (Rosati 2007 **Level IV**). Use of SL sufentanil tablets, dispensed by a computer-controlled PCA system, was compared with IV PCA morphine in patients having major open abdominal surgery or joint replacement surgery (Melson 2014 **Level II**, n=358, JS 3). The sufentanil group had equivalent analgesia compared with morphine, with more rapid onset, higher patient satisfaction and less sedation.

6.5.3 Intranasal PCA

IN PCA fentanyl can be as effective as IV PCA (Striebel 1996 **Level II**, n=50, JS 2; Toussaint 2000 **Level II**, n=57, JS 3; Manjushree 2002 **Level II**, n=40, JS 4; Paech 2003 **Level II**, n=24, JS 3), as is butorphanol (Abboud 1991 **Level II**, n=186, JS 2). As would be expected from the data on IN bioavailability of opioids (see Section 5.5.2), higher doses are needed via the IN route (Striebel 1996 **Level II**, n=50, JS 2; Manjushree 2002 **Level II**, n=40, JS 4). IN PCA pethidine is as effective as IV PCA pethidine, although larger doses are needed (Striebel 1993 **Level II**, n=112, JS 3), and more effective than SC injections of pethidine (Striebel 1995 **Level II**, n=44, JS 2). Diamorphine IN PCA (bolus doses of 0.5 mg) is less effective than IV PCA morphine (higher bolus doses of 1 mg were used) after joint replacement surgery (Ward 2002 **Level II**, n=52, JS 2) but provides better pain relief in doses of 0.1 mg/kg compared with 0.2 mg/kg IM morphine in children with fractures (Kendall 2003 **NR**) (see also Section 6.7.2.2 below).

6.5.4 Transdermal PCA

Iontophoretic TD fentanyl PCA provided analgesia superior to placebo but significantly more patients in the TD group withdrew because of inadequate analgesia compared to IV PCA morphine (Poon 2009 **Level I** [QUOROM], 6 RCTs, n=2,866).

There was no difference in patient global assessment.

Maximum blood concentrations of fentanyl were the same if the fentanyl patient-controlled TD patch was placed on the chest or upper outer arm but less if placed on the lower inner arm; the pharmacokinetics were not affected by gender, ethnicity, age or weight (Gupta 2005 **Level IV PK**) (see also Section 6.7.2.3 below).

6.6 Safety and complications related to PCA

Complications related to the use of PCA can be divided into operator or patient-related errors, and problems due to the equipment, practice environment or opioid used.

An early prospective study of 4,000 patients given PCA postoperatively found nine cases of respiratory depression. These were associated with drug interactions, continuous (background) infusions, nurse- or physician-controlled analgesia and inappropriate use of PCA by patients (Looi-Lyons 1996 **Level IV**). A similar sized prospective survey of 3,785 patients showed that use of PCA was associated with 14 critical events: 8 programming errors (all associated with the setting of a continuous infusion); 3 family members activating PCA; 1 patient tampering; and 3 errors in clinical judgment (Ashburn 1994 **Level IV**).

Analysis of data from the USA FDA's Manufacturer and User Facility Device Experience (MAUDE) database (n=2,009 events) shows that 76.4% of adverse effects related to IV PCA were attributed to technical problems with devices (eg frayed wires or cracks in syringes/ cartridges) and 6.5% were caused by operator error (Schein 2009 **Level IV**). Of these operator errors (n=131 events), most (81%) related to pump misprogramming and 48% were associated with patient harm. In contrast, only 0.5% of technical device problems resulted in patient harm.

A later retrospective analysis (from July 2000–June 2005) reported to a national voluntary medication error-reporting database (MEDMARX), showed that PCA-related medication errors continue (Hicks 2008 **Level IV**). Of 919,241 medication errors reported, 9,571 (1%) were associated with PCA. Of these, 624 (6.5%) were associated with patient harm. By comparison, only 1.5% of medication error reports in general led to harm. The majority of PCA errors occurred during administration of the medicine. Of these, 38% were errors in dose or quantity, 17.4% involved an omission and 17.3% were related to an unauthorised or wrong medicine; human factors were the main cause of errors; distractions (37.8%) and inexperienced staff (26.3%) were the leading contributing factors (Hicks 2008 **Level IV**). Overall, human factors were the leading cause of PCA errors.

The implementation of "smart pump" technologies may reduce the incidence and severity of PCA pump programming errors (Mai 2012 **Level III-3**; Ohashi 2014 **Level IV SR** [PRISMA], 22 studies, n unspecified). These technologies include the adoption of standardised and preselected medicine concentrations and dosages. Additionally, the extent of dose sizes is limited to safe ranges through the use of "soft" and "hard" limits.

The safety of PCA can be improved by the use of a hospital-wide safety improvement program (Paul 2010 **Level III-3**, n=25,198). A large prospective survey initially found that the incidence of errors with the use of PCA was 0.25%. Following the introduction of a safety improvement initiative, the incidence of PCA errors was reduced to 0.09% (OR 0.28; 95%CI 0.14 to 0.53).

The costs and rates of errors due to the use of IV PCA were estimated from two large safety-reporting databases in the USA (Meissner 2009 **Level IV**). The datasets included medication errors and device errors. The estimated average cost of a PCA adverse effect in the medication error dataset was USA$ 733, whereas the cost related to a pump error was USA$ 552. An error leading to patient harm cost 120–250 times more than a nonharmful error. The estimated annual error rates per 10,000 patients in the USA using PCA were 407 for PCA drug errors and 17 for PCA device errors.

The safety of PCA prescribing and patient observation may be improved by the adoption of a common and standardised form and process that incorporates human factors and safety triggers (Agency for Clinical Innovation 2014 **GL**).

For more detail on adverse effects due to the opioid administered, equipment used or operator and patient-related factors, see Sections 6.3, 6.7 and 6.8 respectively.

6.7 Equipment

Both programmable PCA pumps and disposable PCA devices are available.

6.7.1 Programmable PCA pumps

These types of pumps allow significant flexibility of use. Adjustments can be made to the dose delivered and lockout intervals, background infusions can be added and accurate assessments can be made of the total dose of medicine delivered. In addition, access to the syringe (or other medicine reservoir) and the microprocessor program is only possible using a key or access code.

All require disposable items eg generic or dedicated syringes or cartridges, antisiphon valves (to prevent siphoning of medicine from the medicine reservoir) and antireflux valves (to prevent backflow of medicine into the IV infusion line) (see Section 6.7.3).

6.7.2 Disposable PCA devices

There are a variety of disposable PCA devices.

6.7.2.1 Parenteral PCA devices

Disposable PCA devices are often based on the same physical principle; the volume of pressurised fluid delivered (dependent upon spring or elastomer technology) is determined by mechanical restrictions within the flow path and the speed of filling of the bolus dose reservoir determines the lockout interval (Skryabina 2006 **NR**). Advantages include small size

and weight, freedom from an external power source, elimination of programming errors and simplicity of use. Disadvantages include an inability to alter the volume of the bolus dose delivered or add a background infusion, difficulties accurately determining the amount of medicine the patient has received, the possibility of inaccurate flow rates, and long-term costs (Skryabina 2006 **NR**). There may also be security issues as the medicine reservoirs for these devices are more readily accessible.

6.7.2.2 Intranasal PCA devices

Metered-dose PCINA devices are available. The medicines must be administered in small volumes to avoid significant run-off into the pharynx.

Initial PCINA devices delivered sprays of a reasonable dose but large volume (eg 25 mcg fentanyl/0.5 mL) (Striebel 1993 **Level II**, n=112, JS 3; Striebel 1996 **Level II**, n=50, JS 2) or smaller volume but with smaller doses than commonly used with IV PCA (eg 9 mcg fentanyl/180 mcL (O'Neil 1997 **Level IV**). A specially formulated solution of 300 mcg/mL fentanyl has been used in a device that enables fentanyl doses of 54 mcg to be delivered in just 0.18 mL (Paech 2003 **Level III-1**).

6.7.2.3 Transdermal PCA devices

The iontophoretic TD PCA fentanyl system uses a low-intensity electric current to drive the medicine from the reservoir through the skin and into the systemic circulation (Banga 2005 **NR**). The IONSYS device, which is applied to the chest or upper outer arm, delivers a fixed dose of 40 mcg fentanyl over a 10-min period following a patient demand and allows delivery of up to 6 doses/h, up to a maximum of 80 doses in 24 h (Banga 2005 **NR**; Koo 2005 **NR**). This device must be replaced every 24 h and is designed for in-hospital use only.

After initial technical difficulties related to corrosion, the device has now been reapproved by the FDA for short-term use in hospitalised patients (FDA 2015).

6.7.3 Equipment-related complications

In general, modern PCA pumps have a high degree of reliability. However, problems continue to be reported as well as problems related to the disposable items required. Information regarding complications due to equipment problems is mainly case-series or report-based.

While the number of reports of "run-away" pumps, where the PCA pump unexpectedly delivers an unprescribed dose of medicine (Notcutt 1990 **Level IV**), has decreased following changes made to pump design, they continue to occur, including a report of spontaneous triggering (Christie 1998 **CR**) and of a frayed wire in the demand apparatus leading to triggering as a result of an electrical short circuit (Doyle 2001 **CR**).

Uncontrolled siphoning of syringe contents when the PCA machine was above patient level has been reported following cracked glass PCA syringes (Thomas 1988 **CR**; ECRI 1996 **CR**), failure of a damaged drive mechanism to retain the syringe plunger (Kwan 1995 **CR**), improperly secured PCA cassettes (ECRI 1995 **CR**) and broken medicine cartridge syringe (Doyle 2008 **CR**). To minimise the risk of siphoning, the use of antisiphon valves is recommended (ECRI 1996 **CR**).

Antireflux valves are essential if the PCA infusion is not connected to a dedicated IV line. The non-PCA infusion tubing should have an antireflux (one-way) valve upstream from the connection with the PCA line to prevent back-flow up the non-PCA line should distal obstruction occur; otherwise, inappropriate dosing can occur (Paterson 1998 **CR**; Rutherford 2004 **CR**).

In response to concern about problems with infusion pumps, including PCA pumps, in 2010 the FDA commenced the Infusion Pump Improvement Initiative. Areas for improvement included software, design of user interface, and mechanical and electrical defects (FDA 2010 **GL**).

6.8 Patient and staff factors

6.8.1 Patient factors

Patient factors play a role in the effectiveness of PCA as well as complications that can arise from its use; as for equipment issues, much of the information regarding complications due to patient factors is case-based. Psychological factors that may affect PCA use and efficacy are discussed in Section 1.2.2.

6.8.1.1 Education

Few controlled studies have evaluated the influence of information provision on PCA use. Of 200 patients surveyed who used PCA, approximately 20% were worried that they may become addicted, 20% felt that the machine could give them too much medicine and 30% that they could self-administer too much opioid (Chumbley 1998 **Level IV**). In a follow-up study, the same group conducted focus groups with previous PCA users, developed a new information leaflet and then undertook a randomised study comparing the old and new leaflet. They found that patients wanted more information on the medication in the PCA, the possible adverse effects and assurance that they would not become addicted (Chumbley 2002 **Level IV**).

Comparisons have been made between different forms of education given to patients about PCA and results are inconsistent. In an assessment of patient information delivered using structured preoperative interviews or leaflets compared with routine preoperative education, patients given leaflets were better informed and less confused about PCA and became familiar with using PCA more quickly but there were no effects on pain relief, worries about addiction and safety or knowledge of adverse effects; the structured preoperative interview resulted in no benefits (Chumbley 2004 **Level III-2**). Another comparison of structured education vs routine information showed that overall analgesic efficacy, adverse effects and recovery times were not affected by the education program (Lam 2001 **Level II**, n=60, JS 2). Patients who were shown a video on PCA prior to surgery had better knowledge about the technique and reported better pain control after surgery (Knoerl 1999 **Level III-2**; Chen 2005a **Level III-2**).

6.8.1.2 Inappropriate use of PCA

The safety of PCA depends on an adequate understanding of the technique by the patient and the fact that unauthorised persons do not press the demand button.

Oversedation with PCA has followed the patient mistaking the PCA handset for the nurse-call button, and family or unauthorised nurse-activated demands ("PCA by proxy") (Wakerlin 1990 **CR**; Fleming 1992 **Level IV**; Chisakuta 1993 **CR**; Ashburn 1994 **Level IV**; Sidebotham 1997 **Level IV**; Tsui 1997 **Level IV**).

There have been case reports expressing concerns that patients can use PCA to treat increasing pain and therefore mask problems such as compartment syndrome (Harrington 2000 **CR**; Richards 2004 **Level IV**), urinary retention (Hodsman 1988 **CR**), pulmonary embolism (Meyer 1992 **CR**) and myocardial infarction (Finger 1995 **CR**). However, appropriate routine patient monitoring should detect changes in pain scores and analgesic consumption enabling identification of such complications.

6.8.2 Nursing and medical staff

The information regarding complications due to nursing and medical staff factors is also case-based.

Of 9,571 PCA-related adverse effects, 69.8% were related to human factors (Schein 2009 **Level IV**). Improper dose and quantity was the most common factor in 38.9%.

As noted above, operator error is a common safety problem related to PCA use (Ashburn 1994 **Level IV**; Looi-Lyons 1996 **Level IV**). Misprogramming of PCA pumps is thought to account for around 30% of PCA errors, be twice as likely to result in injury or death than errors involving general-purpose infusion pumps and lead to more harm than errors in other types of

medication administration (ECRI 2006). Mortality from programming errors has been estimated to range from 1 in 33,000 to 1 in 338,800 patients prescribed PCA (Vicente 2003 **NR**).

A number of reports involve the programming of medicine concentrations that were lower than the concentration used, with the resultant delivery of an excessive amount of opioid leading to respiratory depression and sometimes death (ECRI 1997 **Level IV**; ECRI 2002 **Level IV**). The use of an incorrect prefilled "standard syringe" for PCA (morphine 5 mg/mL instead of the prescribed 1 mg/mL) also had a fatal outcome (Vicente 2003 **CR**). It has been suggested that medicine concentrations should be standardised within institutions to reduce the chance of administration and programming errors (ECRI 2002 **Level IV**).

PCA pumps using "smart pump" technology now incorporate dose error reduction systems (described in Section 6.2 above).

Inappropriate prescriptions of supplementary opioids (by other routes) and sedative medicines (including some antihistamines) can lead to oversedation and respiratory depression (Ashburn 1994 **Level IV**; Tsui 1997 **Level IV**; Lotsch 2002 **NR**).

6.9 PCA in specific patient groups

For PCA in the paediatric patient, the elderly patient, the patient with obstructive sleep apnoea and the opioid-tolerant patient, see Sections 9.5.2, 10.2, 10.4 and 10.6 respectively.

Key messages

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**U**) (**Level I** [Cochrane Review]).
2. Opioid administration by IV PCA leads to higher opioid consumption, a higher incidence of pruritus and no difference in other opioid-related adverse effects or hospital stay compared with traditional methods of intermittent parenteral opioid administration (**U**) (**Level I** [Cochrane Review]).
3. Patient satisfaction with intravenous PCA is higher when compared with conventional regimens (**U**) (**Level I** [Cochrane Review]).
4. Iontophoretic transdermal fentanyl PCA is not as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**U**) (**Level I** [QUOROM]).
5. When ketamine is added to the opioid in the PCA pump, benefits with regard to analgesia and adverse effects are limited to patients after thoracic surgery (**Q**) (**Level I**).
6. In settings where there are high nurse:patient ratios, there may be no difference in effectiveness of PCA and conventional parenteral opioid regimens (**N**) (**Level I**).
7. Tramadol via intravenous PCA provides effective analgesia comparable to morphine by intravenous PCA **(N) (Level I**).
8. The addition of a background infusion to intravenous PCA morphine increases the incidence of respiratory depression **(S) (Level I)** and does not improve pain relief or sleep, or reduce the number of PCA demands (**U**) (**Level II**).
9. There is little evidence that one opioid via PCA is superior to another with regards to analgesic or adverse effects in general; although on an individual patient basis, one opioid may be better tolerated than another (**U**) (**Level II**).
10. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however the incidence of nausea and pruritus may be decreased (**U**) (**Level II**).
11. Subcutaneous PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
12. Intranasal PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).

13. In the emergency department, PCA morphine compared with IV morphine administered by nursing staff, provides more effective analgesia with more rapid onset and with higher patient satisfaction (**N**) (**Level II**).
14. The safety of PCA use can be significantly improved by hospital-wide safety initiatives (equipment, guidelines, education, monitoring) (**N**) (**Level III-3**).
15. The adoption of "smart pump" technologies in PCA design can reduce programming errors and improve safety (**N**) (**Level IV SR**).
16. Operator-error remains a common safety problem with PCA use, in particular programming error, often leading to patient harm (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Adequate analgesia needs to be obtained prior to commencement of PCA. Initial orders for bolus doses should take into account individual patient factors such as a history of prior opioid use and patient age. Individual PCA prescriptions may need to be adjusted (**U**).
- ☑ The routine addition of antiemetics to PCA opioids is not encouraged, as it is of no benefit compared with selective administration (**U**).
- ☑ PCA infusion systems must incorporate antisiphon valves and, in nondedicated lines, antireflux valves (**U**).
- ☑ Drug concentrations, prescription and observation forms should be standardised to improve patient safety (**S**).
- ☑ The pharmacokinetics of morphine (long equilibration half-time and active metabolites) may make it less suitable for PCA use than other opioids (**N**).
- ☑ Pethidine when used in PCA may cause central nervous system toxicity due the accumulation of norpethidine (**N**).

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7. NONPHARMACOLOGICAL TECHNIQUES

7.1 Psychological interventions

The role of psychological interventions in the management of acute pain is generally seen as adjunctive to pharmacological and physical treatments but evidence for the positive value of their contribution is variable.

Psychological interventions can be grouped under a number of headings but they share some common features. Some of these features may also apply to pharmacological and physical interventions. Typically, the treatment provider is encouraged to firstly establish a degree of rapport with and acceptance by the patient. As well they need to give some information about the purpose and nature of the intervention and reasonable expectations the patient should hold for their outcome. These aspects may be seen as necessary to gain both the informed consent of the patient for treatment, as well as their active cooperation. Preoperative anxiety and heightened catastrophising play a role in the development of CPSP (Theunissen 2012 **Level III-2 SR**, 29 studies, n=6,628). Thus appropriately applied interventions to address both the psychological and medical/surgical modalities may lead to better outcomes than either alone.

Psychological interventions may be divided into four broad categories:

- information provision (procedural information, description of expected sensory experience or behavioural instructions) (see also Section 3.1.1);
- stress or tension reduction (relaxation and hypnotic strategies);
- attentional strategies; and
- cognitive-behavioural interventions.

It should be emphasised that these are rarely "stand-alone" interventions and elements of each may form a single intervention package.

7.1.1 Provision of information

Procedural information is information given to a patient before any treatment that summarises what will happen during that treatment. Here, four information factors were each associated with global evaluations of care by patients: surgical information, recovery information, general information and sensory information (Krupat 2000 **Level IV**, n=3,602).

Procedural information (often combined with behavioural instructions, like exercises or body positions) has been found to be effective in reducing pain reports in 3 of 7 RCTs and reducing pain medications in 7 of 12 RCTs (Johnston 1993 **Level I**, 38 RCTs, n=1,734). Preoperative education given prior to orthopaedic surgery may have some beneficial effects on patients' anxiety and knowledge but no effects on outcomes including pain, function or length of hospitalisation in studies of variable quality (Johansson 2005 **Level I**, 11 RCTs, n=1,044). Similar findings were reported in the setting of total knee or hip joint replacement (McDonald 2004 **Level I** [Cochrane], 9 RCTs, n=782); again no benefits other than a slight reduction of preoperative anxiety (WMD -5.64/100; 95%CI -7.45 to -3.82) were found. In support, an updated systematic review on the same population found a beneficial effect of education (centred on a biomedical model of anatomy as well as procedural information) on postoperative pain in only 1 of 13 studies (Louw 2013 **Level III-1 SR**, 12 RCTs and 1 study, n=1,021).

In contrast, one subsequent RCT in a different setting and using a different approach showed a dramatic effect of preoperative education on postoperative opioid requirements and pain intensity and duration after cosmetic day-surgery procedures (Sugai 2013 **Level II**, n=135). Preoperative education (two sessions by the same surgeon) on the adverse (nausea, vomiting) and negative effects of opioids (on endorphin production thereby leading to more and prolonged pain) resulted in 90% of the treatment group declining an opioid prescription (vs 100% filling their opioid prescription in the control group); the control group had average pain scores significantly greater than the experimental group and also a significantly longer duration of pain. (See Section 3.1.1 for further information.)

Sensory information is information that describes the sensory experiences that the patient may expect during treatment. Sensory information given alone has some positive, albeit inconsistent, effects compared with no instruction (Suls 1989 **Level III-3 SR**, 21 studies, n unspecified). With all but two studies involving adults, sensory information reduced self-rated pain more than procedural information; however, the effect sizes were variable. In contrast, a subsequent meta-analysis (7 RCTs [sensory information]), shows beneficial effect on pain in three RCTs and shows a reduction in use of pain medication in two of five RCTs (Johnston 1993 **Level I**, 38 RCTs, n=1,734).

Combined sensory-procedural preparatory information, when compared to procedural information and sensory information given alone, yielded the strongest and most consistent benefits in reducing negative affect, pain reports and other related distress (Suls 1989 **Level III-3 SR**, 21 studies, n unspecified). However, many studies relate to medical procedures such as pelvic examination or to experimental pain.

Multiple psychological interventions for acute pain after open heart surgery do not reduce postoperative pain intensity or enhance mobility but do improve postoperative mental distress in RCTs of low quality (Koranyi 2014 **Level I** [Cochrane] 19 RCTs, n=2,164). Interventions investigated include the provision of information about medical procedures and associated emotional responses and sensations before, during and after surgery, and instructions about how to adhere to medical advice to support the recovery, with teaching or instructing patients in different relaxation techniques or helping patients to understand their thoughts and feelings that influence their behaviour.

In some patients, especially those with an avoidant coping style, giving too much information or asking them to make too many decisions may exacerbate anxiety and pain (Wilson 1981 **Level II**, n=70, JS 2). However, later evidence suggested that this may not be a strong effect (Miro 1999 **Level II**, n=92, JS 3). Nevertheless, it may be useful to assess a patient's normal approach to managing stress to identify the best option for that patient. This concept is supported by the finding in patients undergoing colposcopy that stress related to the procedure was reduced when information was tailored to individual coping styles (Kola 2013 **Level II**, n=117, JS 2).

7.1.2 Stress and arousal reduction

7.1.2.1 Relaxation

Relaxation training usually involves teaching a patient ways to reduce their feelings of stress and/or arousal. Techniques used may be taught by audio recording or written or spoken instructions. The use of audio recording often includes the use of calming music or suitable imagery (mental pictures of relaxing scenes). Typically, all methods require the patient to practise the technique regularly, especially when feeling stressed. Some methods focus on altering muscle tension, often sequentially, while others focus on altering breathing patterns (eg emphasising releasing tension with exhalation). Relaxation techniques are closely related to, and often indistinguishable from, forms of meditation and self-hypnosis.

A systematic review of relaxation techniques, when used alone for the management of pain after surgery and during procedures, concluded that there was weak evidence to support the use of relaxation in these settings; three of the seven studies reported significant reductions in pain and distress (Seers 1998 **Level I**, 7 RCTs, n=362). Methodological shortcomings in the RCTs included in the review meant that a meta-analysis was not possible, limiting the strength of the findings. Similar conclusions were made in another systematic review, which found that eight of fifteen studies (again, most had weaknesses in methodology) demonstrated reductions in pain (Kwekkeboom 2006 **Level I**, 15 RCTs, n 1,269); the most supported methods were progressive muscle relaxation for arthritis pain and a systematic relaxation technique for postoperative pain. Little evidence was found for autogenic training (a relaxation technique) and no support for rhythmic breathing or other relaxation techniques. Another review of studies using relaxation techniques for burns pain (overlapping by one RCT, n=500) also found insufficient high-quality evidence to draw any conclusions but did recommend further research into the use of a technique that combined focusing on breathing and jaw muscle relaxation (de Jong 2006, **Level III-3 SR**, 11 studies, n=1,541). There was no difference found in pain

scores after surgery in patients given either relaxation training or routine information prior to spinal surgery; however, morphine use was higher in the relaxation group (Gavin 2006 **Level II**, n=47, JS 4).

A systematic review of studies (many with significant risk of bias; overlapping with the above by two and one study respectively) of preoperative mind-body therapy effects on postoperative outcome grouped studies according to three types of therapy (relaxation, guided imagery and hypnosis) (Nelson 2013 **Level III-1 SR**, 20 studies, n=1,297). Relaxation (8 studies) is partially supported for improvements in psychological wellbeing measures but has no effect on analgesic intake and length of hospital stay. Guided imagery (8 studies) has strong evidence for improvements in psychological wellbeing measures and moderate support for reducing analgesic intake. Hypnosis (4 studies) has partial support for improvements in psychological wellbeing measures (see also below). Overall evidence for the effect of mind-body therapies on physiological indices is limited, with minimal effects on vital signs and inconsistent changes in endocrine measures reported.

Studies of relaxation techniques with cancer patients (in acute pain) provides moderately strong support for its effectiveness in improving nausea, pain, pulse rate and blood pressure, as well as emotional adjustment variables (depression, anxiety and hostility) (Luebbert 2001 **Level I**, 15 RCTs, n=742).

7.1.2.2 Hypnosis

Hypnosis shares many features of relaxation with imagery and has a long history of use in acute pain conditions. Techniques vary but they have the common feature of one person responding to suggestions made by another regarding experiences involving changes in perception, memory and voluntary actions (Kihlstrom 1985 **NR**). The variable nature of hypnotic procedures has made it difficult to compare studies or draw general conclusions (Ellis 1994 **NR**), however systematic reviews examining studies of hypnosis in a range of acute pain conditions have been published.

Preoperative hypnosis was investigated as one of several methods to reduce postoperative pain in surgical patients; there is no effect on postoperative pain but partial support for improvements in psychological wellbeing measures (Nelson 2013 **Level III-1 SR**, 4 studies [hypnosis], n=144). Similarly, preoperative hypnosis in women having breast cancer surgery does not reduce postoperative pain but reduces perioperative distress (Holger 2012 **Level I**, 4 RCTs, n=550).

Hypnosis (six antenatal and one intrapartum intervention) has no effect on use of pharmacological pain relief in labour, rate of spontaneous vaginal birth or satisfaction with pain relief (Madden 2012 **Level I** [Cochrane], 7 RCTs, n=1,213).

Hypnosis for procedures in children reduces reported pain (SMD -1.4; 95%CI -2.3 to -0.5) and also distress scores (SMD -2.5; 95%CI -3.9 to -1.1) (5 RCTs, n=176) and behavioural measures of distress (SMD -1.2; 95%CI -1.8 to -0.5) (6 RCTs, n=193) (Uman 2013 **Level I** [Cochrane]**,** 39 RCTs, n=3,394). Analgesic benefits of hypnosis are confirmed in children undergoing cancer-related procedures (5 RCTs overlap) (Tome-Pires 2012 **Level I**, 10 RCTs [procedural pain], n=394) (see Section 9.7.5).

7.1.3 Attentional techniques

A range of attention-based strategies has been reported, from those involving distraction from the pain though to attention to imagined scenes/sensations or to external stimuli such as music, scenes or smells. Some techniques also involve deliberately attending to the pain but in ways intended to modify the threat value of pain (Logan 1995 **Level II**, n=330, JS 2). Attempting to alter the patient's emotional state, from distress or fear to relative comfort or peace, is also a common feature of many of these techniques. Commonly, these techniques are used in conjunction with relaxation methods and at times may be inseparable (Williams 1996 **NR**).

Music reduces acute pain (MD -0.51/10; 95%CI -0.87 to -0.15) (11 RCTs) and postoperative opioid requirements by 18.4% at 2 h (MD -1.0 mg; 95% CI: -2.0 to -0.2) (3 RCTs) and by 15.4% at 24 h after surgery (MD -5.7 mg; 95%CI -8.8 to -2.6) (5 RCTs) compared to unexposed

subjects. (Cepeda 2006 **Level I** [Cochrane], 51 RCTs, n=3,663). Music therapy may be either active or passive: active therapy is when the patient participates in creating sounds; in passive music therapy, the patient listens to recorded or live music. A systematic review of subsequently published RCTs on the effect of music therapy alone or combined with relaxation techniques for hospitalised patients confirmed that music has a positive effect on pain relief (15/17 RCTs) (Cole 2014 **Level I**, 17 RCTs, n=1,937). Seven RCTs were conducted in surgical patients. Music also has positive effects on other parameters including anxiety, muscle tension, blood pressure and heart rate. Similarly, music reduces pain in cancer patients moderately (SMD -0.59; 95%CI -0.92 to -0.27) (Bradt 2011 **Level I** [Cochrane], 30 RCTs, n=1,891). In children undergoing procedures, active and passive music therapy reduces pain and anxiety (Klassen 2008 **Level I,** 19 RCTs, n= 1,513). For details of the effects of attentional techniques on children see Section 9.7.5.

Virtual reality (VR) has led to reductions in pain unpleasantness and pain-related brain activity in volunteers using thermal pain stimulation and measuring pain-related brain activity with fMRI: where both opioids and immersive VR reduced pain and the combination was more effective than opioid alone (Hoffman 2007 **Level III-2 EH**). Immersive VR distraction has also been reported to provide effective analgesia in clinical situations (eg in burns patients) (Hoffman 2000 **Level III-2**; Das 2005 **Level III-2**; Hoffman 2011 **NR**).

There is some evidence that instructions to focus attention on the pain site, rather than shifting attention away from the pain, can alter pain perception but possibly mainly among subgroups of patients (Baron 1993 **NR**; Logan 1995 **Level III-2**; Haythornthwaite 2001 **Level II**, n=42, JS 1).

Mindfulness meditation is a type of attentional technique that includes attending to pain sensations. It has much in common with breathing-based relaxation techniques. This approach encourages the patient to deliberately experience their pain in a calm manner just like any nonpainful sensation (ie without judging it as good or bad), often while engaging in slowed breathing styles (Kabat-Zinn 2003 **NR**). This approach derives from ancient Buddhist methods. Mindfulness has been used in people experiencing chronic pain (McCracken 2007 **Level IV**).

Mindfulness/acceptance strategies for experimental pain compared to other emotion-regulation techniques are superior for pain tolerance (except for distraction) but not for pain intensity (Kohl 2012 **Level I EH** [PRISMA], 30 RCTs, n=2,085). Two subsequent RCTs have provided slightly conflicting findings. In healthy participants undergoing experimental pain (electric shock), both acceptance methods and suppression were equally effective and both were superior to a control condition in reducing pain and anxiety (Braams 2012 **Level II EH**, n=123, JS 3). In contrast, in healthy students, mindfulness was as ineffective as relaxation training in reducing experimental pain (with the cold-pressor method) (Sharpe 2013 **Level II EH**, n=140, JS 1).

There are no data on mindfulness or acceptance methods in the management of clinical acute pain. However, a clinical trial protocol on the use of preoperative mindfulness for total hip joint replacement has been published (Dowsey 2014).

7.1.4 Cognitive-behavioural interventions

Typically, cognitive-behavioural interventions involve the application of a range of behaviour-change principles, such as differential positive reinforcement of desired behaviours, identification and modification of unhelpful thoughts, and goal setting, in order to achieve change in targeted behaviours. In the context of acute pain this could include encouraging the appropriate use of the techniques outlined above.

Cognitive-behavioural methods focus on both overt behaviours and cognitions (thought processes) in patients but interactions with environmental factors are also often addressed. This means that interactions between patients and others, especially medical and nursing staff as well as families, may need to be addressed to support the desired responses in the patient. The latter may entail displaying a calm and reassuring manner and encouragement to persevere with a given task or procedure. Specific training in skills (eg relaxation and other coping strategies), other behavioural techniques (eg modelling and systematic

desensitisation), information provision and reconceptualisation of the experiences of the patient may also be provided as part of this approach.

Cognitive-behavioural interventions are usually aimed at reducing the distressing or threat value of pain and enhancing a patient's sense of his or her ability to cope with pain. In this context, coping usually refers to acceptance of pain rather than pain control or relief. Effective coping with pain may be reflected in minimal pain-related distress (eg reduced catastrophising) or disability (interference in normal activities). If patients are able to perceive their pain as less threatening, they might also evaluate their pain as less severe. But in this context reduced severity would be seen more as a by-product than as the primary goal.

Critically, in using cognitive-behavioural methods, the patient must be an active participant in the process, rather than a passive recipient, as he or she must apply the methods taught as needed.

7.1.4.1 Applying pain coping strategies within a cognitive-behavioural intervention

Some responses of patients to their pain may be helpful, others may not. For example, those who respond with overly alarmist (or catastrophising) thoughts tend to experience more pain and distress, compared with those who do not respond in this way (Jensen 1991 **NR**; Haythornthwaite 2001 **Level II**, n=42, JS 1; Sullivan 2001 **NR**). Identifying unhelpful responses, whether they are cognitive or behavioural, and changing these responses is a key feature of cognitive-behavioural interventions. Thus, identifying and reducing catastrophising thoughts about pain has become a key intervention within this approach, whether the pain is acute or persistent (Sullivan 2006 **Level III-2**). It has also been recognised that a given coping strategy may not always be useful and that this may depend upon circumstances and timing (Turk 2002 **NR**). For example, ignoring or denying the presence of pain may be useful when first injured (to reduce distress) but, if it means that appropriate help is not sought, it could place the person in danger or at risk of treatment for complications being delayed.

During preparation for surgery, or painful medical procedures, postsurgical pain and distress, patients found that training in cognitive coping methods and behavioural instructions in addition to relaxation training and procedural information, improved pain measures and reduced postoperative use of analgesics (Johnston 1993 **Level I**, 38 RCTs, n=1,734). These interventions were effective in achieving improvements in measures of negative affect, length of stay (not cognitive methods in this case) and recovery.

An early review of studies (randomised and nonrandomised) using cognitive-behavioural interventions in the treatment of procedure-related pain in children and adolescents concluded that cognitive-behavioural interventions may be considered a well-established treatment in this setting (Powers 1999 **NR**). Treatments included breathing exercises and other forms of relaxation and distraction, imagery and other forms of cognitive coping skills, filmed modelling, reinforcement/incentive, behavioural rehearsal and active coaching by a psychologist, parents, and/or medical staff member.

Another review included nonrandomised studies of behavioural interventions in the care of children and adolescents with cancer pain undergoing a wide range of cancer-related diagnostic and treatment procedures including bone marrow aspiration, lumbar puncture, venipuncture and chemotherapy (DuHamel 1999 **NR**; see also section 9.7.4). The behavioural interventions included hypnosis, relaxation, procedural information, distraction techniques, modifications of children's fears, anxiety and pain, contingency management, systematic desensitisation and behavioural rehearsal. Experience of pain during diagnostic and treatment procedures was included as an outcome measure in 9 of the 23 studies; all 9 studies found a clinically significant reduction in pain following behavioural intervention.

A further review examined the effectiveness of behavioural intervention methods in studies (randomised and nonrandomised) looking at the control of aversive adverse effects of cancer treatment, including pain (Redd 2001 **NR**). These authors concluded that although a variety of behavioural methods have been shown to reduce acute treatment-related pain, the methods are not equally effective and hypnotic-like methods, involving relaxation, suggestion and

distracting imagery, hold the greatest promise for pain management in acute treatment-related pain (Redd 2001 **NR**).

In subsequent studies, information plus training in coping strategies achieved the greatest pain reduction (35%) compared with information only, coping strategies only, and a control condition in adolescent patients following spinal fusion surgery for scoliosis (LaMontagne 2003 **Level II**, n=109, JS 3). The effect was found in those subjects aged 11–13 y, while in the 14–18 y age range no differences between interventions were found.

Pain coping skills training for patients with elevated pain catastrophising (eight sessions) awaiting total knee joint replacement reduced pain severity and catastrophising and improved function as compared to the usual care cohort (Riddle 2011 **Level III-3**). An RCT to confirm these results is planned (Riddle 2012).

Breast cancer patients undergoing surgery who received stress management training (mainly relaxation and coping skills) were less depressed and fatigued up to 3 mth post surgery but there were no differences for anxiety, pain and sleep problems compared to a usual care control group (Garssen 2013 **Level II**, n=70, JS 3).

The concept of a "back-café" after lumbar spinal fusion (over an 8-wk period, patients meet for three occasions in an informal way with a physical therapist to discuss coping and postoperative progress with other patients who have previously had lumbar spinal fusion) was compared to two other groups using either a training program or a video of exercise (Christensen 2003 **Level II**, n=90, JS 1). The "back-café" group had less pain (comparable to the video group), improved function, better return to work and less use of healthcare visits than the other groups at 2 y.

Different combinations of cognitive-behavioural components (at least two or more cognitive or behavioural strategies) for needle-related paediatric procedural pain did not yield any significant effects on pain (2 RCTs [cancer] and 1 RCT [initial venipuncture], n=250) or distress (3 RCTs [cancer], n=105) (Uman 2013 **Level I** [Cochrane], 4 RCTs [CBT], n=305).

Key messages

1. Listening to music produces a small reduction in postoperative pain and opioid requirement (**S**) (**Level I** [Cochrane Review]).
2. Distraction reduces pain (**Q**) (**Level I** [Cochrane Review]) and hypnosis reduces both pain and distress associated with needle-related procedures in children and adolescents (**S**) (**Level I** [Cochrane Review]).
3. Procedural information has no effect on postoperative pain (**Q**) (**Level I**), in particular when provided before joint replacement surgery (**Q**) (**Level I** [Cochrane Review]).
4. Active and passive music therapy reduces pain and anxiety associated with needle-related procedures in children (**N**) (**Level I**).
5. The evidence that sensory and combined sensory-procedural information is effective in reducing procedure-related pain is equivocal and not sufficient to make recommendations (**Q**) (**Level I**).
6. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative affect and analgesic use (**U**) (**Level I**).
7. Hypnosis is not effective in the management of postoperative and labour pain (**Q**) (**Level I**).
8. Evidence for any benefit of relaxation techniques in the treatment of acute pain is weak and inconsistent (**U**) (**Level I**).
9. Immersive virtual reality distraction is effective in reducing pain in some clinical situations (**U**) (**Level III-2**).

7.2 Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) reduces acute pain (procedural and nonprocedural) compared to no treatment (MD -19/100; 95%CI -27.3 to -10.8) (6 RCTs, n=413) and sham TENS (MD 24.6/100; 95%CI -31.79 to -17.46) (6 RCTs, n=376), with a higher proportion of participants achieving ≥50% reduction in pain (RR 3.91; 95%CI 2.42 to 6.32) (4 RCTs, n=157) compared to sham TENS (Johnson 2015 **Level I** [Cochrane], 19 RCTs, n=1,346). These results are limited by a high risk of bias due to inadequate sample sizes in the trials and unsuccessful blinding including the use of non-TENS-naïve patients. Minor adverse effects reported were mild erythema, itching and participants disliking the TENS sensation (7 RCTs).

After thoracic surgery (thoracotomy or sternotomy), TENS reduces pain intensity compared to sham TENS (thoracotomy -1.29/10; 95%CI -1.94 to -0.65; sternotomy -1.33/10; 95%CI -1.89 to -0.77) (Sbruzzi 2012 **Level I** [PRISMA], 11 RCTs, n=570). Although TENS was not more effective than a PVB in relieving pain or reducing PCA usage following thoracotomy procedures, it had fewer adverse effects (Baki 2015, **Level II,** n=40, JS 4).

In labour, TENS has no effect on pain, interventions or outcomes compared with sham TENS (10 RCTs) or routine care (7 RCTs), when applied to the back (13 RCTs, n=1,150) or cranium (2 RCTs, n=140), with the exception of a reduction in reports of severe pain when applied to acupuncture points (2 RCTs, n=190) (Dowswell 2009 **Level I** [Cochrane], 17 RCTs, n=1,466). These findings of no analgesic effect were confirmed by two subsequent meta-analyses overlapping by 14 RCTs (Bedwell 2011 **Level I**, 14 RCTs, n=1,456) and 3 RCTs (Mello 2011 **Level I**, 9 RCTs, n=1,076).

High-frequency TENS is effective in primary dysmenorrhoea (Proctor 2002 **Level I** [Cochrane], 7 RCTs, n=164).

Key messages

1. Transcutaneous electrical nerve stimulation (TENS) compared to sham TENS reduces acute pain (procedural and nonprocedural) (**N**) (**Level I** [Cochrane Review]), including pain after thoracic surgery (**N**) (**Level I** [PRISMA).
2. High-frequency transcutaneous electrical nerve stimulation is effective in primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
3. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour with the exception of a reduction of reports of severe pain when applied to acupuncture points (**Q**) (**Level I** [Cochrane Review]).

7.3 Acupuncture and acupressure

Acupuncture, originally a Chinese practice, involves inserting fine needles through the skin at specific points to cure disease or relieve pain. Electroacupuncture is a form of acupuncture where a small electric current is passed between pairs of acupuncture needles. Other techniques of stimulation of these points can also be applied eg by laser (laser acupuncture) or by pressure (acupressure). Acupuncture needling or acupressure can be applied to the specific points on the ears and this form of technique is called auricular acupuncture or auriculotherapy.

A significant amount of the literature is published in the Chinese language; these references were excluded from this assessment in line with the agreed methodology.

7.3.1 Postoperative pain

The effect of acupuncture on postoperative pain has been examined in different surgical procedures, such as heart, abdominal, orthopaedic, gynaecological and obstetric surgery.

Overall, acupuncture compared with sham controls reduces postoperative pain (at 8 and 72 h) and opioid consumption at 8, 24, and 72 h (at 72 h MD -9.14 mg; 95%CI -16.07 to -2.22) as well as nausea (not vomiting), sedation, pruritus and urinary retention (Sun 2008 **Level I**, 15 RCTs, n=1,166). There was wide variability in the types of surgery and acupuncture regimens

(including type of acupuncture, time of application and type and duration of stimulation) in the studies included in this review and the magnitude of benefit was small. A subsequent specific systematic review of auricular acupuncture (overlap 3 RCTs) for postoperative pain confirmed these findings demonstrating that acupuncture consistently reduces pain intensity (SMD 1.56; 95%CI 0.85 to 2.26) (8 RCTs) and analgesic use (SMD 0.54; 95%CI 0.30 to 0.77) (5 RCTs) compared to controls (sham auriculotherapy, placebo tablets or standard medical care) (Asher 2010 **Level I** [PRISMA], 8 RCTs [postoperative], n=551).

Similar findings were reported for a number of specific postoperative settings as outlined below.

7.3.1.1 General surgery

Combined pre-emptive acupuncture on body points and intraoperative acupuncture at the incision site for inguinal hernia repair reduced postoperative pain intensity at 0.5–6 h postoperatively as well as PCA requirements and dizziness (Taghavi 2013 **Level II**, n=90, JS 1). Pre and intraoperative electroacupuncture resulted in a late reduction in pain scores at postoperative d 4 and 7 only (Dias 2010 **Level II**, n=33, JS 5). For inguinal herniorrhaphy under spinal anaesthesia, preoperative acupuncture on body points enhanced intraoperative sedation and reduced postoperative pain intensity and opioid requirements (Parthasarathy 2009 **Level II**, n=50, JS 3). Intraoperative electroacupuncture for laparoscopic cholecystectomy (n=52) had no impact on pain, PCA use or PONV compared to no acupuncture (El-Rakshy 2009 **Level II**, n=107, JS 5).

Sustained acupressure with acuband after appendectomy was better than sham acupressure in relieving postoperative pain (Adib-Hajbaghery 2013 **Level II**, n=70, JS 3). One to two sessions of postoperative acupuncture also reduced pain scores after laparoscopic abdominal surgery (mean reduction 6.4/10 [SD 2.3]; p<0.0001) (n=25) (Kreindler 2014 **Level IV**).

7.3.1.2 Orthopaedic surgery

Acupuncture after back surgery reduces pain at 24 h (SMD -0.67; 95%CI -1.04 to -0.31) (Cho 2015 **Level I** [PRISMA], 5 RCTs, n=480). After ambulatory knee surgery, auricular acupuncture reduces ibuprofen requirements, but not pain intensity, compared to sham interventions (Barlow 2013 **Level I** [PRISMA], 4 RCTs [acupuncture], n=222). After total knee replacement, acupressure reduced analgesic usage and improved range of motion compared to sham control (Chang 2012 **Level II**, n=68, JS 5; He 2013 **Level II**, n=90, JS 5).

One session of postoperative acupuncture performed in PACU reduced pain after arthroscopic shoulder surgery on postoperative d 1 and improved sleep quality when compared with nonacupuncture control (Ward 2013 **Level III-1**).

Pre and intraoperative auricular pressure were also found to reduce fentanyl usage by 15% (p=0.008) and the incidence of nausea and vomiting when compared with a sham control after hip arthroplasty (Wetzel 2011 **Level II**, n=120, JS 5).

7.3.1.3 Cardiac surgery

Preoperative electroacupuncture administered 12–18 h before cardiac surgery (including myocardial revascularisation and valve replacement) reduced postoperative pain intensity (2.5/10 SD 1.1 vs 4.0/10 SD 2.0; p<0.04) and PCA fentanyl use by 41% (p<0.003) when compared with placebo control (Coura 2011 **Level II**, n=22, JS 5). Postoperative acupressure reduced pain intensity after cardiac surgery via median sternotomy and improved lung function when compared with acupressure to nonspecific points or no acupressure control (Maimer 2013 **Level II**, n=100, JS 5). When acupuncture was repeated daily for 7 d, the benefit for pain and lung function accumulated and improved over time (Colak 2010 **Level II**, n=30, JS 3).

7.3.1.4 Gynaecological and obstetric surgery

After hysterectomy, electroacupuncture improved postoperative analgesia over 24 h compared to control and sham acupuncture (Lee 2011 **Level II**, n=47, JS 3). Postoperative auricular electroacupuncture reduced pain at rest and on movement compared to control

and sham stimulation, when applied 24 h after hysterectomy (Tsang 2011 **Level II**, n=48, JS 5). After gynaecological surgery for malignancy, electroacupuncture was superior to traditional acupuncture in relieving pain initially but not at 48 h (Gavronsky 2012 **Level II**, n=20, JS 1). Auricular electroacupuncture did not affect pain or opioid requirements after laparoscopic gynaecological surgery (Holzer 2011 **Level II**, n=40, JS 5). In the only adult trial to employ electroacupuncture during surgery under general anaesthesia, no benefit compared to no acupuncture controls was demonstrated for pain, PCA opioid use or PONV after abdominal hysterectomy and laparoscopic cholecystectomy (El-Rakshy 2009 **Level II**, n=107, JS 5).

For oocyte retrieval, conscious sedation plus electroacupuncture reduces procedural and postoperative pain more than sedation plus placebo, or sedation alone (Kwan 2013 **Level I** [Cochrane], 6 RCTs, n=1,159). However when added to a paracervical block, procedural sedation achieved lower procedural pain scores than electroacupuncture (4 RCTs, n=781).

After Caesarean delivery, postoperative electroacupuncture and acupuncture reduced pain scores and PCA requirements for up to 2 h (Wu 2009a **Level II**, n=60, JS 3). Acupuncture for perineal pain after episiotomy reduced requirements for rescue analgesia compared to controls (Marra 2011 **Level III-1**).

7.3.1.5 Ear, nose and throat surgery

Electroacupuncture to auricular points or body points vs subthreshold stimulation reduced postoperative pain after tonsillectomy (Kager 2009 **Level II**, n=33, JS 3) and reduced episodes of nausea and vomiting after nasal septoplasty in adults (Sahmeddini 2010 **Level II**, n=90, JS 5).

7.3.1.6 Children and adolescents

Acupuncture has also been studied to treat postoperative pain in children and adolescents aged between 7 mth and 18 y. Intraoperative acupuncture reduced postoperative pain, agitation and analgesic use and time to first analgesic request after bilateral myringotomy and tympanostomy tube insertion compared to controls (Lin 2009 **Level II**, n=60, JS 3). One to two sessions of postoperative acupuncture reduced postoperative pain after tonsillectomy (Ochi 2013 **Level IV**) and in the ICU post spinal fusion and other surgery (Wu 2009b **Level IV**).

7.3.2 Other acute pain states

7.3.2.1 Emergency department and acute trauma setting

Auricular acupuncture improves pain relief over the control treatment for pain due to acute hip fracture (1 RCT), acute biliary colic (1 RCT) and acute burn and acute emergency conditions (SMD 1.35; 95%CI 0.08 to 2.64) (2 RCTs, n=111) (Asher 2010 **Level I** [PRISMA], 4 RCTs [acute pain], n=197). Compared with sham control, acupuncture significantly reduced pain on movement in bed and cough after rib fracture but not pain on deep breathing (Ho 2014 **Level II**, n=58, JS 5).

In the ED, acupuncture reduced pain (by 2.3/10) and nausea (by 1.2/6) in patients with acute pain (n=400 [59% musculoskeletal, 25% abdominal pain]) compared to retrospectively matched controls, with a high satisfaction rate (98%) (Zhang 2014 **Level III-3**). Acupuncture treatment provided before medical consultation reduced the staff time spent managing the patient, when compared with acupuncture given after medical consultation. In eight cases of acute pain due to sports injury, athletes had significant pain reduction (4–8/10) after auricular acupuncture treatment (deWeber 2011 **Level IV**).

Acupressure performed during prehospital transport led to better pain relief after hip fracture (Barker 2006 **Level II**, n=38, JS 5) and radial fracture (Lang 2007 **Level II**, n=32, JS 5) compared to sham acupressure, and after minor trauma compared to sham and no acupressure (Kober 2002 **Level II**, n=60, JS 5).

7.3.2.1 Acute back pain

Compared to sham acupuncture, one session of acupuncture reduces pain intensity (MD 9.38/100; 95%CI -17.00 to -1.76) (2 RCTs, n=100) but not function or disability in acute back pain (3 RCTs, n=148) (Lee 2013a **Level I** [PRISMA], 11 RCTs, n= 1,139). Slightly more patients improved with acupuncture than NSAIDs (RR 1.11; 95%CI 1.06 to 1.16) (5 RCTs, n=662).

In a large well-designed RCT, five sessions of acupuncture over 14 d were added to conventional treatment for acute low-back pain (Vas 2012 **Level II**, n=275, JS 5); acupuncture was more effective in reducing pain and analgesic use and improving work readiness compared to conventional treatment alone but there was little difference between real acupuncture, sham acupuncture (penetrating) and placebo acupuncture (nonpenetrating) groups. One session of acupuncture with concurrent gentle exercise produced better analgesia for acute low-back pain accompanied by severe disability (Oswestry Disability Index [ODI] value ≥60%) than diclofenac (75 mg IM) (Shin 2013 **Level II**, n=58, JS 3). Patients in the acupuncture group had less pain at 30 min after treatment (MD 3.12/10; 95%CI 2.26 to 3.98), much improved function (decreased ODI by 33%; 95% CI 27 to 39) and fewer hospital admissions (66 vs 93%). The pain reduction was maintained at the 2-wk and 4-wk follow-ups.

The NICE clinical guideline *Low Back Pain: Early Management of Persistent Non-specific Low Back Pain* recommends acupuncture as a treatment for acute back pain; the acupuncture treatment was defined as needling technique with 10 sessions over 12 wk (NICE 2009 **GL**).

7.3.2.2 Labour pain

Acupuncture and acupressure reduce pain, use of pharmacological pain relief and Caesarean delivery rates and increase satisfaction with pain management in a range of comparative trials vs standard care or placebo interventions (Smith 2011a **Level I** [Cochrane], 13 RCTs, n=1,986). However, a critical review (Levett 2014 **NR**) of this and another meta-analysis (Cho 2010b **Level I**, [PRISMA], 10 RCTs, n=2,038) suggests that these meta-analyses may compare very different approaches in very different settings, in particular by comparing trials of efficacy with trials of effectiveness. Two subsequent RCTs confirmed that women who had electroacupuncture had shorter labour duration and were less likely to have epidurals (Mucuk 2013 **Level II**, n=120, JS 1; Vixner 2014 **Level II**, n=303, JS 3); in the latter RCT, electroacupuncture was better than manual acupuncture and standard care. (See also Section 10.1.2.)

7.3.2.3 Dysmenorrhoea

Acupuncture (6 RCTs), acupressure (4 RCTs) (Smith 2011b **Level I** [Cochrane], 10 RCTs, n=944) and acupoint stimulation (Chung 2012 **Level I,** 25 RCTs, n=3,109) may reduce pain in primary dysmenorrhoea compared to placebo control, NSAIDs and Chinese herbal medicine. A subsequent meta-analysis also supports analgesic benefit vs no treatment (WMD 2.3/10; 95%CI 1.6 to 2.9) (Kannan 2014 **Level I** [PRISMA], 2 RCTs [acupuncture vs no treatment], n=46). The main drawback of all RCTs included in these meta-analyses is the poor methodology and conclusions are thus consistent with a previous meta-analysis that concludes: "The evidence for the effectiveness of acupuncture for the treatment of primary dysmenorrhoea is not convincing compared with sham acupuncture" (Cho 2010a **Level I** [PRISMA], 10 RCTs, n=2,038). A subsequent large RCT demonstrated that electroacupuncture on points specific for dysmenorrhoea achieved minor (clinically insignificant) differences in pain scores than the same stimulation applied to nonspecific points (-4.0/100; 95%CI -7.1 to -0.9) and nonacupuncture point (-4.0/100; 95%CI -7.0 to -0.9) (Liu 2014 **Level II**, n=501, JS 5).

7.3.2.4 Dental pain

A previous meta-analysis showed that acupuncture may be useful for pain during dental procedures (Ernst 1998 **Level I**, 16 RCTs, n=941). Acupuncture reduced dental pain from 6.6/10 to ≈1.0/10 in an ED case series, with 119/120 patients responding (Grillo 2014 **Level IV**).

7.3.2.5 Acute neuropathic pain

In severe pain due to acute herpes zoster (NRS >7/10), acupuncture was as effective as standard pharmacological treatment (pregabalin, local anaesthetics and TD buprenorphine or oral oxycodone) at 4 wk (Ursini 2011 **Level II**, n=102, JS 3).

7.3.2.6 Headache

Acupuncture provides clinically relevant improvement in pain for TTH over 3 mth compared to standard care (2 RCTs, n=1,205) but only minimal clinical improvement compared to sham

treatment (5 RCTs, n=753) (Linde 2009b **Level I** [Cochrane], 11 RCTs, n=2,317). Similarly, acupuncture has prophylactic effects in migraine over 3–4 mth, superior to no treatment or routine care (4 RCTs, n=2,366) but not to a range of sham treatments (14 RCTs, n=1,343) (Linde 2009a **Level I** [Cochrane], 22 RCTs, n=4,419). Acupuncture has slightly better outcomes and fewer adverse effects than pharmacological prophylaxis (4 RCTs, n= 780).

In the guidelines for headache by the National Clinical Guideline Centre of the UK, 10 sessions of acupuncture are recommended for TTH treatment and as a prophylaxis, and for migraine when prophylactic medications are ineffective (NICE 2012 **GL**).

While these meta-analyses examined acupuncture as a prophylactic treatment, acupuncture as a treatment for acute migraine attacks is also better than sham control (Wang 2012 **Level II**, n=150, JS 5).

7.3.2.7 Children and adolescents

Two moderate-size trials studied acupuncture for infantile colic using different acupuncture and management protocols. One found that acupuncture significantly reduced crying time compared to the no treatment group (Landgren 2010 **Level II**, n=85, JS 5); whereas the other found no difference between real and placebo acupuncture (Skjeie 2013 **Level II**, n=79, JS 5).

Key messages

1. Acupuncture and acupressure for labour pain reduces pain, use of pharmacological pain relief, Caesarean delivery rates and may increase satisfaction with pain management compared to standard care or placebo (**S**) (**Level I** [Cochrane Review]).
2. For oocyte retrieval, electroacupuncture when added to conscious sedation reduces procedural and postoperative pain more than sedation plus placebo or sedation alone, but not when added to paracervical block (**N**) (**Level I** [Cochrane Review]).
3. Acupuncture or acupressure may be effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).
4. Acupuncture may be effective in other acute pain settings (**S**) (**Level I** [PRISMA]), including acute burns and back pain (**N**) (**Level I** [PRISMA]), tension-type headaches and migraine (**N**) (**Level I** [Cochrane Review]).
5. Acupuncture (**S**) (**Level I**), specifically auricular acupuncture (**N**) (**Level I** [PRISMA] reduces postoperative pain, opioid requirements as well as opioid-related adverse effects compared to a variety of controls.
6. Beneficial effects of acupuncture on postoperative pain have been confirmed after back surgery and ambulatory knee surgery (**N**) (**Level I** [PRISMA]) and total knee joint replacement (**N**) (**Level II**).

7.4 Physical therapies

7.4.1 Manual and massage therapies

Evidence for any benefit for the use of massage in the treatment of postoperative pain is mixed. Following cardiac surgery, massage of the back, neck, shoulders, hands or feet has been shown to significantly reduce pain in some (Braun 2012 **Level II**, n=152, JS 3; Bauer 2010 **Level II**, n=113, JS 4; Cutshall 2010 **Level II**, n=58, JS 2) but not all studies (Albert 2009 **Level II**, n=252, JS 3; Hattan 2002 L**evel II**, n=25, JS 1). Irrespective of pain reductions, massage does not appear to lower analgesic usage or reduce length of hospital stay (Bauer 2010 **Level II**, n=113, JS 4; Albert 2009 **Level II**, n=252, JS 3).

Massage has been shown to reduce postoperative pain intensity and unpleasantness after a variety of major operations (Mitchinson 2007 **Level II**, n=605, JS 3). Massage reduced pain in patients following Caesarean delivery (Abbaspoor 2014 **Level II**, n=80, JS 2; Degirmen 2010 **Level II**, n=75, JS 2) and may reduce pain in postmastectomy patients (Drackley 2012, **Level IV)**. In patients after abdominal surgery, the use of a mechanical massage device (which leads to intermittent

negative pressure on the abdominal wall) resulted in significantly lower pain scores and analgesic use on d 2 and 3 after surgery, as well as reduced time to first flatus (Le Blanc-Louvry 2002 **Level II**, n=50, JS 1). However, massage after abdominal or thoracic (via sternotomy) surgery did not reduce pain scores or analgesic use, although a significant reduction in the unpleasantness of pain was reported (Piotrowski 2003 **Level II**, n=202, JS 2).

There is some evidence to support the use of massage in other acute pain conditions. Massage around the localised wound area reduced pain, itching and anxiety in patients with burns (Parlak Gurol 2010, **Level III-2**) (see also Section 9.7.2 for benefit in paediatric burns dressing changes). Massage of the sacrum and low back has been shown to reduce pain during the active phase of labour (Smith 2012, **Level I** [Cochrane], 5 RCTs, n=326; Silva Gallo 2013, **Level II**, n=46, JS 4) and abdominal massage may reduce pain associated with dysmenorrhoea (Apay 2012, **Level III-2**). Massage may also be reducing acute low-back pain, even more so in combination with exercises or education (Furlan 2008 **Level I** [Cochrane], 13 RCTs, n unspecified).

Spinal manipulative therapy for acute low-back pain is not more effective than inert interventions or sham spinal manipulative therapy based on limited studies with wide heterogeneity (Rubinstein 2012 **Level I** [Cochrane], 20 RCTs, n=2,674). Combined chiropractic treatment in comparison to other treatment improves short- and medium-term pain relief in acute and subacute back pain slightly with unclear clinical relevance (Walker 2010 **Level I** [Cochrane], 12 RCTs, n=2,887). Manual therapy is also considered in The Australian Acute Musculoskeletal Pain Guidelines and thus not referred to here any further (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**) (see Section 8.4).

7.4.2 Warming and cooling intervention

Evidence for any benefits from postoperative local cooling is mixed. Studies are constrained by the inability to blind the active treatment groups. A Cochrane review concluded that there is very low-quality evidence that postoperative local cooling after total knee arthroplasty reduces pain at 48 h (MD -1.32/10; 95%CI -2.37 to -0.27) but not at 24 or 72 h (4 RCTs, n=322), and blood loss by 225 mL (95%CI 39 to 410 mL) (10 RCTs, n=666) (Adie 2012 **Level I** [Cochrane], 11 RCTs, n=809).

Significant reductions in opioid consumption and pain scores with local cooling after a variety of other orthopaedic operations (including back surgery) have been reported (Brandner 1996 **Level II**, n=30, JS 2; Barber 1998 **Level III-1**; Saito 2004 **Level II**, n=46, JS 2; Fang 2012, **Level III-2**; Yu 2015, **Level II**, n=59, JS 4). Other studies have shown no such reductions (Leutz 1995 **Level III-2**; Edwards 1996 **Level II**, n=72, JS 1; Konrath 1996 **Level II**, n=103, JS 3; Meyer-Marcotty 2011 **Level II**, n=54, JS 3; Leegwater 2012 **Level II**, n=30, JS 3).

In other postsurgical settings, there is limited evidence to support the use of local cooling for pain relief following cardiac (Chailler 2010 **Level III-1**), cranial (Shin 2009 **Level II**, n=97, JS 3) and abdominal (Watkins 2014 **Level II**, n=55, JS 3) surgery. No benefit in terms of pain relief or opioid requirements was seen after total abdominal hysterectomy (Finan 1993 **Level II**, n=27, JS 3).

For pain associated with childbirth, there is limited evidence to support the use of hot showers vs standard care (Lee 2013b **Level II**, n=80, JS 3) and ice massage in the first stage of labour vs acupressure or standard care (Hajiamini 2012, **Level III-1**) as well as perineal warmed moist packs in the second stage of labour vs standard care (Dahlen 2009, **Level II**, n=717 , JS 3).

There is only limited evidence to support the effectiveness of local cooling treatments (ice packs, cold gel pads, cold/iced baths) for relieving pain from perineal trauma sustained during childbirth (East 2012 **Level I** [Cochrane], 10 RCTs, n=1,825). No benefit was found in the use of cold therapy following Caesarean delivery (Amin-Hanjani 1992 **Level II**, n=62, JS 2).

Evidence for the effect of local skin cooling or warming on reducing injection-related pain is mixed. There is evidence that vapocoolant sprays are not effective at reducing venipuncture-related pain in children or adults (Hogan 2014, **Level I** [PRISMA], 12 RCTs, n=1,266) and that ice packs do not reduce pain immunisation-related pain in children (Taddio 2009, **Level I**, 2 RCTs [ice packs], n=78). On the other hand, four studies found local cooling with an ice pack reduced injection-related pain in adults (Sarifakioglu 2004 **Level III-1**; Saeliw 2010, **Level II**, n=60, JS 3;

Al-Qarqaz 2012 **Level IV**; Haynes 2015, **Level II**, n=82, JS 3). Local warming also reduced injection-related pain in adults (Mahajan 2010, **Level III-1**).

7.4.3 Other therapies

7.4.3.1 Magnet therapy/magnetic stimulation

There is no evidence to support the use of static magnet therapy for the treatment of pain generally (Pittler 2007, **Level I**, 9 RCTs, n=721) or on postoperative pain or analgesic requirements (Cepeda 2007, **Level II**, n=165, JS 4). There is no evidence that magnetic acupressure is more effective than sham at reducing pain associated with ear, nose and throat or gynaecological procedures (Klaiman 2008, **Level II**, n=58, JS 5). Two small, single-blind trials found that a single session of postoperative repetitive transcranial magnetic stimulation (rTMS) led to lower PCA-opioid requirements (Borckardt 2006 **Level II**, n=20, JS 3; Borckardt 2008 **Level** II, n=20, JS 4) in patients following gastric bypass surgery. In a follow-up trial, the same group found no difference in PCA-opioid requirements associated with rTMS but significant decreases in pain intensity associated with two sessions of rTMS (Borckardt 2014 **Level II**, n=113, JS 3).

7.4.3.2 Low-level laser therapy

Low-level laser therapy was associated with reduced pain intensity following surgery when compared to placebo but only when multiple areas were irradiated and total energy was between 5 and 19.5 Joules (Bjordal 2006 **Level I**, 9 RCTs, n=609). When multiple areas were irradiated, low-level laser therapy was associated with reduced postoperative pain and opioid use post surgery for tibial fracture (Nesioonpour 2014 **Level II**, n=54, JS 2). There was no difference in postoperative analgesic requirements following use of millimetre wave therapy after total knee arthroplasty (Usichenko 2008 **Level II**, n=80, JS 5).

7.4.3.3 Healing touch

There was no difference in postoperative analgesic requirements following healing touch after CABG surgery (MacIntyre 2008 **Level II**, n=237, JS 3), although postoperative anxiety was reduced (p=0.01). A systematic review of healing touch in clinical practice concluded that any conclusions on the clinical effectiveness of healing touch were premature due to limited studies of modest quality (Anderson 2011 **Level I**, 5 RCTS, n=763).

7.4.3.4 Preoperative exercise ("prehabilitation")

A meta-analysis of the effects of preoperative exercise, often called "prehabilitation", on peri and postoperative outcomes compared to standard care found that in a majority of studies postoperative pain, length of stay and physical function are improved (Santa Mina 2014 **Level IV SR**, 21 studies, n=1,371). However, these results are limited by modest study quality and significant risk of bias.

Key message

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Conclusions regarding the efficacy of physical therapies in postoperative pain are not possible at present due to limited, poor quality evidence and the inability to conduct blinded trials (**N**).

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8. SPECIFIC CLINICAL SITUATIONS

8.1 Postoperative pain

One of the most common sources of pain is postoperative pain. A large amount of the evidence presented so far in this document is based on studies of pain relief in the postoperative setting. However, many of the management principles derived from these studies can be applied to the management of acute pain in general, as outlined in this and other sections that follow.

The treatment of postoperative pain in specific settings such as day-stay surgery will be discussed later in this chapter.

8.1.1 Multimodal postoperative pain management

The concept of multimodal (or "balanced") analgesia has been advocated as being beneficial for the management of postoperative pain (Kehlet 1993 **NR**). This concept suggests that combinations of analgesics with different modes or sites of action can improve analgesia, reduce opioid requirements ("opioid-sparing effect") and thereby reduce adverse effects of opioids in the postoperative period (Gritsenko 2014 **NR**).

As outlined in previous chapters, there is Level I evidence to support a large number of nonopioid analgesics, adjuvants and regional anaesthetic techniques as potential components of multimodal analgesia by fulfilling the above criteria: local anaesthetic techniques (local anaesthetic infiltration, peripheral nerve blocks and neuraxial blocks), systemic local anaesthetics, paracetamol, nsNSAIDs and coxibs, steroids, ketamine, alpha-2 agonists and alpha-2-delta ligands (Lui 2011 **NR**; Young 2012a **NR**; Zukowski 2012 **NR**; Rosero 2014 **NR**).

In this context, depth of general anaesthesia (BIS 30–40 vs 45–60) had no effect on postoperative pain or opioid requirements (Law 2014 **Level II**, n=135, JS 4).

Comparative studies of solely opioid-based analgesia with multimodal approaches show benefits not only with regard to analgesia and patient satisfaction but also for other postoperative outcomes. After total knee joint replacement, multimodal analgesia (including local anaesthetic infiltration, nsNSAIDs, tramadol and oxycodone) in comparison to IV PCA hydromorphone alone resulted in lower pain scores, opioid-sparing, fewer adverse effects, higher satisfaction scores and earlier achievement of physical therapy milestones (Lamplot 2014 **Level II**, n=36, JS 3). After cardiac surgery, multimodal analgesia (paracetamol, nsNSAID, dexamethasone, alpha-2-delta ligand and rescue morphine) vs paracetamol and morphine resulted in lower pain scores for the first 3 d, reduced PONV and a trend towards reduced complications (Rafiq 2014 **Level II**, n=180, JS 3). After upper extremity orthopaedic surgery, multimodal analgesia (including NSAID and alpha-2-delta ligand) compared to IV PCA opioid alone provided similar quality of analgesia with reduced incidence of opioid-related complications and greater patient satisfaction (Lee 2013b **Level II**, n=61, JS 3). After rhinoplasty, multimodal analgesia (pregabalin alone and combined with dexamethasone added to IV tramadol and diclofenac IM) vs IV PCA tramadol alone reduced pain scores, tramadol consumption, rescue opioid and nausea (Demirhan 2013 **Level II**, n=60, JS 5). After spinal surgery the use of multimodal analgesia (paracetamol, NSAIDs, gabapentin, S-ketamine, dexamethasone, ondansetron and epidural local anaesthetic infusion or IV PCA morphine) compared to historical controls, reduced opioid consumption, nausea, sedation and dizziness and improved postoperative mobilisation (Mathiesen 2013 **Level III-3**).

An additional benefit of a multimodal approach to pain relief after joint replacement (paracetamol, pregabalin and celecoxib or ketorolac) was a reduction of the incidence of postoperative fever (5 vs 25%; $p<0.001$) resulting in fewer patients undergoing tests (1.8 vs 9.8%; $p < 0.001$) (n=3,901) (Karam 2014 **Level III-3**).

Key messages

1. Multimodal analgesia compared to mainly opioid-based analgesia improves pain control and reduced opioid consumption ("opioid-sparing") and adverse effects (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ The concept of multimodal (or "balanced") analgesia suggests the use of combinations of analgesics with different mode or site of action (**N**).

8.1.2 Procedure-specific postoperative pain management

In addition to the overall assessment of the efficacy of acute pain management, there is also a need for information on postoperative pain management that relates to the site of surgery and specific surgical procedures (Rowlingson 2003 **NR**; Kehlet 2005a **NR**; Ward 2014 **NR**).

This becomes obvious when considering that even a simple analgesic, like paracetamol, has different efficacy in different surgical settings; it is significantly less effective after orthopaedic surgery (RR [of achieving >50% maximal pain relief] 1.87; 95%CI 1.36 to 2.57) than after dental extraction (RR 3.77; 95%CI 2.80 to 5.07) (Gray 2005 reanalysing Barden 2004b **Level I**, 43 RCTs [paracetamol], n unspecified). Although calculation of NNTs requires the pooling of data from at least 500 patients to be credible (McQuay 2002 **NR**), pooling of data from different postoperative pain states may ignore the specific effects of a specific analgesic in a specific postoperative pain state (Joshi 2013b **NR**).

Similarly, different surgical procedures cause different pain states (eg musculoskeletal vs visceral) of different severity in different locations, thereby requiring a procedure-specific approach. The recognition of this need has led to the development of the PROSPECT (PROcedure-SPECific postoperative pain managemenT) initiative, which aims to provide procedure-specific evidence-based recommendations for the treatment of pain after a wide range of operations (Neugebauer 2007b **NR**; Kehlet 2007 **NR**). Their guidelines can be found at the website of the PROSPECT initiative: http://www.postoppain.org. The methodology underlying this approach has been described in detail (Neugebauer 2007b **NR;** Joshi 2014 **NR**); it uses an evidence-based approach including meta-analysis of available procedure-specific data and considers appropriately matched transferable evidence (Neugebauer 2007a **NR**). Surgical factors contributing to postoperative pain are also considered (eg trochar size in laparoscopic cholecystectomy) (McCloy 2008 **Level I**, 13 RCTs, n unspecified).

Procedure-specific evidence for the following operations is currently available at the website with most of the underlying meta-analyses also published in the peer-reviewed literature:

- laparoscopic cholecystectomy (Kehlet 2005b **Level I**, 69 RCTs, n unspecified);
- primary total hip arthroplasty (Fischer 2005 **Level I**, 55 RCTs, n unspecified);
- abdominal hysterectomy;
- colonic resection (Joshi 2013a **Level I**, 12 RCTs [laparoscopic], n unspecified);
- herniorraphy (Joshi 2012 **Level I**, 79 RCTs, n unspecified);
- thoracotomy (Joshi 2008 **Level I**, 74 RCTs [regional techniques], n unspecified);
- total knee arthroplasty (Fischer 2008 **Level I**, 112 RCTs, n unspecified);
- noncosmetic breast surgery;
- haemorrhoidectomy (Joshi 2010 **Level I**, 65 RCTs, n unspecified);
- open prostatectomy; and
- Caesarean delivery.

Key messages

1. An analgesic may have different efficacy in different surgical settings (**N**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Pooling of data from different postoperative pain states may ignore the specific effects of a specific analgesic in a specific postoperative pain state (**N**).

☑ Different surgical procedures cause different pain states (eg musculoskeletal vs visceral) of different severity in different locations, thereby requiring a procedure-specific approach (**N**).

8.1.3 Acute rehabilitation after surgery, "fast-track" surgery and enhanced recovery after surgery

The concept of fast-track surgery is underpinned by a multimodal approach to the perioperative care of the patient (Wilmore 2001 **NR**; Kehlet 2008 **NR**; Nanavati 2014 **NR**). The approach uses combinations of perioperative interventions to facilitate the postoperative recovery involving a multidisciplinary team approach of surgeons, anaesthetists, nutritionists, physiotherapists and nurses. Management of the surgical stress response, perioperative fluids and pain are key factors of this approach (Kehlet 2011 **NR**).

Evidence-based approaches following these principles have resulted in a significantly reduced hospital stay for many operations without increasing, and often reducing, complications and readmissions. Evidence-based detailed protocols for enhanced recovery after surgery have been published for multiple operations by the ERAS©Society on their website (ERAS©Society 2015).

For example, application of an enhanced-recovery protocol to colorectal surgery results in reduced hospital stay (WMD -2.55 d; 95%CI -3.24 to -1.85) and complication rates (RR 0.53; 95%CI 0.44 to 0.64) (Varadhan 2010 **Level I**, 6 RCTs, n=452). However, it is of note that the number of individual enhanced-recovery after surgery elements employed ranged from 4–12, with a mean of 9 elements targeting perioperative care. The use of multiple components in enhanced recovery confirms previous findings that provision of good analgesia alone may have only minimal effects on speed and quality of postoperative recovery (Kehlet 1997 **NR**). This is not surprising given the numerous triggers of the injury response, of which acute pain is only one.

Even TEA, showing superior analgesic effect and faster return of bowel function, does not shorten length of stay or improve morbidity and mortality compared with alternative analgesic techniques when used within an enhanced-recovery protocol for open abdominal surgery (Hughes 2014 **Level I** [PRISMA], 7 RCTs, n=378). This finding highlights the importance of other elements of these protocols. Similarly, after laparoscopic colectomy, TEA significantly improves return of bowel function assessed by time to first bowel motion (WMD -0.62 d; 95%CI -1.11 to -0.12) and pain scores (WMD -1.23/10; 95%CI -2.4 to -0.07) but does not reduce duration of hospital stay (WMD -0.47 d; 95%CI; -1.55 to 0.61) (Khan 2013 **Level I** [PRISMA], 6 RCTs, n=340).

The importance of the many elements of enhanced-recovery protocols is well demonstrated in an analysis of the ERAS register for elective primary colorectal cancer resection (Eras Compliance Group 2015 **Level IV**, n=2,352). Elements associated with shorter length of stay were laparoscopic surgery (OR 0.83; p<0.001), increasing enhanced-recovery protocol compliance (OR 0.88; p<0.001), preoperative carbohydrate and fluid loading (OR 0.89; p=0.001) and total IV anesthesia (OR 0.86; p<0.001). Here epidural analgesia increased the duration of hospital stay (OR 1.07; p=0.019). Restrictive perioperative IV fluids reduced complications (OR 0.35; p<0.001) as well as laparoscopic surgery (OR 0.68; p<0.001) and increasing enhanced-recovery protocol compliance (OR 0.69; p<0.001).

Another similar analysis identified analgesic factors that reduced length of stay after elective colorectal surgery including avoidance of oral opioids in the postoperative period (OR 0.39; 95%CI 0.18 to 0.84) and the use of shorter duration of epidural analgesia (OR 0.44; 95%CI

0.12 to 0.94) (Ahmed 2010 **Level IV**, n=231). Opioid-sparing analgesic techniques reduced postoperative ileus (Barletta 2011 **Level IV**; Barletta 2012 **NR**).

It follows that provision of analgesia by appropriate techniques remains an important component of enhanced-recovery protocols (Kehlet 2003 **NR**; White 2007 **NR**; Kehlet 2011 **NR**). Effective analgesia facilitates other elements of enhanced-recovery protocols enabling early enteral feeding and mobilisation/ambulation. Independent predictors of early recovery after open and laparoscopic colorectal surgery were enforced advancement of oral intake (normal diet at postoperative d 1–3) and early mobilisation (Vlug 2012 **Level III-2**, n=400).

Key messages

1. Adherence to multimodal enhanced recovery after surgery protocols results in reduced hospital stay and complication rates (**N**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Provision of appropriate analgesia is only one of several elements of enhanced recovery after surgery protocols (**N**).

☑ Analgesic techniques, which permit early mobilisation and early enteral feeding, in particular those that are opioid-sparing, may contribute to early recovery after surgery protocols (**N**).

8.1.4 Risks of acute postoperative neuropathic pain

Neuropathic pain has been recently redefined as "pain caused by a lesion or disease of the somatosensory nervous system" (Jensen 2011 **NR**). Although neuropathic pain is often considered a chronic pain state, it can occur acutely. Acute causes of neuropathic pain can be iatrogenic, traumatic, inflammatory or infective (Gray 2008a **NR**). Nerve injury is a risk in many surgical procedures and may present as acute neuropathic pain postoperatively. The incidence of acute neuropathic pain has been reported as 1–3%, based on patients referred to an APS, primarily after surgery or trauma (Hayes 2002 **Level IV**). The majority of these patients had persistent pain at 12 mth, suggesting that acute neuropathic pain is a risk factor for chronic pain. The role of acute neuropathic pain as a component of postoperative pain is possibly underestimated; after sternotomy 50% of patients had dysaesthesia in the early postoperative period, which was closely associated with severity of postoperative pain (Alston 2005 **Level IV**). After cancer surgery, a prospective study using a screening tool identified acute neuropathic pain in 10% of cases in the first week postoperatively (Jain 2014 **Level IV**, n=300). In a general surgical population (n=165), the incidence was 3–4.2% (Sadler 2013 **Level IV**). Similarly, a high incidence of acute neuropathic pain in the lower limbs with lumbosacral plexus injury after pelvic trauma has been reported (Chiodo 2007 **Level IV**)

Management of acute neuropathic pain is primarily based on extrapolation of data from the chronic neuropathic pain setting (see Sections 4.6 to 4.10). However, selection of a preferred treatment in the acute setting may be based on a faster onset of effect; tramadol, opioids and alpha-2-delta ligands are suggested (Dworkin 2010 **GL**; Macintyre 2015 **NR**). In two small series of acute neuropathic pain due to SCI, all patients responded positively to IV ketamine followed by oral ketamine (n=13) (Kim 2013a **Level IV**) and salmon calcitonin (n=3) (Humble 2011 **Level IV**).

There is some evidence that specific early analgesic interventions may reduce the development of chronic pain (often neuropathic pain) after some operations (eg thoracotomy, amputation). For more details see Sections 1.4, 1.5, 8.1.5 and 8.1.6.

Key messages

1. Acute neuropathic pain occurs after trauma and surgery (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Treatment of acute neuropathic pain should follow guidelines for chronic neuropathic pain; ketamine, opioids (including tramadol and tapentadol in particular) and alpha-2-delta ligands may offer faster onset of effect than other treatment options (**N**).

☑ Diagnosis and subsequent appropriate treatment of acute neuropathic pain might prevent development of chronic pain (**U**).

8.1.5 Acute postamputation pain syndromes

Following amputation of a limb, and also breast, tongue, teeth, genitalia, the eye and even inner organs such as the rectum, or a deafferentiation injury such as brachial plexus avulsion (Bates 1991 **Level IV**; Boas 1993 **Level IV**; Ahmed 2014 **Level IV**; Andreotti 2014 **NR**), a number of phenomena can develop. These require differentiation.

- *Stump pain* is pain localised to the site of amputation. It can be acute (usually nociceptive) or chronic (usually neuropathic) and is most common in the immediate postoperative period (Jensen 1985 **Level IV**; Nikolajsen 2001 **NR**). The overall incidence of stump pain is uncertain but the risk of early stump pain is increased by the presence of severe preamputation pain (Nikolajsen 1997 **Level IV**).
- *Phantom sensation* is defined as any sensory perception of the missing body part with the exclusion of pain. Almost all patients who have undergone amputation experience phantom sensations (Jensen 1983 **Level IV**). These sensations range from a vague awareness of the presence of the missing body part via associated paraesthesia, to complete sensation including size, shape, position, temperature and movement.
- *Phantom pain* is defined as any noxious sensory phenomenon in the missing body part. The incidence of phantom limb pain is estimated to be 30–85% after limb amputation and usually occurs in the distal portion of the missing limb (Jensen 1985 **Level IV**; Perkins 2000 **NR**; Nikolajsen 2001 **NR**). Pain may be early, 75% of patients will report phantom pain within the first few days after amputation (Nikolajsen 1997 **Level IV**), or delayed in onset. The pain is typically intermittent and diminishes with time after amputation. Factors that may be predictive of postamputation phantom pain are the severity of preamputation pain, the degree of postoperative stump pain, and chemotherapy or radiotherapy (see Section 1.3). If preamputation pain was present, phantom pain might resemble that pain in character and localisation (Katz 1990 **Level IV**). The intensity of preamputation pain and acute postoperative pain were strong predictors of the intensity of chronic pain after amputation (Hanley 2007 **Level III-3**). Preoperative passive coping strategies, in particular catastrophising, were other strong predictors of phantom limb pain 6 mth later (Richardson 2007 **Level III-3**).

There is a strong correlation between phantom limb and stump or site pain, and they may be inter-related (Jensen 1983 **Level IV**; Kooijman 2000 **Level IV**). All three of the above phenomena can coexist (Nikolajsen 1997 **Level IV**).

A survey identified the high incidence of these pain syndromes after amputation in 537 amputees; only 14.8% were pain-free, 74.5% had phantom limb pain, 45.2% stump pain and 35.5% a combination of both (Kern 2009 **Level IV**).

Phantom breast pain has also been described; however, the incidence was low in the range of 7% at 6 wk and 1% at 2 y (Dijkstra 2007 **Level III-3**). Phantom sensations are more common; reported in 19% of patients more than 5 y after surgery (Peuckmann 2009 **Level IV**).

8.1.5.1 Prevention of phantom limb pain

Evidence for the benefit of epidural analgesia in the prevention of all phantom limb pain is inconclusive (Halbert 2002 **Level III-2 SR**, 3 studies [epidural], n=106). However, perioperative (pre, intra and postoperative) epidural analgesia reduced the incidence of severe phantom limb pain (NNT 5.8; 95%CI 3.2 to 28.6) (Gehling 2003 **Level III-2 SR**, 9 studies, n=836).

A small observational study found that the overall incidence of long-term phantom limb pain was similar in patients given IV ketamine (bolus dose followed by an infusion, started prior to skin incision and continued for 72 h postoperatively) compared with no ketamine; however the incidence of severe phantom limb pain was reduced in the ketamine group (Dertwinkel 2002 **Level III-3**); both groups received regional analgesia. Another RCT looking at the effects of IV ketamine reported a numerical, but not statistically significant, difference in the incidence of phantom limb pain at 6 mth after amputation (47% in the ketamine group and 71% in the control group) (Hayes 2004 **Level II**, n=45, JS 4). Perioperative ketamine given by the epidural route showed no preventive effect (Wilson 2008 **Level II**, n=53, JS 5).

Perioperative gabapentin was ineffective in reducing incidence and severity of phantom limb pain (Nikolajsen 2006 **Level II**, n=46, JS 5).

Infusions of local anaesthetics via peripheral nerve sheath catheters, usually inserted by the surgeon at the time of amputation, showed no benefit in preventing phantom pain or stump pain (Halbert 2002 **Level III-SR**, 3 studies, n=101; McCormick 2014 **Level I**, 2 RCTs [perineural], n=151).

8.1.5.2 Therapy for phantom limb pain

A survey in 1980 identified over 50 different therapies used for the treatment of phantom limb pain (Sherman 1980 **NR**), suggesting limited evidence for effective treatments.

With regard to pharmacological treatment, most conclusions are based on studies limited by their small sample size (Alviar 2011 **Level III-1 SR** [Cochrane], 13 studies, n=255). Oral and IV morphine is effective in the short-term (2 RCTs, n=43) as are the NMDA-antagonists ketamine and dextromethorphan, but not memantine (4 RCTs and 2 studies, n=81). Gabapentin also has an analgesic effect (MD -1.16/10; 95%CI -1.94 to -0.38) (2 RCTs, n=43). A subsequent meta-analysis of gabapentin specifically in this setting identified a third trial that showed no benefit (Nikolajsen 2006 **Level II**, n=46, JS 5) and which therefore weakens this conclusion (Abbass 2012 **Level I**, 3 RCTs, n=89).

Amitriptyline was ineffective in acute phantom limb pain management (1 RCT, n=39) (Alviar 2011 **Level III-1** [Cochrane], 13 studies, n=255). The results on calcitonin were inconclusive (2 RCTs): the study in acute phantom limb pain (within 7 d of amputation) showed a pronounced effect (Jaeger 1992 **Level II**, n=21 [cross-over], JS 3), while the study in chronic phantom limb pain showed no effect (Eichenberger 2008 **Level II**, n=20, JS 5). Systemic lignocaine (1 RCT, n=31) was ineffective, while contralateral myofascial injection of bupivacaine given once reduced phantom pain in a very small study (1 RCT, n=8 [cross-over]) (Alviar 2011 **Level III-1** [Cochrane], 13 studies, n=255).

A subsequent systematic review reports similar results in a less thorough way (McCormick 2014 **Level III-2 SR**, 28 studies, n unspecified [plus multiple **Level IV** studies]). With regard to morphine an additional RCT (n=12) confirms long-term benefits (with a slow-release preparation). Botulinum toxin is ineffective (1 RCT, n=14). An RCT excluded from the Cochrane review above due to its complex study design is incorrectly interpreted by this systematic review; the RCT shows that amitriptyline as well as tramadol provided good control of phantom limb pain (Wilder-Smith 2005 **Level II**, n=94 [cross-over], JS 4).

Neurostimulation has also been shown to be effective in case series for the treatment of phantom limb pain in the form of spinal cord (McAuley 2013 **Level IV**) and peripheral nerve stimulation (Rauck 2014 **Level IV**).

Nonpharmacological treatment options for phantom limb pain based on concepts of cortical reorganisation are also effective. These include mirror therapy (Rothgangel 2011 **Level I**, 2 RCTs [mirror therapy], n=32), sensory discrimination training (Flor 2001 **Level II**, n=10, JS 2) and

mental imagery of limb movement (MacIver 2008 **Level IV**). Maladaptive changes in cortical organisation were reversed during mirror treatment, which over 4 wk resulted in an average decrease of phantom limb pain intensity of 27% (Foell 2014 **Level IV**); mirror therapy was also effective if self-administered at the home of patients (Darnall 2012 **Level IV**). Use of a hand prosthesis with somatosensory feedback on grip strength reduced phantom limb pain (Dietrich 2012 **Level IV**). Illusory touch is another effective approach in this context (Schmalzl 2013 **Level IV**).

Key messages

1. Morphine, gabapentin, ketamine and dextromethorphan reduce phantom limb pain compared to placebo (**S**) (**Level I** [Cochrane Review]).
2. Calcitonin reduces phantom limb pain in the acute (<7 days post amputation) but not the chronic setting (**Q**) (**Level I** [Cochrane Review]).
3. Continuous regional block via nerve sheath catheters provides postoperative analgesia after amputation but has no preventive effect on phantom limb pain (**S**) (**Level I**).
4. Treatments aiming at cortical reorganisation such as mirror therapy (**S**) (**Level I**), sensory discrimination training and motor imagery reduce chronic phantom limb pain (**S**) (**Level II**).
5. Perioperative epidural analgesia reduces the incidence of severe phantom limb pain (**U**) (**Level III-2**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Perioperative ketamine may prevent severe phantom limb pain (**U**).

8.1.6 Other postoperative pain syndromes

Increasing evidence for the development of postoperative chronic pain syndromes has led to the more detailed study of some of them. The progression from acute to chronic pain and specific early analgesic interventions to reduce the incidence of chronic pain after some operations are discussed in Sections 1.4 and 1.5.

8.1.6.1 Post-thoracotomy pain syndrome

Post-thoracotomy pain syndrome is one of the most common chronic pain states. The incidence of chronic pain after thoracotomy was 57% at 3 mth (95%CI 51 to 64%) (17 studies, n=1,439) and 47% at 6 mth (95%CI 39 to 56%) (15 studies, n=1,354) (Bayman 2014 **Level IV SR**, 17 studies, n=1,439). The average severity of pain at these time points was respectively 30/100 (95%CI 26 to 35) and 32/100 (95%CI 17 to 46). QoL was reduced in the SF-36 domains of physical functioning (p=0.049), bodily pain (p=0.0002) and vitality (p=0.044) (Kinney 2012 **Level IV**).

Post-thoracotomy pain syndrome is thought to be caused primarily by trauma to intercostal nerves and most patients relate their pain directly to the site of surgery (Karmakar 2004 **NR**). Neurophysiological assessments (QST) have revealed that patients with post-thoracotomy pain, but also pain-free patients after thoracotomy, show increased thresholds suggesting nerve injury in both groups (Wildgaard 2009 **Level III-3**). However, only pain patients show increased sensitivity to heat and cold and hyperaesthesia; this suggests that nerve injury by itself is not a predictor for this pain syndrome and other factors need to be present. Furthermore, sensory dysfunction on the nonoperated side was found in patients with post-thoracotomy pain, while such “mirror-image sensory dysfunction” was not accompanied by mirror pain (Werner 2013 **Level IV**). However, myofascial pain syndromes as a consequence of thoracotomy have also been described (Hamada 2000 **Level IV**).

Following thoracotomy, epidural anaesthesia reduces the incidence of CPSP at 6 mth compared to systemic analgesia or cryoanalgesia (NNT 4) (OR 0.33; 95%CI 0.20 to 0.56) (Andreae 2013 **Level I** [Cochrane], 3 RCTs [thoracotomy], n=250).

Cryoanalgesia provides pain relief superior to other techniques only in 6 of 12 RCTs in the immediate postoperative period but increased the incidence of post-thoracotomy pain in 4 of 4 RCTs evaluating this outcome (Khanbhai 2014 **Level I**, 12 RCTs, n unspecified).

A detailed review of preventive treatments for post-thoracotomy pain syndrome has been published (Romero 2013 **NR**).

8.1.6.2 Postmastectomy pain syndrome

Chronic pain after mastectomy is common. In epidemiological studies, the incidence was 24% at 1.5 y (Vilholm 2008b **Level IV**), 27.6% at 2–3 y (Meijuan 2013 **Level IV**) and 29% in patients (with no recurrence of cancer) more than 5 y after surgery (Peuckmann 2009 **Level IV**). At an average time of 38.3 mth after mastectomy, 32.5% patients reported pain ≥3/10 in the breast, axilla, side or arm (Belfer 2013 **Level IV**, n=611). Phantom breast pain has also been described, however, the incidence was low in the range of 7% at 6 wk and 1% at 2 y (Dijkstra 2007 **Level III-3**). Phantom sensations are more common; reported in 19% of patients >5 y after surgery (Peuckmann 2009 **Level IV**). Postmastectomy pain syndrome has a negative effect on many domains of quality of life (Meijuan 2013 **Level IV**).

Sensory testing (thermal thresholds, cold allodynia and temporal summation of repetitive stimulation) showed that postmastectomy pain is a neuropathic pain condition (Vilholm 2009 **Level III-2**); in line with this, 64% of patients after mastectomy describe sensory disturbances with an increased risk of chronic pain (Meijuan 2013 **Level IV**).

Significant predictors for the development of postmastectomy chronic pain were younger age (Meijuan 2013 **Level IV**) and radiotherapy (Peuckmann 2009 **Level IV**; Henderson 2014 **Level III-2**). Other risk factors were higher postoperative pain scores and inclusion of major reconstructive surgery (Chang 2009 **Level IV**). Psychosocial factors, including catastrophising, somatisation, anxiety and sleep disturbance were significant predictors (Belfer 2013 **Level IV**, n=611). Type of surgery, axillary node dissection, surgical complication, recurrence, tumour size and, contrary to above findings, radiation and chemotherapy were not significantly associated with postmastectomy chronic pain. Immediate breast reconstruction (implant or pedicled flap) does not increase postmastectomy pain compared to mastectomy alone (Henderson 2014 **Level III-2**, n=272).

PVB reduces postmastectomy pain syndrome at 6 mth compared with systemic analgesia (NNT 5) (OR 0.37; 95%CI 0.14 to 0.94) (Andreae 2013 **Level I** [Cochrane], 2 RCTs [mastectomy], n=89).

Following mastectomy, 10-d treatment with venlafaxine commencing preoperatively was associated with significantly lower burning and stabbing pain after 6 mth (Amr 2010 **Level II**, n=150, JS=3).

Perioperative use of gabapentin or mexiletine after mastectomy reduced the incidence of neuropathic pain at 6 mth postoperatively, from 25% in the placebo to 5% in both treatment groups (Fassoulaki 2002 **Level II**, n=75, JS 4). Similar protective results were reported by the same group by the use of a eutectic mixture of local anaesthetics alone (Fassoulaki 2000 **Level II**, n=46, JS 4) or in combination with gabapentin (Fassoulaki 2005 **Level II**, n=50, JS 5).

Autologous fat graft into the scar area reduced postmastectomy pain compared to a control group (by 3.1/10 vs 0.9/10; p≤0.005) (n=96) (Maione 2014 **Level III-2**).

Levetiracetam was ineffective in the treatment of postmastectomy syndrome (Vilholm 2008a **Level II**).

8.1.6.3 Postherniotomy pain syndrome

This syndrome is thought to be mainly neuropathic pain as a result of nerve injury. This assumption was confirmed in a study that showed that all patients with chronic postherniotomy pain had features of neuropathic pain (Aasvang 2008 **Level IV**). Ejaculatory pain

is a feature of this syndrome and occurs in around 2.5% of patients after herniotomy (Aasvang 2007b **Level IV**).

At 6 mth after herniotomy, 12.4% had "moderate/severe" pain (Aasvang 2010 **Level IV**, n=442) and 16.0% had substantial pain-related functional impairment (Bischoff 2012 **Level III-3**, n=244). The following risk factors were identified: preoperative Activity Assessment Scale score, preoperative pain to tonic heat stimulation, 30-d postoperative pain intensity and sensory dysfunction in the groin at 6 mth (nerve damage) (all p<0.03). An attempt to predict risk also identified open vs laparoscopic herniotomy as an additional intraoperative risk factor (OR 0.45; 95%CI 0.23 to 0.87).

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of CPSP (from 21–6%) in one RCT (Malekpour 2008 **Level II**, n=100, JS 4) and in another study (Smeds 2010 **Level III-2**), while an earlier nonrandomised multicentre prospective study (n=973) found this increased CPSP risk (Alfieri 2006 **Level III-2**). Intraoperative nerve identification of the iliohypogastric, ilioinguinal and genitofemoral nerves did not reduce the risk of development of sensory loss or postherniotomy pain syndrome compared with nonidentification (Bischoff 2012 **Level III-3**, n=244).

Very young age may be a protective factor as hernia repair in children <3 mth age did not lead to chronic pain in adulthood (Aasvang 2007a **Level IV**).

Mesh removal and selective neurectomy of macroscopically injured nerves reduced impairment in patients with postherniorrhaphy pain syndrome (Aasvang 2009 **Level III-3**).

Evidence-based consensus guidelines for prevention and management of postoperative chronic pain following inguinal hernia surgery have been published (Alfieri 2011 **GL**). Recommended approaches include to identify and preserve all three inguinal nerves and to perform elective resection of a suspected injured nerve. Patients with a postherniotomy pain syndrome not responding to other pain management treatment should be offered surgical treatment (including all three nerves) after at least 1 y from the previous hernia repair.

8.1.6.4 Posthysterectomy pain syndrome

Chronic pain is reported by 17–32% of women after hysterectomy (Brandsborg 2012 **NR**). In most women the pain was present preoperatively; at a 1–2 y follow-up, pain was reported as a new symptom in 1–15% of patients (Brandsborg 2008 **NR**). The origin and risk factors for persisting pain after hysterectomy are not clear. However, in a small prospective survey postoperative pain intensity, as well as preoperative nonpelvic pain, were associated with the presence of pain 4 mth after surgery (Brandsborg 2009 **Level III-3**). For pain reported 1 y after surgery, risk factors were preoperative pelvic and nonpelvic pain and previous Caesarean delivery; there was no difference found between vaginal or abdominal hysterectomy or the type of incision for abdominal hysterectomy (Brandsborg 2007 **Level IV**). Preoperative pain sensitisation (cutaneous and vaginal hypersensitivity) is associated with acute pain after hysterectomy but only preoperative brush-evoked allodynia was associated with chronic pain at 4 mth postoperatively (p<0.01) (n=90) (Brandsborg 2011 **Level IV**).

Patients given perioperative gabapentin and a postoperative ropivacaine wound infusion had lower opioid requirements after surgery and less pain 1 mth later compared with patients given placebo, although there was no difference in pain scores for the first 7 d postoperatively (Fassoulaki 2007 **Level II**, n=60, JS 5). Perioperative pregabalin (150 mg 3 times/d for 5 d) reduced postoperative opioid requirements but had no effect on any pain outcome at 3 mth (Fassoulaki 2012 **Level II**, n=80, JS 5).

Spinal anaesthesia in comparison with general anaesthesia reduced the risk of chronic postsurgical pain after hysterectomy (OR 0.42; 95%CI 0.21 to 0.85) (Brandsborg 2007 **Level IV**). Propofol-based general anaesthesia compared to sevoflurane-based anaesthesia reduced the incidence (17.5 vs 52.5%; p<0.01) and severity of posthysterectomy pain (0.78/10 ±0.55 vs 2.23/10 ±0.73; p<0.01) at 3 mth postoperatively (Ogurlu 2014 **Level II**, n=80, JS 5).

Key messages

1. Following thoracotomy, epidural analgesia reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
2. Following breast cancer surgery, paravertebral block reduces the incidence of chronic postsurgical pain (**S**) (**Level I** [Cochrane Review]).
3. Cryoanalgesia of the intercostal nerves at the time of thoracotomy results in no improvement in acute pain, but an increase in chronic pain (**S**) **(Level I**).
4. Post-thoracotomy, postmastectomy, postherniotomy and posthysterectomy pain syndromes occur frequently (**N**) (**Level IV**).

8.1.7 Day-stay or short-stay surgery

Ever increasing numbers of surgical procedure are now performed on a day- or short-stay basis, here defined as hospital stay <24 h. Adequate postoperative pain management is often the limiting factor when determining whether a patient can have surgery performed as a day procedure.

Provision of effective analgesia after ambulatory surgery remains poor. In two Swedish nationwide surveys of ambulatory surgery, pain was the most common problem at follow-up after discharge in a mixed (Segerdahl 2008b **Level IV**) and a paediatric population (Segerdahl 2008a **Level IV**). Another survey from a single institution found that at 3 and 4 d after day-stay surgery, 10 and 9% of patients respectively reported moderate to severe pain (Greengrass 2005 **Level IV**). Even after cataract day-stay surgery, ocular pain was reported by 10% of patients at 24 h, 9% at 7 d and 7% at 6 wk (Porela-Tiihonen 2013 **Level IV**).

After paediatric adenotonsillectomy, 52% patients had pain >5 on a VAS at 3 d (33% had nausea) and 30% at 7 d (Stanko 2013 **Level IV**). Pain scores during the first 24 h were slightly increased for day-stay tonsillectomy compared to overnight inpatient stay, although maximal pain scores at 24 h and 7 d were unchanged (Norrington 2013 **Level III-2**). Differences in parental attitudes, understanding and access to medications, nausea or fear of adverse effects may explain some of these differences. Barriers have been summarised as parental, child, medication and system factors (Dorkham 2014 **NR**). Neither supplying a discharge medication package (Hegarty 2013 **Level II**, n=200, JS 2) nor nurse telephone follow-up improved pain relief after ambulatory tonsillectomy (Paquette 2013 **Level II**, n=45, JS 2). An audit of 200 children found that pain reports were significantly higher at home than in hospital (Shum 2012 **Level IV**). Pain scores, functional limitation and analgesic use are greater after tonsillectomy than after inguinal hernia repair or orchidopexy in children discharged from day-stay surgery, with the majority requiring at least one analgesic medication for 7 d after surgery and more than half of the patients requiring visits to a general practitioner (Stewart 2012 **Level IV**).

The best predictive factor of postoperative pain is the presence of preoperative pain; other factors include high expectations of postoperative pain, anticipation of pain by clinicians and younger age (Gramke 2009 **Level IV**).

8.1.7.1 Adverse effects of pain

Inadequate analgesia delays patient discharge; pain was the most common cause of delayed recovery affecting 24% of patients (Pavlin 2002 **Level IV**). Uncontrolled pain is also a major cause of nausea and vomiting, further extending the patient's stay in the recovery room (Eriksson 1996 **Level IV**; Michaloliakou 1996 **Level IV**). The most common reason for unplanned hospital admission across 14 day-surgery units in Finland was unrelieved pain (Mattila 2009 **Level III-2**).

Inadequate pain management may cause sleep disturbance and limit early mobilisation, which may be crucial for early return to normal function and work (Strassels 2002 **Level IV**).

8.1.7.2 Analgesic drugs and techniques

More complex surgery continues to be performed on a day-stay or short-stay basis and therefore the analgesic drugs and techniques required are similar to those used for inpatient pain relief. Multimodal analgesia is therefore recommended in this setting (Elvir-Lazo 2010 **NR**); see relevant sections of this document:

- systemically administered analgesic drugs (Chapter 4);
- regionally and locally administered analgesics drugs (Chapter 4); and
- regional and other local analgesia techniques (Chapter 5).

Paracetamol, nonselective NSAIDs and coxibs

Paracetamol/codeine provided similar analgesia but with more discontinuation due to adverse effects compared to paracetamol/ibuprofen after day-stay breast surgery (Mitchell 2012 **Level II**, n=145, JS 5).

Following outpatient surgery, ibuprofen (1,200 mg/d) or celecoxib (400 mg/d) for 4 d, when compared to placebo, reduced the need for breakthrough analgesia in the early postdischarge period leading to improved patient satisfaction and quality of recovery (White 2011 **Level II**, n=180, JS 4).

For ambulatory laparoscopic cholecystectomy, parecoxib preoperatively (30 min prior to surgery) compared to postoperatively and placebo was associated with less pain and analgesic requirements for up to 24 h leading to shorter times to attain PACU and hospital discharge criteria (Shuying 2014 **Level II**, n=120, JS 4). However, for minor day-stay gynaecological surgery, paracetamol or parecoxib, either alone or in combination, did not produce a clinically significant impact on pain in the first 24 h after surgery compared to placebo (Mohamad 2014 **Level II**, n=240, JS 4).

Opioids

Paracetamol/tramadol provided similar analgesia to tramadol alone after ambulatory hand surgery and resulted in a reduced rate of adverse effects (Rawal 2011 **Level II**, n=80, JS 5). Paracetamol/tramadol was also superior to combination paracetamol/codeine with better analgesia, fewer adverse effects and higher patient satisfaction in a mixed day surgery population (Alfano 2011 **Level II**, n=122, JS 2).

Systemic adjuvant drugs

In an ambulatory gynaecology surgery population, dexamethasone 0.1 mg/kg was associated with improved QoR score (QoR-40) and less opioid consumption in the first 24 h postoperatively compared to dexamethasone 0.05 mg/kg or placebo (De Oliveira 2011 **Level II**, n=120, JS 5). Similarly in a paediatric setting, the addition of systemic dexamethasone (0.5 mg/kg to a maximum of 10 mg) to caudal blocks for day-stay orchidopexy improved and extended postoperative analgesia (Hong 2010 **Level II**, n=77, JS 5). This was found also when systemic dexamethasone was added to a glossopharyngeal nerve block for tonsillectomy (Mohamed 2009 **Level II**, n=150, JS 3).

Local anaesthesia techniques

Certain local and regional techniques offer specific benefits to patients after day-stay or short-stay surgery. There has been increasing interest in the use of single dose ("single-injection") as well as CPNB in patients discharged home (Schug 2009 **NR**).

Local and peritoneal infiltration

After day-stay hernia repair, wound infiltration with levobupivacaine provided analgesia for 24 h (Ausems 2007 **Level II**, n=120, JS 5). However, after day-case laparoscopic gynaecological surgery, wound infiltration did not significantly reduce pain or opioid requirements (Fong 2001 **Level II**, n=100, JS 5).

After ambulatory hallux valgus repair, mid foot infiltration and sciatic nerve block provided similar analgesia but infiltration permitted earlier ambulation (Adam 2012 **Level II**, n=40, JS 3).

In a systematic review of interventions for day-stay laparoscopic cholecystectomy six of eight RCTs showed analgesic benefit with local anaesthetic infiltration compared to placebo, with preincisional infiltration being superior to postincisional administration (Ahn 2011 **Level I**, 8 RCTs [local infiltration], n unspecified). Intraperitoneal local anaesthetic was beneficial in seven of nine RCTs, with one of the two negative RCTs using local anaesthesia at the end of the procedure (Ahn 2011 **Level I**, 9 RCTs [intraperitoneal], n unspecified). Local anaesthetic was more effective when applied before the commencement of pneumoperitoneum and use of aerosolised local anaesthetic was more effective than simple instillation. Two of the RCTs showed the combination of incisional and intraperitoneal local anaesthesia was more effective than either intervention alone.

Intraperitoneal instillation of local anaesthetic at gynaecological laparoscopy reduced pain scores for up to 6 h postoperatively (Marks 2012 **Level I**, 7 RCTs, n=478).

Single-injection peripheral nerve block

PNBs are useful in ambulatory surgery as they provide site-specific anaesthesia with prolonged analgesia and minimal haemodynamic changes (Salinas 2014 **NR**).

The decision to discharge ambulatory patients following PNB with long-acting local anaesthesia is controversial due to the potential risk of harm to an insensate limb. A prospective study including 1,119 upper and 1,263 lower extremity blocks demonstrated that long-acting PNBs were safe and that patients could be discharged with an insensate limb (Klein 2002a **Level IV**). Therefore, provided patients are given verbal and written information regarding the risks as well as appropriate follow-up, it would seem reasonable to discharge these patients with the benefit of prolonged analgesia. After outpatient shoulder arthroscopy with single-injection interscalene block, 15% of patients experienced severe pain at home in the first 3 d and 5% contacted their general practitioner for analgesia issues (Trompeter 2010 **Level IV**).

Ilioinguinal and iliohypogastric block

Herniorrhaphy performed under ilioinguinal and iliohypogastric nerve block led to superior pain relief, less morbidity, less urinary retention and cost advantages (Ding 1995 **Level II**, n=30, JS 4). The analgesic benefit with bupivacaine lasted around 6 h (Toivonen 2001 **Level II**, n=100, JS 3). For open inguinal hernia surgery, US-guided ilioinguinal and iliohypogastric blocks with bupivacaine vs saline reduced pain scores at rest and on movement in the PACU, although opioid consumption and time to discharge did not differ (Baerentzen 2012 **Level II**, n=60, JS 5).

In children undergoing unilateral groin surgery, US-guided ilioinguinal/iliohypogastric block (0.1ml/kg 0.25% bupivacaine) provided equivalent analgesia to caudal block (0.7 mL/kg 0.25% bupivacaine) (Abdellatif 2012 **Level II**, n=50, JS 4). When compared to IV morphine 0.1 mg/kg for paediatric orchidopexy surgery, ilioinguinal/iliohypogastric blocks provided inferior analgesia in the first 1 h postoperatively but equivalent analgesia over 24 h with less vomiting and pruritus (Al-Zaben 2014 **Level II**, n=70, JS 4). After paediatric inguinal hernia repair, 0.4 ml/kg of 0.25 % levobupivacaine was superior to the same volume of 0.125% with regard to quality and duration of analgesia in an ambulatory setting (Disma 2009 **Level II**, n=73, JS 4).

Transversus abdominis plane blocks

After day-stay laparoscopic cholecystectomy, TAP block with ropivacaine vs placebo reduced opioid requirements for 2 h and pain on coughing, but not at rest, for up to 4 h (Petersen 2012 **Level II**, n=80, JS 5).-

After day-stay inguinal hernia repair, local infiltration for surgical anaesthesia alone when compared with local infiltration and TAP blocks reduced the need for intraoperative rescue analgesia (36–8%) and improved postoperative pain scores for 12 h (Milone 2013 **Level II**, n=150, JS 3). When blind ilioinguinal/iliohypogastric nerve blocks were compared to US-guided TAP blocks for day-stay open inguinal hernia surgery, there was a small reduction in pain at rest (but not on movement) in the TAP group for up to 24 h (Aveline 2011 **Level II**, n=273, JS 5). There was also a modest reduction in postoperative oral morphine requirement over the first 2 d. The primary outcome for this study was pain at 6 mth, where no difference was found.

In children undergoing inguinal hernia repair, TAP block with 0.5 ml/kg of 0.25% bupivacaine vs wound infiltration with 0.2mL/kg of 0.25% bupivacaine markedly reduced pain scores and analgesic consumption during the first postoperative 24 h (Sahin 2013 **Level II**, n=57, JS 4). In contrast, a study in adult patients failed to demonstrate benefit from TAP block compared to blind ilioinguinal block with wound infiltration or placebo in adults undergoing open hernia repair (Petersen 2013 **Level II**, n=90, JS 5); patients in the ilioinguinal/infiltration group had lower pain scores in the first 6 h compared to both other groups.

Paravertebral block

PVBs provided better analgesia for 12 h after day-stay inguinal herniorrhaphy compared to general anaesthesia with multimodal analgesia and wound infiltration resulting in earlier PACU and hospital discharge and less nausea (Akcaboy 2010 **Level II**, n=60, JS 3). PVBs provided better analgesia than more distal nerve blocks (combination of ilioinguinal and iliohypogastric nerve block with infiltration) after inguinal herniorrhaphy, with earlier discharge, higher patient satisfaction and fewer adverse effects (Klein 2002b **Level II**, n=46, JS 2). Their successful use has also been reported after outpatient lithotripsy (Jamieson 2007 **Level IV**).

US-guided multilevel PVB and propofol-based anaesthesia compared to sevoflurane anaesthesia with morphine analgesia for outpatient breast cancer surgery significantly reduced pain scores, QoR scores, opioid consumption and time to discharge (Abdallah 2014 **Level II**, n=64, JS 5). After ambulatory breast augmentation, PVB was superior to direct surgical infiltration with ropivacaine with regard to pain scores and requirements for rescue analgesia (Gardiner 2012 **Level II**, n=40, JS 3). However, comparing PVB to general anaesthesia for minor breast surgery in a day-care setting, the benefits were small and may not justify the increased risk (Terheggen 2002 **Level II**, n=30, JS 3).

Upper and lower limb blocks

A single-injection femoral nerve block with bupivacaine or ropivacaine for anterior cruciate ligament reconstruction provided superior postoperative analgesia to placebo block for up to 24 h (Mulroy 2001 **Level II**, n=53, JS 5; Wulf 2010 **Level II**, n=280, JS 3). There was an associated decreased requirement for recovery-room stay and unplanned hospital admission with the potential for cost savings (Williams 2004 **Level III-3**). After complex outpatient knee surgery, femoral-sciatic nerve block provided better pain relief than femoral nerve block alone, and both techniques reduced unplanned hospital admissions similarly compared to no block at all (Williams 2003 **Level IV**).

In patients undergoing ambulatory arthroscopic medial meniscectomy, an US-guided adductor canal block compared to sham block as part of a multimodal analgesic regimen significantly reduced resting pain scores in PACU and for up to 24 h with a 38% reduction in 24 h opioid requirements and no clinical episodes of leg weakness (Hanson 2013 **Level II**, n=50, JS 5).

Interscalene (Bishop 2006 **Level IV;** Faryniarz 2006 **Level IV**) and supraclavicular (Liu 2010 **Level IV**) plexus block provided safe and effective analgesia after ambulatory shoulder surgery. For hand and wrist surgery, infraclavicular nerve blocks with propofol sedation, compared with general anaesthesia followed by local anaesthetic wound infiltration, resulted in less postoperative pain, less nausea, earlier ambulation and earlier hospital discharge (Hadzic 2004 **Level II**, n=52, JS 3). US-guided peripheral nerve blocks with ropivacaine can be added to brachial plexus anaesthesia with lignocaine to prolong analgesia after hand surgery, while avoiding significant motor block (Dufeu 2014 **Level IV**).

Pelvic plexus block

Pelvic plexus block provided better intra and postoperative analgesia than periprostatic nerve block for ambulatory transrectal US-guided prostate biopsy (Cantiello 2012 **Level II**, n= 180, JS 3).

Paracervical block

In awake patients, paracervical local anaesthesia for cervical dilatation and uterine intervention reduced intraoperative pain compared to placebo (10 studies), but failed to show a benefit over sedation (6 studies) or other local anaesthesia techniques for postoperative

pain. Overall, no recommendations regarding benefits could be made (Tangsiriwatthana 2013 **Level I** [Cochrane], 26 RCTs, n=2,790).

Adjuvants to single-injection peripheral nerve block

Dexamethasone

Caudal dexamethasone improved the quality and duration of caudal epidural ropivacaine analgesia in a paediatric day-stay orchidopexy population (Kim 2014a **Level II**, n=80, JS 5). For arthroscopic ambulatory shoulder surgery, interscalene block with 0.5% ropivacaine was significantly prolonged by both systemic and perineural dexamethasone (10 mg), with both dexamethasone groups requiring less analgesics in the first 48 h compared to placebo (Desmet 2013 **Level II**, n=150, JS 5). When dexamethasone 4 mg was added to interscalene ropivacaine for shoulder arthroscopy, median duration of analgesia was significantly longer than systemic administration (18 h vs 14 h), which was similar to placebo. (Kawanishi 2014 **Level II**, n=39, JS 3)

Dexmedetomidine

When added to caudal ropivacaine for paediatric day-stay patients undergoing lower abdominal and perineal surgery, dexmedetomidine 0.5–1.5 mcg/kg prolongs analgesia with minor prolongation of motor block, time to void and sedation, without increased hypotension or delay in hospital discharge (Bharti 2014 **Level II**, n=80, JS 5). In a similar study, the incidence of postoperative agitation and analgesic use in the first 24 h were significantly reduced by caudal adjuvant dexmedetomidine 1 mcg/kg (Saadawy 2009 **Level II**, n=60, JS 4). Dexmedetomidine added to ropivacaine for interscalene plexus block improved and prolonged duration of analgesia (14 vs 18 h) (Fritsch 2014 **Level II**, n=62, JS 5).

Buprenorphine

Buprenorphine added to local anaesthetic for brachial plexus and intraoral blocks increased the duration of analgesia compared to local anaesthetic alone (Candido 2001 **Level II**, n=40, JS 5; Modi 2009 **Level II**, n=50, JS 3; Kumar 2013 **Level II**, n=100, JS 3). However, with infragluteal sciatic block for foot and ankle surgery, when buprenorphine was either added to bupivacaine or given IM, there was only a modest analgesic benefit, with increased vomiting in the groups receiving buprenorphine (Candido 2010 **Level II**, n=103, JS 5).

Ketamine

A systematic review of ketamine 0.25–0.5 mg/kg added to caudal local anaesthetic prolongs analgesia (time to first request) by a median difference of 5.6 h without prolonged motor block (Schnabel 2011 **Level I** [PRISMA], 13 RCTs, n=884). Of the 13 RCTs, 9 were in the ambulatory paediatric population. Although many adverse effects were more frequent in the ketamine group, there was no significant difference to placebo. However, concerns of local neurotoxicity *in vitro* continue to limit the use of neuraxial ketamine, in particular when combined with lignocaine (Werdehausen 2011 **NR**).

Continuous peripheral nerve block

Upper and lower limb blocks

Patients may suffer intense pain following resolution of a PNB, although it maximises pain relief in the first 12–24 h (Chung 1997 **Level IV**). CPNB using perineural catheters and continuous infusions of local anaesthetic led to sustained postoperative analgesia (Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5; Zaric 2004 **Level II**, n=63, JS 5), was opioid-sparing (Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5; Ilfeld 2003 **Level II**, n=25, JS 5) and resulted in less sleep disturbance (Ilfeld 2002b **Level II**, n=30, JS 5; Ilfeld 2002a **Level II**, n=30, JS 5) and improved rehabilitation (Capdevila 1999 **Level II**, n=56, JS 2).

Patients achieved discharge criteria significantly earlier in a number of settings approaching short-stay discharge times: after total shoulder arthroplasty with use of continuous interscalene blocks (21 vs 51 h) (Ilfeld 2006 **Level II**, n=29, JS 5); after hip arthroplasty with use of continuous lumbar plexus block (29 vs 52 h) (Ilfeld 2008a **Level II**, n=47, JS 5); and after total knee arthroplasty with the use of continuous FNBs (25 vs 71 h) (Ilfeld 2008b **Level II**, n=50, JS 5). These benefits have the potential to reduce hospital costs (Ilfeld 2007 **Level III-3**). Similar benefits have

been observed with a range of CPNBs in a predominantly paediatric population (Gurnaney 2014 **Level IV**).

Compared with a single-injection interscalene block, a 2-d interscalene infusion at home after shoulder surgery was opioid-sparing and improved pain relief, sleep and patient satisfaction (Mariano 2009 **Level II**, n=32, JS 5). Patient-controlled bolus added to continuous infusion of ropivacaine improved analgesia and function more than a continuous infusion and even more so compared with IV morphine PCA (Capdevila 2006 **Level II**, n=86, JS 4).

While patient satisfaction is high, failure of brachial plexus catheters within 72 h of insertion in the ambulatory setting may be as high as 26% for supraclavicular and 19% for infraclavicular approaches (Ahsan 2014 **Level IV**). Continuous popliteal sciatic nerve block for foot and ankle surgery has a high success rate and a low rate of complications, with a catheter dislocation rate of 0.2%. (Borgeat 2006 **Level IV**)

Paravertebral blocks

Continuous PVB after short-stay mastectomy with 0.4% ropivacaine vs saline at 5 mL/h for 3 d demonstrated improved pain scores and less pain-induced physical and emotional dysfunction for the infusion duration (Ilfeld 2014 **Level II**, n=60, JS 5). Adding a continuous infusion to maintain the PVB after a single-injection block for outpatient breast cancer surgery did not add further benefits (Buckenmaier 2010 **Level II**, n=94, JS 5).

Safety and management of continuous peripheral nerve blocks in an ambulatory setting

The safety and efficacy of CPNBs in an ambulatory setting has been confirmed in adult (Swenson 2006 **Level IV**; Fredrickson 2008 **Level IV;** Nye 2013 **Level IV**) and paediatric patients (Ganesh 2007 **Level IV**; Ludot 2008 **Level IV;** Gurnaney 2014 **Level IV**).

Inadvertent intravascular catheter placement needs to be excluded prior to patient discharge using a test dose of local anaesthetic and adrenaline (epinephrine) (Rawal 2002 **NR**). Patients and their carers should be given extensive oral and written instructions about management, adverse effects and care of the local anaesthetic catheter, and have 24 h telephone access to an anaesthesiologist during the postoperative period while CNPB is in use (Swenson 2006 **Level IV**) as 30% of patients make unscheduled phone calls regarding catheter infusions despite been given adequate written and verbal instructions (Ilfeld 2002a **Level IV**). A review of 620 outpatients with CPNB (including popliteal fossa, fascia iliaca and interscalene) showed that 4.2% required assistance by the anaesthesiologist after discharge from hospital for problems relating to issues such as patient education, inadequate analgesia and equipment malfunction; only one patient was unable to remove their catheter (Swenson 2006 **Level IV**), although patients may have significant anxiety about catheter removal at home (Ilfeld 2004 **Level IV**).

Detailed narrative reviews of the use of CPNBs for ambulatory surgery have been published (Ilfeld 2011 **NR;** Salinas 2014 **NR**)

Discharge analgesia

A survey of day-surgery practices in 100 hospitals in 8 European countries reported take-home analgesics were provided as a "tablet-package" by 69% or as prescription by 80% of hospitals (Stomberg 2013). Strong opioids on discharge were given or prescribed by 59% of units. Written instructions about management of pain were provided by 69% of units.

Early discharge after day-stay surgery with a prescription of opioids or NSAIDs carries an increased risk of subsequent long-term use of these analgesics. In a population of 391,139 opioid-naïve patients aged >65 y having short-stay surgery, patients receiving an opioid prescription within the 7 d after surgery were more likely to become long-term opioid users within 1 y in comparison to those without a prescription (OR 1.44; 95%CI 1.39 to 1.50) (Alam 2012a **Level IV**). Discharge NSAID prescriptions were also more likely to be associated with persistent use (OR 3.74; 95%CI 3.27 to 4.28) (see Section 8.11).

8.1.7.3 Nonpharmacological techniques

Nonpharmacological techniques such as TENS, acupuncture, hypnosis, US, laser and cryoanalgesia have also been used in the treatment of acute pain management after

ambulatory surgery. Pressure on acupoints decreased pain following knee arthroscopy (Felhendler 1996 **Level II**, n=44, JS 3). TENS resulted in a significant, but clinically trivial reduction of pain after endometrial biopsy compared to placebo TENS (Yilmazer 2012 **Level II**, n=65, JS 1). Continuous-flow cold therapy has been shown to be effective following outpatient anterior cruciate ligament reconstruction, also reducing analgesic requirements (Barber 1998 **Level II**, n=100, JS 1).

Key messages

1. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia, but not motor block (**N**) (**Level I** [PRISMA]); however concerns regarding neurotoxicity remain.
2. Wound infiltration and intraperitoneal instillation with local anaesthetics for short-stay laparoscopic cholecystectomy has good analgesic efficacy, in particular when administered prior to trocar insertion and at commencement of pneumoperitoneum respectively (**N**) (**Level I**).
3. Intraperitoneal instillation with local anaesthetic provides good analgesia for up to 6 hours after short-stay gynaecologic laparoscopy (**N**) (**Level I**).
4. In the short-stay surgery setting, anti-inflammatories (nonselective NSAIDs, coxibs and dexamethasone) contribute to reduced pain and improved recovery (**N**) (**Level II**).
5. Infiltration of the wound with local anaesthetic provides effective and long-lasting analgesia after many short-stay procedures (**S**) (**Level II**).
6. Single-injection peripheral nerve blocks with long-acting local anaesthetics provide long-lasting postoperative analgesia after short-stay surgery (**S**) (**Level II**).
7. Continuous peripheral nerve blocks provide extended analgesia after short-stay surgery, leading to reduced opioid requirements, earlier achievement of discharge criteria, less sleep disturbance and improved early rehabilitation (**S**) (**Level II**).
8. Paravertebral block improves pain-related outcomes after short-stay major breast surgery and hernia repair (**N**) (**Level II**).
9. Buprenorphine or dexmedetomidine added to local anaesthetics for peripheral nerve blocks prolongs duration of analgesia after short-stay surgery (**N**) (**Level II**).
10. Dexamethasone added to local anaesthetics or given systemically in peripheral nerve blocks prolongs duration of analgesia after short-stay surgery (**N**) (**Level II**).
11. Pain relief after short-stay surgery remains poor (**U**) (**Level IV**) and is a common cause of unplanned re-presentation (**U**) (**Level III-3**).
12. Continuous peripheral nerve blocks have been shown to be safe at home after short stay surgery, if adequate resources and patient education are provided (**U**) (**Level IV**).

8.1.8 Cranial neurosurgery

There is a widespread belief that intracranial surgery does not result in much patient discomfort and pain. However, surveys have shown that patients have significant pain in the early phase after intracranial surgery; the incidence of acute post craniotomy pain varies from 27% (de Oliveira Ribeiro Mdo 2013 **Level IV**) to 80% of patients (Gottschalk 2007 **Level IV;** Nemergut 2007 **Level IV**). These findings are in line with other studies that found incidences of 56% moderate and 25% severe pain (Thibault 2007 **Level IV**) and of 87% pain overall in the first 24 h (NRS 1–3: 32%; NRS 4–7: 44%; NRS 8–10: 11%) despite conventional pain management (Mordhorst 2010 **Level IV**). In a paediatric population, 35% of patients had moderate to severe pain in the immediate postoperative setting but this reduced to 8% at 1 d (Bronco 2014 **Level IV**). Similarly, 42% of children had at least one episode of pain ≥3/10 in the first 72 h after craniotomy (Teo 2011 **Level IV**).

However, the pain is not as severe as after other surgical procedures such as extracranial maxillary/mandibular surgery or lumbar surgery (Dunbar 1999 **Level III-2**; Klimek 2006 **Level III-2**).

The findings that the pain is more severe after an infratentorial rather than a supratentorial approach (Gottschalk 2007 **Level IV**) are disputed by another study (Irefin 2003 **Level III-2**). Noncraniotomy neurosurgery, for example trans-sphenoidal surgery, seems to be associated with very limited pain and minimal morphine requirements (Flynn 2006 **Level IV**).

It is noteworthy that craniotomy can lead to significant chronic headache, defined as postcraniotomy headache by the International Headache Society (Headache Classification Committee 2013). At 6 mth after supratentorial craniotomy for aneurysm repair, 40% of patients reported headache, of whom 10.7% had acute and 29.3% chronic headache (Rocha-Filho 2008 **Level IV**). A review of the issues related to postcraniotomy headache has been published (Molnar 2014 **NR**).

The management of postoperative pain after intracranial surgery is often poor. The problems of postcraniotomy analgesia were analysed in a survey of UK neurosurgical centres (Roberts 2005 **Level IV**); the principal analgesic was IM codeine, only 3 of 23 centres used morphine and only one used PCA. Pain was only assessed in 57% of cases (Roberts 2005 **Level IV**). Similar data are reported in a survey of Canadian neurosurgeons, with 59% describing codeine as their first-line opioid (Hassouneh 2011 **Level IV**). This practice has changed little since 1995, when IM codeine was the primary analgesic used by 97% of centres (Stoneham 1995 **Level IV**).

Concerns about the adverse effects of opioids and their ability to interfere with recovery and neurological assessment contribute to this, as well as the concern that opioid-induced respiratory depression will lead to hypercarbia and increased intracranial pressure (Nemergut 2007). Similarly, there is a concern that NSAIDs could interfere with haemostasis and increase intracranial bleeding. Furthermore, there is poor evidence on which to base protocols for the assessment and treatment of pain after cranial surgery (Nemergut 2007 **NR**); the limited number of trials are heterogeneous and have many weaknesses in study design and methodology. The question remains as to whether all craniotomies are the same with regard to analgesic requirements.

8.1.8.1 Treatment of acute postoperative pain after cranial neurosurgery

A systematic review of pain treatment after craniotomy identified scalp infiltration and morphine use as the only evidence-based approaches but could not make firm recommendations due to limited data (Hansen 2011 **Level I**, 9 studies, n=519).

Paracetamol

A trial comparing paracetamol (acetaminophen) alone with paracetamol plus tramadol or paracetamol plus nalbuphine was stopped early as paracetamol alone gave ineffective pain relief in most patients (Verchere 2002 **Level II**, n=64, JS 5). Another case series found that oral paracetamol only reduced pain effectively in 27% of patients post supratentorial craniotomy (Nair 2011 **Level IV**).

Nonselective NSAIDs

Ketoprofen was more effective than paracetamol in reducing PCA opioid requirements after craniotomy but with minimal benefits in regard to pain scores and no change in adverse effects (Tanskanen 1999 **Level II**, n=45, JS 4). Similarly, diclofenac was superior to placebo and comparable to another nonopioid analgesic, flupirtine, for pain post craniotomy (Yadav 2014 **Level II**, n=390, JS 2). However, a single-centre, retrospective cohort study of 6,668 cases over 5 y identified an association between the development of postoperative haematoma and the use of aspirin or nsNSAIDs (Palmer 1994 **Level IV**).

Coxibs

There was no benefit with a single dose of parecoxib over the first 24 h postoperatively with regard to pain scores, morphine use and analgesia-related adverse effects in one study (Williams 2011 **Level II,** n=100, JS 5), although another study showed limited benefit over the first 6 h postoperatively (Jones 2009 **Level II**, n=82, JS 5).

Opioids

IV PCA morphine (with or without ondansetron) was superior to placebo after infratentorial craniotomy (Jellish 2006 **Level II**, n=120, JS 5). Morphine was also more effective than codeine following craniotomy; this was found for IM PRN administration of both compounds (Goldsack 1996 **Level II**, n=40, JS 3), but also in a comparison of PCA morphine with IM codeine (Sudheer 2007 **Level II**, n=60, JS 3). PCA morphine provided better analgesia than PCA tramadol (Sudheer 2007 **Level II**, n=60, JS 3). PCA fentanyl was more effective than PRN IV fentanyl and did not increase the risk of adverse effects after craniotomy, although more fentanyl was used in the PCA group (Morad 2009 **Level II**, n=79, JS 2; Jalili 2012 **Level II**, n=80, JS 5).

Codeine 60 mg IM was more effective than tramadol 50 mg or 75 mg IM (Jeffrey 1999 **Level II**, n=75, JS 5). However, the addition of tramadol 100 mg twice daily to a paracetamol and morphine or oxycodone analgesic regimen improved analgesia and reduced opioid requirements compared to placebo (Rahimi 2010 **Level II**, n=50, JS 2).

The intraoperative use of remifentanil may result in increased pain and/or increased analgesia requirements postoperatively (see Section 4.1.3). This was found when compared with both fentanyl (Gelb 2003 **Level II**, n=91, JS 4) and sufentanil (Gerlach 2003 **Level II**, n=36, JS 3).

Local anaesthetic scalp block

A meta-analysis found that regional scalp block improved pain scores up to 12 h postoperatively and reduced opioid requirements until 24 h postoperatively against placebo block (Guilfoyle 2013 **Level I** [PRISMA], 7 studies, n=325). An RCT performed after this meta-analysis confirmed not only better analgesia after aneurysm clipping but also improved outcome (reduced PCA consumption, requirement for a postoperative antihypertensive agent and PONV incidence) with scalp block (0.75% levobupivacaine compared to placebo) (Hwang 2015 **Level II**, n=52, JS 5). Scalp blocks have also been used in children following craniosynostosis repair (Pardey Bracho 2014 **Level IV**).

Adjuvant drugs

Clonidine did not improve analgesia after supratentorial craniotomy (Stapelfeldt 2005 **Level II**, n=34, JS 3).

Gabapentin improved postoperative analgesia and reduced opioid consumption, but increased sedation and delayed extubation (by 12 min), when compared to phenytoin perioperatively for supratentorial craniotomy (Ture 2009 **Level II**, n=80, JS 2). This was contradicted by a later study, which was however inadequately powered with pain relief only as a secondary outcome (Misra 2013 **Level II**, n=79, JS 4).

Physical therapies

Cryotherapy (cold bags and ice gel packs) improved pain control along with eyelid oedema and facial ecchymosis after craniotomy (Shin 2009 **Level II**, n=97, JS 3).

Key messages

1. Local anaesthetic infiltration of the scalp provides early analgesia after craniotomy (**S**) (**Level I** [PRISMA]).
2. Morphine is more effective than codeine and tramadol for pain relief after craniotomy (**U**) (**Level II**).
3. Craniotomy leads to significant pain in the early postoperative period (**U**) (**Level IV**), which is however not as severe as pain from other surgical interventions (**U**) (**Level III-2**).
4. Craniotomy can lead to significant chronic headache (**U**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Acute pain following craniotomy is underestimated and often poorly treated (**N**).

8.1.9 Spinal surgery

A considerable number of patients presenting for surgery on the spine have pre-existing persistent and/or acute pain and some may be on long-term analgesic medications. Therefore managing acute postoperative pain can be more difficult with an increased risk of persistent postoperative pain.

8.1.9.1 Paracetamol

Use of IV paracetamol compared to placebo is associated with better analgesia postoperatively, although an opioid-sparing effect was not demonstrated (Cakan 2008 **Level II**, n=40, JS 4).

8.1.9.2 NSAIDs

Consistent with general postoperative data, nsNSAIDs have demonstrated analgesic benefit and are opioid-sparing in spinal surgery (Jirarattanaphochai 2008 **Level I** [QUOROM], 11 RCTs, n=486).

A meta-analysis of retrospective studies of spinal fusion concluded that the use of normal doses of nsNSAIDs or coxibs for <14 d postoperatively was not associated with increased nonunion (Li 2011 **Level III-3 SR**, 5 studies, n=1,403). However, high-dose ketorolac (>120 mg/d) was associated with increased rates of nonunion (RR 2.9; 95%CI 1.5 to 5.4).

8.1.9.3 Opioids

A small RCT comparing a single dose of methadone to sufentanil infusion intraoperatively showed methadone provided better pain relief at 48 h and reduced opioid requirements at 48 h and 72 h after surgery (Gottschalk 2011 **Level II**, n=29, JS 5).

8.1.9.4 Local infiltration anaesthesia

LIA with local anaesthetic and steroid is associated with less pain and analgesic requirement compared to placebo infiltration (Gurbet 2014 **Level II**, n=60, JS 5). Preincision infiltration with local anaesthetic provided additional benefits compared to infiltration at wound closure; addition of steroid did not improve analgesic efficacy (Ersayli 2006 **Level II**, n=75, JS 3; Gurbet 2008 **Level II**, n=100, JS 1).

8.1.9.5 Adjuvants

Alpha-2-delta ligands (gabapentin and pregabalin)

Both gabapentin and pregabalin reduced postoperative pain and opioid requirements after lumbar spinal surgery (Yu 2013 **Level I** [PRISMA], 7 RCTs, n=434). Two of the studies included in this meta-analysis examined variable doses suggesting that the maximal benefit of gabapentin is achieved with 600 mg (Pandey 2005 **Level II**, n=100, JS 5) to 900 mg (Khan 2011 **Level II**, n=175, JS 5) with no further benefit in larger doses.

Long-term benefits of perioperative gabapentin or pregabalin use beyond the acute postoperative period after lumbar spine surgery were found in three studies. After lumbar discectomy, pain intensity was reduced and functional outcome improved at 3 mth with perioperative pregabalin administration (Burke 2010 **Level II**, n=40, JS 5; Khurana 2014 **Level II**, n=90, JS 4) and quality of life was improved at 3 mth but not at 1 y (Gianesello 2012 **Level II**, n=60, JS 5). In one of these studies, 75 mg pregabalin every 8 h for 7 d was more effective than 300 mg gabapentin administered in the same way (Khurana 2014 **Level II**, n=90, JS 4).

Dexamethasone

High-dose dexamethasone (16 mg) improved the analgesic effect of perioperative pregabalin for 48 h with functional benefits extending to 1 mth postoperatively (Choi 2013 **Level II**, n=108, JS 5).

Lignocaine

A perioperative lignocaine infusion reduced pain scores and postoperative opioid requirements (Farag 2013 **Level II**, n=116, JS 5; Kim 2014c **Level II**, n=51, JS 5).

Ketamine

Ketamine as an adjunct to PCA fentanyl after lumbar spinal surgery decreased fentanyl requirements, but increased nausea with no other benefits (Song 2013 **Level II**, n=50, JS 5).

Magnesium

A perioperative magnesium infusion reduced pain scores and analgesic requirements and improved patient satisfaction (Levaux 2003 **Level II**, n=24, JS 5). However, this might be due to reduction of OIH associated with perioperative remifentanil infusion rather than an additional analgesic benefit.

Epidural analgesia

Epidural analgesic paste containing methylprednisolone and/or morphine applied to the epidural space at the site of removed lamina has limited efficacy (see Section 4.1.2).

Key messages

1. Perioperative use of gabapentin or pregabalin improves analgesia and reduces opioid requirements after spinal surgery (**N**) **(Level I)** [PRISMA].
2. NSAIDs provide analgesic benefits as well as opioid-sparing effects after spinal surgery (**N**) (**Level I** [QUOROM]).
3. Perioperative pregabalin improves functional outcome after laminectomy at 3 months (**N**) (**Level II**).
4. Local infiltration anaesthesia improves analgesia and reduces opioid requirements after spinal surgery; this benefit is enhanced with preincision infiltration compared to infiltration at wound closure (**N**) (**Level II**).
5. Perioperative systemic lignocaine infusion improves analgesia and reduces opioid requirements after spinal surgery (**N**) (**Level II**).
6. NSAID use for less than 14 days does not increase the risk of nonunion after spinal fusion, except with high-dose ketorolac (**N**) (**Level III-3**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Acute pain management following spinal surgery is often complicated by preoperative chronic pain and long-term medication use (**N**).

8.2 Acute pain following spinal cord injury

Acute pain following SCI is common, with over 90% of patients experiencing pain in the first 2 wk following injury (Siddall 1999 **Level IV**). Acute pain may also develop during the rehabilitation phase due to intercurrent disease (eg renal calculus) or exacerbation of a chronic pain syndrome.

Pain associated with SCI usually falls into two main categories: neuropathic pain, either at or below the level of the injury, and nociceptive pain, from somatic and visceral structures (Bryce 2012 **GL**). Neuropathic pain associated with a lesion or disease of the central somatosensory nervous system is termed central neuropathic pain (Jensen 2011 **GL**). Phantom pain and complex regional pain syndromes may also develop in patients with SCI.

Table 8.1 Taxonomy of acute pain associated with spinal cord injury pain

Pain type	Pain subtype	Primary pain source or pathology
Neuropathic pain	At level	eg cauda equina compression, nerve root compression, spinal cord compression
	Below level	eg spinal cord compression or ischaemia
	Other	eg trigeminal neuralgia, diabetic neuropathy
Nociceptive pain	Somatic	eg musculoskeletal pain (eg vertebral fracture, muscle spasms, overuse syndromes)
		procedure-related pain (eg pressure sore dressings)
	Visceral	eg renal calculus, pain due to bowel impaction
Other		eg complex regional pain syndrome

Source: *Based on the International Spinal Cord Injury Pain Classification (*Siddall 2002 **GL***;* Bryce 2012 **GL***).*

8.2.1 Treatment of acute neuropathic pain after spinal cord injury

There are only case series specifically examining the treatment of acute neuropathic pain following SCI.

Three patients with acute neuropathic pain following SCI were administered 100 IU of calcitonin SC in addition to other medications with improved pain relief in each person and reduced analgesic requirements (Humble 2011 **Level IV)**.

Thirteen patients with acute neuropathic SCI pain received IV ketamine (50 mg over 2 h, twice daily for several days followed by 50 mg orally for up to 3 mth) with a mean pain reduction of 75% at the time of treatment cessation (mean 17 d) with further benefit over the subsequent months (Kim 2013a **Level IV).**

Treatment of acute neuropathic pain must therefore be based on evidence from studies of chronic central neuropathic pain and other neuropathic pain syndromes (see below). An algorithm for the treatment of pain in patients with SCI has been promulgated (Siddall 2006b **GL**).

8.2.2 Treatment of chronic neuropathic pain after spinal cord injury

8.2.2.1 Opioids and tramadol

Under experimental conditions, IV alfentanil decreased central pain following SCI compared with placebo and ketamine (Eide 1995 **Level II**, n=9, JS 5). IV morphine decreased tactile allodynia but had no effect on other neuropathic pain components in SCI and poststroke patients (Attal 2002 **Level II**, **n=**21, JS 5). Tramadol was effective for the treatment of neuropathic pain after SCI but the incidence of adverse effects was high (Norrbrink 2009 **Level II**, n=35, JS 4). A review of animal studies is concerning here as it shows that high doses of opioids in the acute (<14 d) period following SCI may be associated with impaired locomotor recovery and increased risk of the development of pain and infection (Woller 2013 **BS**). Although these findings have not been verified in clinical studies, they suggest the need for caution in administering high doses of opioids in the acute period post injury.

8.2.2.2 Ketamine

Ketamine infusion decreased acute (see above) and chronic neuropathic pain in SCI patients. IV Ketamine is superior to placebo and comparable to IV lignocaine and IV alfentanil in the treatment of pain after SCI (Teasell 2010 **Level I**, 2 RCTs [ketamine], n=19).

8.2.2.3 Membrane stabilisers

There is good evidence to support the effectiveness of lignocaine and mexiletine, when data from neuropathic pain studies done in a variety of conditions including neuropathic SCI pain are grouped together (Challapalli 2005 **Level I** [Cochrane], 30 RCTs, n=750). However, the effects

in SCI specifically are mixed. IV lignocaine reduced neuropathic pain in SCI (Finnerup 2005a **Level II**, n=24, JS 5) and reduced spontaneous pain and brush allodynia in central pain (Attal 2000 **Level II**, n=16, JS 4). Other trials have found that lignocaine reduced pain in only one of ten SCI patients (Kvarnstrom 2004 **Level II**, n=10, JS 5) and that mexiletine was ineffective (Chiou-Tan 1996 **Level II**, n=11, JS 2). Lignocaine was most effective in the treatment of neuropathic pain due to peripheral nerve lesions (Kalso 1998 **Level I**, 17 studies, n=450).

8.2.2.4 Antidepressants

There was no significant difference in pain or disability in SCI patients with chronic pain treated with amitriptyline or placebo (Cardenas 2002 **Level II**, n=84, JS 4); however amitriptyline improved below-level neuropathic pain in patients with depression (Rintala 2007 **Level II**, n=38, JS 5). There are no studies of SSRIs in the treatment of central neuropathic pain (Finnerup 2005b **Level I**, 0 RCTs [SSRIs], n=0). There was no significant effect of duloxetine on the intensity of neuropathic pain in patients with either brain injury or SCI (Vranken 2011 **Level II**, n=48, JS 5).

8.2.2.5 Anticonvulsants

Alpha-2-delta ligands (gabapentin and pregabalin) are effective for the treatment of neuropathic pain after SCI (Mehta 2014 **Level I**, 8 RCTs, n=524). Included within these are three RCTs that support the use of pregabalin for the treatment of neuropathic pain following SCI (Siddall 2006a **Level II**, n=136, JS 5; Vranken 2008 **Level II**, n=21, JS 5; Cardenas 2013 **Level II**, n=220, JS 5). Smaller trials support the effectiveness of gabapentin in decreasing central neuropathic pain and improving QoL (Levendoglu 2004 **Level II**, n=20, JS 4; Tai 2002 **Level II**, n=7, JS 5).

Lamotrigine reduced spontaneous and evoked pain in patients with incomplete SCI (Finnerup 2002 **Level II**, n=30, JS 5). Valproate was ineffective in the treatment of SCI pain (Drewes 1994 **Level II**, n=20, JS 3).

8.2.2.6 Cannabinoids

The cannabinoid dronabinol did not improve pain intensity in people with chronic neuropathic SCI pain (Rintala 2010 **Level II**, n=7, JS 5).

8.2.2.7 Intravenous anaesthetics

An IV bolus of low-dose propofol reduced the intensity of central neuropathic pain and allodynia for up to 1 h in approximately 50% of patients (Canavero 2004 **Level II**, n=21, JS 4).

8.2.2.8 Nonpharmacological treatment

TENS has been trialled in people with chronic neuropathic SCI pain but the results are mixed. A case series using both low-frequency and high-frequency TENS found no effect in relieving pain with either modality (Norrbrink 2009 **Level III-2**). However, a more recent case-control study found that low-frequency TENS was effective in reducing pain intensity in people with neuropathic SCI pain (Celik 2013 **Level III-1**). Self-hypnosis has also been found to be beneficial in people with neuropathic SCI pain (Jensen 2009 **Level II**, n=37, JS 5).

8.2.3 Treatment of nociceptive and visceral pain after spinal cord injury

There is no specific evidence to guide the treatment of acute nociceptive and visceral pain in SCI patients. Treatment is therefore based on evidence from other studies of nociceptive and visceral pain and is usually directed at treating the specific underlying cause of the pain.

Key messages

1. Alpha-2-delta ligands (gabapentin/pregabalin) are effective in the treatment of neuropathic pain following spinal cord injury (**S**) (**Level I**).
2. Intravenous opioids, ketamine ((**S**) (**Level I**), lignocaine (lidocaine), tramadol and self-hypnosis are effective in the treatment of neuropathic pain following spinal cord injury (**U**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Treatment of acute spinal cord injury pain is largely based on evidence from studies of other neuropathic and nociceptive pain syndromes (**U**).

8.3 Acute burns injury pain

Acute pain following burns injury can be nociceptive and/or neuropathic in nature (Gray 2008a **NR**) and may be constant (background pain), intermittent or procedure-related. The multifaceted character of burns injury pain requires a broad-based assessment tool for clinical application and research, which is currently not available (Mahar 2012 **Level I**, 25 RCTs, n≈800).

Burns pain is often undertreated, particularly in the elderly (Choiniere 2001 **NR**). However, effective pain management after acute burns injury is essential, not only for humanitarian and psychological reasons but also to facilitate procedures such as dressing changes and physiotherapy and possibly to minimise the development of chronic pain, which is reported in 18–58% of burns patients (Choiniere 1989 **NR;** Dauber 2002 **Level IV**; Browne 2011 **Level IV**).

More severe acute pain following burns injury leads to a greater risk of post-traumatic stress disorder (McGhee 2011 **Level IV**; Browne 2011 **Level IV**). Increased early use of opioids in children with burns injury reduces post-traumatic stress symptoms up to 4 y after the injury (Sheridan 2014 **Level III-3**).

There is limited evidence for the management of pain in burns injury, and treatment continues to be largely based on evidence from several randomised clinical trials, case reports and case series, or data extrapolated from other relevant areas of pain medicine. The use of a highly protocolised pain management flowchart may be helpful in improving the pain experience (Yang 2013 **Level III-3**).

8.3.1 Management of background nociceptive pain

Immediately after the injury, simple measures such as cooling (Davies 1982 **NR**), covering and immobilising the burn may provide analgesia (Kinsella 1991 **NR**; Gallagher 2000b **NR**; Allison 2004a **GL**). Cooling under running tap water for 20 min or the application of a wet towel (ANZBA 2014 **GL**) is supported by porcine data (Rajan 2009 **BS**) and is useful up to 3 h post initial burn injury. Temporary burns dressings such as cellophane type kitchen wrap and clean sterile sheets reduce pain caused by contact and draft; they should not be applied circumferentially as swelling is inherent (Allison 2004a **GL**; ANZBA 2014 **GL**).

In the initial presentation of severe burn, analgesia is best achieved by titration of IV opioids. Absorption of IM and SC opioids may be unreliable in the presence of hypovolaemia and vasoconstriction associated with burns (Kinsella 2008). PCA with morphine is effective for burns pain in adults (Choiniere 1992 **Level II**, n=24, JS 4) and children (Gaukroger 1991 **Level IV**). Conversion to oral opioids is possible once normal gastrointestinal function has returned; even severe burns injury does not affect gastric emptying or the absorption of oral paracetamol (Hu 1993 **Level III-2**).

Morphine doses do not require adjustment in burns injury, as its pharmacokinetics are unchanged in burns patients (Perreault 2001 **PK**; Kinsella 2008 **NR**)

8.3.2 Management of acute neuropathic pain and hyperalgesia

Animal and human volunteer studies in burns injury have shown that secondary hyperalgesia develops around the injured site. In addition, burns injury results in damage to cutaneous nociceptors and conducting neurons that may lead to acute neuropathic pain. There is growing evidence that the addition of antihyperalgesic agents is an important part of multimodal treatment of burn injury pain.

Gabapentin reduced pain and opioid consumption following acute burns injury (Cuignet 2007 **Level III-3**) and reduced neuropathic pain descriptors in a small case series (Gray 2008b **Level IV**).

Pregabalin reduced pain in outpatient burns patients (Wong 2010 **Level IV**) and reduced "hot" and "sharp" pain as well as itch and procedural pain in severe burns injury (Gray 2011 **Level II**, n=90, JS 5).

Parenteral methylprednisolone or ketorolac reduced secondary hyperalgesia surrounding an experimental burns injury in human volunteers, however further clinical research is required prior to recommending these agents (Stubhaug 2007 **Level II**, n=12, JS 5).

There is also evidence in human volunteers for beneficial effects of ketamine (McGuinness 2011 **Level I**, 4 RCTs, n=67) and dextromethorphan (Ilkjaer 1997 **Level II**, n=24, JS 3) in a burns injury model. The systematic review of ketamine showed efficacy as an analgesic and in reducing secondary hyperalgesia without relevant adverse effects; however the limitations of the studies included (no clinical studies, heterogeneity of results, small study size) preclude any definitive recommendations on clinical use of ketamine in a burns setting (McGuinness 2011 **Level I EH**, 4 RCTs, n=67).

8.3.3 Management of procedural pain

Treatment and rehabilitative procedures for burns patients may be associated with frequent and prolonged periods of pain. It was previously reported that up to 84% of burns patients experience extreme and intense pain during therapeutic procedures (Ashburn 1995 **NR**). Analgesic strategies have more recently improved but managing procedural pain remains a significant and ongoing challenge that requires a balance of pharmacological and nonpharmacological approaches.

8.3.3.1 Opioids

Opioid therapy is the mainstay of analgesia for burns procedures. However, very high doses may be required (Linneman 2000 **Level IV**) and opioid-related sedation and respiratory depression may develop when the pain stimulus decreases following the procedure.

Short-acting opioids such as fentanyl (Prakash 2004 **Level II**, n=60, JS 4) or alfentanil (Sim 1996 **Level IV**) administered via PCA or target-controlled IV infusions (Gallagher 2000a **Level IV**) successfully provide analgesia during burns dressing changes. IN fentanyl was a viable alternative to oral morphine in children for burns dressings (Borland 2005 **Level II**, n=28, JS 4). In adults, there was no difference in pain scores or rescue analgesic requirements between IN fentanyl and oral morphine for burns dressings (total surface less than 26%) (Finn 2004 **Level II**, n=26, JS 5). Oral transmucosal fentanyl provided similar analgesia to oral oxycodone (Sharar 2002 **Level II**, n=20, JS 4) and hydromorphone (Sharar 1998 **Level II**, n=14, JS 4) with a similar adverse-effect profile in children and adolescents (see Section 9.7.2).

8.3.3.2 Adjuvants

N_2O, ketamine and IV lignocaine infusions (Jonsson 1991 **Level IV**) have also been used to provide analgesia for burns procedures (see Sections 4.5.1, 4.6.1 and 4.4.1). However, efficacy of IV lignocaine for procedural pain could not be confirmed in an RCT (Wasiak 2011 **Level II**, n=45, JS 5) and a subsequent Cochrane review found no further trials (Wasiak 2012 **Level I** [Cochrane], 1 study, n=45).

A systematic review of ketamine in volunteers with a burns injury model has been discussed above (McGuinness 2011 **Level I EH**, 4 RCTs, n=67). PCA with a ketamine/midazolam mixture was effective and well tolerated when used for analgesia and sedation during burns dressings

(MacPherson 2008 **Level IV**). Oral ketamine/midazolam may provide superior pain reduction compared to an oral midazolam/paracetamol/codeine combination for burns dressing changes in children aged 1–5 y (Norambuena 2013 **Level III-1**). IM ketamine/tramadol/ dexmedetomidine was found to be more effective than IM ketamine/tramadol/midazolam or IM ketamine alone in adult burns patients (Zor 2010 **Level III-1**). In contrast, there was no difference in the pain experience between three groups receiving ketamine/midazolam, ketamine/ dexmedetomidine or ketamine alone in the same setting (Gunduz 2011 **Level II**, n=90, JS 3). Oral ketamine was better than oral dexmedetomidine for pain reduction during dressing changes in adult burns patients (Kundra 2013 **Level II**, n=30, JS 4).

The heterogeneous nature of the studies and the lack of pain outcome data in a meta-analysis of dexmedetomidine in burns patients mean no conclusions can be drawn as to its effect on burn pain (Asmussen 2013 **Level I**, 4 studies, n=266). Only improved sedation is identified.

Sedation and anxiolysis as an adjunct to analgesia can improve pain relief. This has been shown for lorazepam combined with morphine (Patterson 1997 **Level II**, n=79, JS 5). However, a retrospective case series of patients receiving midazolam for dressing changes did not demonstrate a reduction in overall pain or opioid use during the hospital admission (Bidwell 2013 **Level III-2**). Patient-controlled sedation with propofol may also be effective (Coimbra 2003 **Level IV**). A propofol/ketamine combination resulted in less "restlessness" during burns dressing changes compared with a propofol/fentanyl combination, with no difference in emergence phenomena (Tosun 2008 **Level II**, n=32, JS 5).

Inhaled methoxyflurane may be helpful for dressing changes for burns patients in an ambulatory setting but further evidence is required prior to recommending routine use (Wasiak 2014 **Level IV**).

Topical analgesic techniques, such as lignocaine as a cream (Brofeldt 1989 **Level IV**) or a spray (Desai 2014 **Level II**, n=29, JS 5) or morphine-infused silver sulfadiazine cream (Long 2001 **Level IV**) may be effective; however a topical gel dressing containing morphine was not more effective than other gel dressing in reducing burns injury pain in the ED (Welling 2007 **Level II**, n=59, JS 5). The use of biosynthetic dressings is associated with a reduction in pain during dressing changes and a decrease in time to healing (Wasiak 2013 **Level I** [Cochrane], 30 RCTs of various dressings, n unspecified). The use of a soft silicone wound contact layer on split thickness skin grafts reduced pain on dressing changes in comparison to conventional dressings (Patton 2013 **Level II**, n=43, JS 2).

Puerarin, a Chinese herb extract, was found to be analgesic and anti-inflammatory for dressing changes. However, the control group received no analgesia (Zhang 2013b **Level II**, n=32, JS 5).

8.3.4 Regional analgesia for donor site pain management

Traditionally, regional analgesia is often avoided in burns patients due to the high incidence of bacteraemia and bacterial colonisation. However, recent research suggests that well-selected patients may benefit from regional analgesia for donor site pain management.

US-guided local anaesthetic block of the lateral femoral cutaneous nerve in 16 consecutive patients resulted in no pain 4 h after surgery at the donor site (lateral thigh) (Shteynberg 2013 **Level IV**); however longer-term effects of this intervention are not known. Fascia iliaca compartment block reduced dynamic, but not rest pain, at the skin donor site and injection of local anaesthetic through the catheter placed in the compartment reduced pain at the first dressing change on d 3 following surgery (Cuignet 2005 **Level II**, n=81, JS 3).

8.3.5 Nonpharmacological pain management

Hypnosis, distraction, relaxation breathing (Park 2013a **Level III-2**), auricular electrical stimulation, therapeutic touch techniques and massage therapy have been used for the treatment of burns pain, including procedural pain. A lack of prospective randomised trials makes comparisons with conventional therapies impossible (Kinsella 2008 **NR**) (see Section 8.1.3). A study comparing two psychological support interventions, hypnosis and stress-reducing strategies, found that VAS anxiety scores were significantly better after hypnosis, although there was no significant effect on pain (Frenay 2001 **Level II**, n=30, JS 3).

A systematic review of VR techniques including studies reaching from RCTs to case reports concluded that these techniques in combination with pharmacological measures reduce the pain experience during dressing changes and physiotherapy in children (Morris 2009 **Level IV SR**, 9 studies, n=152). These findings are confirmed by a subsequent study in children (Schmitt 2011 **Level II**, n=54, JS 3) and also in adults undergoing a range of physical therapies (Carrougher 2009 **Level III-1**). The efficacy is maintained with repeated use over 6 d (Faber 2013 **Level III-3**).

Simply watching television during burns care may be as effective as VR techniques in reducing pain scores (van Twillert 2007 **Level III-3**) and use of commercially available video games may be another option (Parry 2012 **Level III-2**). However, a commercially available VR device was not more effective in pain reduction than standard care during dressing changes (Kipping 2012 **Level II**, n=41, JS 3). Surprisingly, VR relaxation administered prior to a dressing change resulted in an increase in the pain experience (Konstantatos 2009 **Level II**, n=88, JS 3). Finally, providing a VR service requires significant physical and staffing resources (Markus 2009 **Level IV**).

Augmented reality techniques (interactive computer programmes) produced a statistically significant reduction in pain compared with usual care during paediatric burns dressings lasting longer than 30 min (Mott 2008 **Level II**, n=42, JS 3). A multimodal distraction method was helpful in an outpatient setting compared to standard distraction techniques (Miller 2010 **Level III-1**; Miller 2011 **Level II**, n=40, JS 3).

Key messages

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during dressings changes (**U**) (**Level I** [Cochrane]).
2. Virtual reality distraction, augmented reality techniques and multimodal distraction methods reduce pain during burns dressings (**S**) (**Level II**).
3. Opioids, particularly via PCA, are effective in burns pain, including procedural pain (**U**) (**Level II**).
4. Pregabalin reduces pain following acute burns injury (**S**) (**Level II**).
5. Sedation and anxiolysis with lorazepam improves procedural pain relief in acute burns injury (**N**) (**Level II**).
6. Regional analgesia reduces donor site pain in selected burns patients (**N**) (**Level II**).
7. Gabapentin reduces pain and opioid consumption following acute burns injury (**U**) (**Level III-3**).
8. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burns dressings (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Acute pain following burns injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related (**U**).

☑ Acute pain following burns injury requires aggressive multimodal and multidisciplinary treatment and may benefit from protocolised management approaches (**S**).

8.4 Acute back pain

Acute back pain in the cervical, thoracic or, in particular, lumbar and sacral regions, is a common problem affecting most adults at some stage of their lives. The causes are rarely serious, most often nonspecific and the pain is usually self-limiting.

Appropriate investigations are indicated in patients who have signs or symptoms that might indicate the presence of a more serious condition ("red flags"). Such "red flags" include symptoms and signs of infection (eg fever), risk factors for infection (eg underlying disease processes, immunosuppression, penetrating wounds), history of trauma or minor trauma, history of osteoporosis and taking corticosteroids, past history of malignancy, age >50 y,

failure to improve with treatment, unexplained weight loss, pain at multiple sites or pain at rest, and the absence of aggravating features (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**). In assessment of new, acute back pain, "red flags" to predict potential cancer as a cause have been proposed, yet the only evidence-based predictor of spinal malignancy is "previous history of cancer" (Henschke 2013 **SR** of diagnostic studies; Downie 2013 **SR** of diagnostic studies) (see Section 8.7.7.1). A full neurological examination is warranted in the presence of lower limb pain and other neurological symptoms.

Psychosocial and occupational factors ("yellow flags") appear to be associated with an increased risk of progression from acute to chronic pain. Such factors should be assessed early in order to facilitate appropriate interventions (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**).

NHMRC guidelines for the evidence-based management of acute musculoskeletal pain include chapters on acute neck, thoracic spinal and low-back pain (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**). In view of the high quality and extensiveness of these guidelines, and the presence of more recent international guidelines, no independent assessment of these topics has been undertaken for this document even though the Australian guidelines have been rescinded by the NHMRC because of their age. Subsequent international guidelines include those produced by:

- the American Pain Society and American College of Physicians — these cover acute and chronic low-back pain (Chou 2007c **GL**; Chou 2007b **GL**; Chou 2007a **GL**);
- the Michigan Quality Improvement Consortium (MQIC 2010 **GL**);
- the Institute for Clinical Systems Improvement (ICSI 2012 **GL**); and
- the Orthopedic Section of the American Physical Therapy Association (APTA) — these also cover acute and chronic back pain (Delitto 2012 **GL**).

The following key messages are an abbreviated summary of key messages from these guidelines. The practice points recommended for musculoskeletal pain in general are listed in Section 8.5 and represent the consensus of the Steering Committee of these guidelines. These guidelines can be found on the NHMRC website (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**).

Key messages

1. Acute low-back pain is nonspecific in about 95% of cases and serious causes are rare; common examination and investigation findings also occur in asymptomatic controls and may not be the cause of pain (**U**) (**Level I**).
2. Advice to stay active, use of heat-wrap therapy, provision of "activity-focused" printed and verbal information and use of behavioural therapy interventions are all beneficial in acute low-back pain (**U**) (**Level I**).
3. Advice to stay active and to exercise, use of multimodal therapy and use of pulsed electromagnetic therapy are all effective in acute neck pain (**U**) (**Level I**).
4. Soft collars are not effective for acute neck pain (**U**) (**Level I**).
5. Appropriate investigations are indicated in cases of acute low back pain when alerting features ("red flags") of serious conditions are present (**U**) (**Level III-2**).
6. Psychosocial and occupational factors ("yellow flags") appear to be associated with progression from acute to chronic back pain; such factors should be assessed early to facilitate intervention (**U**) (**Level III-2**).

8.5 Acute musculoskeletal pain

Other than acute back pain, acute shoulder and anterior knee pain are two common painful musculoskeletal conditions.

A summary of findings relating to acute musculoskeletal pain can be found in *Evidence-based Management of Acute Musculoskeletal Pain*, published by the Australian Acute Musculoskeletal Pain Guidelines Group and endorsed by the NHMRC (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**). In view of the high quality and extensiveness of these guidelines, no further assessment of these topics has been undertaken for this document, even though these guidelines have been rescinded by the NHMRC in view of a lack of an update. There have been no more recent general guidelines for this condition published by any relevant national or international organisation. However guidelines for specific conditions such as acute shoulder pain by the American College of Radiology (Wise 2011 **GL**) or even more specific for acute and chronic subacromial pain by the Dutch Orthopaedic Association have been published (Diercks 2014 **GL**).

The following is an abbreviated summary of key messages from the 2003 guidelines and represents the consensus of the Steering Committee of these guidelines.

These guidelines can be found on the NHMRC website (Australian Acute Musculoskeletal Pain Guidelines Group 2003 **GL**).

Key messages

1. Topical and oral NSAIDs improve acute shoulder pain (**U**) (**Level I**).
2. Subacromial corticosteroid injection relieves acute shoulder pain in the early stages (**U**) (**Level I**).
3. Exercises improve acute shoulder pain in patients with rotator cuff disease (**U**) (**Level I**).
4. Therapeutic ultrasound may improve acute shoulder pain in calcific tendonitis (**U**) (**Level I**).
5. Advice to stay active, and the use of exercises, injection therapy and foot orthoses are effective in acute patellofemoral pain (**U**) (**Level I**).
6. Low-level laser therapy is ineffective in the management of patellofemoral pain (**U**) (**Level I**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ A management plan for acute musculoskeletal pain should comprise the elements of assessment (history and physical examination but ancillary investigations are not generally indicated), management (information, assurance, advice to resume normal activity, pain management) and review to reassess pain and revise management plans (**U**).
- ☑ Information should be provided to patients in correct but neutral terms with the avoidance of alarming diagnostic labels to overcome inappropriate expectations, fears or mistaken beliefs (**U**).
- ☑ Regular paracetamol then, if ineffective, NSAIDs may be used for acute musculoskeletal pain (**U**).
- ☑ Oral opioids, preferably short-acting agents at regular intervals, may be necessary to relieve severe acute musculoskeletal pain; ongoing need for such treatment requires reassessment (**U**).
- ☑ Adjuvant agents such as anticonvulsants, antidepressants and muscle relaxants are not recommended for the routine treatment of acute musculoskeletal pain (**U**).

8.6 Acute medical pain

Acute pain in medical wards is common (Vallano 2006 **Level IV**) with a prevalence of up to 43% in one UK survey (Dix 2004 **Level IV**). It may be higher than in surgical wards and be less well treated (Korczak 2013 **Level IV**).

8.6.1 Acute abdominal pain

Acute abdominal pain may originate from visceral or somatic structures or may be referred; neuropathic pain states should also be considered. Recurrent acute abdominal pain may be a manifestation of a chronic visceral pain disorder such as chronic pancreatitis, pelvic pain or irritable bowel syndrome and will require a multidisciplinary pain management approach.

8.6.1.1 Analgesia and the diagnosis of acute abdominal pain

A common misconception is that analgesia masks the signs and symptoms of abdominal pathology and should be withheld until a diagnosis is established. Pain relief (usually in the form of opioids) does not interfere with the diagnostic process in acute abdominal pain in adults (Manterola 2011 **Level I**, 8 RCTs, n=922) or in children (Kim 2002 **Level II**, n=60, JS 5; Green 2005 **Level II**, n=108, JS 5) and does not lead to increased errors in clinical management (Ranji 2006 **Level I**, 12 RCTs, n=1,389).

8.6.1.2 Renal and ureteral colic/stones

Nonselective NSAIDs, opioids (Holdgate 2005b **Level I** [Cochrane], 20 RCTs, n=1,613) and metamizole (dipyrone) (Edwards 2002b **Level I** [Cochrane], 11 RCTs, n=1,053) provide effective analgesia for renal colic. Nonselective NSAIDs reduce requirements for rescue analgesia, cause less vomiting than opioids (particularly pethidine [meperidine]) (Holdgate 2005b **Level I** [Cochrane], 20 RCTs, n=1613) and reduce the number of episodes of renal colic experienced before passage of the renal calculi (Kapoor 1989 **Level II**, n=41, JS 5; Laerum 1995 **Level II**, n=80, JS 3).

Onset of analgesia was fastest when nsNSAIDs were administered IV (Tramer 1998 **Level I**, 26 RCTs, n=2,225), although suppositories were also effective (Lee 2005a **Level II**, n=200, JS 3). A combination of IV ketorolac/morphine provided a greater reduction in pain scores, earlier onset of complete pain relief and a reduced need for rescue analgesia, compared with using either analgesic alone (Safdar 2006 **Level II**, n=130, JS 5).

IV paracetamol (1 g) was as effective as IV morphine (0.1 mg/kg) (Serinken 2012 **Level II**, n=80, JS 4; Bektas 2009 **Level II**, n=165, JS 5) and had a higher responder rate than IM piroxicam (20 mg) in the treatment of renal colic (Grissa 2011 **Level II**, n=100, JS 3).

Pethidine has commonly been used in the treatment of renal colic in the belief that it causes less smooth muscle spasm. However, there was no difference in analgesia when IV morphine and pethidine were compared in the treatment of renal colic (O'Connor 2000 **Level II**, n=94, JS 5).

The smooth muscle relaxant buscopan failed to improve analgesia when combined with nsNSAIDs (Jones 2001 **Level II**, n=59, JS 3; Song 2012 **Level II**, n=89, JS 5), opioids (Holdgate 2005a **Level II**, n=192, JS 4) or metamizole (Edwards 2002b **Level I** [Cochrane], 11 RCTs, n=1,053).

Papaverine was as effective as IV diclofenac in the initial treatment of renal colic but required increased use of rescue analgesia (Snir 2008 **Level II**, n=90, JS 2). However, as a rescue analgesic, papaverine was of similar efficacy to pethidine and superior to hyoscine in patients who failed to respond to initial treatment with a diclofenac-hyoscine combination (Yencilek 2008 **Level II**, n=110, JS 2).

IV ondansetron produced analgesia in 42% of patients with renal colic but was less effective than IM diclofenac (Ergene 2001 **Level II**, n=64, JS 3).

Ureteral calculus expulsive therapy using alpha-blockers such as tamsulosin compared to standard therapy reduces the number of pain episodes, the need for analgesic medication and even hospitalisation (Campschroer 2014 **Level I** [Cochrane], 32 RCTs, n=5,864). Tamsulosin

was more effective in reducing analgesic requirements than nifedipine in this setting (Ye 2011 **Level II**, n=3,189, JS 2).

IV lignocaine provided superior analgesia to IV morphine in renal colic (Soleimanpour 2012b **Level III-1**).

IV fluid therapy has no effect on pain outcomes or stone transition in renal colic (Worster 2012 **Level I** [Cochrane], 2 RCTs, n=118).

TENS applied over the painful flank during prehospital transport reduced pain scores, anxiety and nausea in patients with renal colic (Mora 2006 **Level II**, n=73, JS 4).

8.6.1.3 Biliary colic and acute pancreatitis

All opioids increase sphincter of Oddi tone and bile duct pressures in animal and human experimental models (Thompson 2001 **NR**). Morphine increased sphincter of Oddi contractions more than pethidine during cholecystectomy (Thune 1990 **Level IV**). However, there is no difference in the risk of pancreatitis complications or clinically serious adverse effects between the use of opioids or other analgesic options when treating acute pancreatitis (Basurto Ona 2013a **Level I** [Cochrane], 5 RCTs, n=227). Similarly, a systematic review of parenteral analgesia in acute pancreatitis found mainly RCTs of low quality and could not identify any analgesic of specific benefit (Meng 2013 **Level I**, 8 RCTs, n=356).

Butorphanol, which is presumed to cause less biliary spasm than other opioids, and ketorolac produced a clinically significant and similar reduction in acute biliary colic within 30 min in patients in the ED (Olsen 2008 **Level II**, n=946, JS 5).

NSAIDs for treatment of biliary colic pain result in better pain relief than placebo or spasmolytics with no difference to opioids (Colli 2012 **Level I** [PRISMA], 11 RCTs, n=1,076). NSAIDs also resulted in a lower rate of complications, in particular preventing progression to cholecystitis.

IM atropine was no more effective than saline in the treatment of acute biliary colic (Rothrock 1993 **Level II**, n= 55, JS 4).

There was no difference in outcomes including exacerbation of pain between nasogastric and nasojejunal feeding in patients with acute pancreatitis (Chang 2013b **Level I**, 3 RCTs, n=151).

The perioperative use of rectal indomethacin for ERCP reduces the risk of post ERCP pancreatitis (OR 0.49; 95%CI 0.34 to 0.71) compared with placebo (NNT 17) (Ahmad 2014 **Level I**, 4 RCTs, n=1,422).

8.6.1.4 Irritable bowel syndrome and colic

Bulking agents are not more effective than placebo for treating pain in irritable bowel syndrome (Ruepert 2011 **Level I** [Cochrane], 4 RCTs, n=186), while antispasmodics (cimetropium/dicyclomine, peppermint oil, pinaverium and trimebutine) (Ruepert 2011 **Level I** [Cochrane], 13 RCTs, n=1,392) and antidepressants (TCAs but not SSRIs) are effective here (Ruepert 2011 **Level I** [Cochrane], 8 RCTs, n=517).

8.6.1.5 Primary dysmenorrhoea

The management of primary dysmenorrhoea embraces both biological and psychosocial aspects and frequently uses multimodal pharmacological approaches (eg paracetamol, NSAIDs and the oral contraceptive pill). However there is no evidence base for any of these with clinical trials restricted to single agents.

The oral contraceptive pill has limited evidence for better pain relief than placebo (OR 2.01; 95%CI 1.32 to 3.08) (7 RCTs [vs placebo], n=497) with no differences between different preparations (Wong 2009 **Level I** [Cochrane], 10 RCTs, n unspecified).

Nonselective NSAIDs are more effective analgesics in dysmenorrhoea than placebo, however they have an increased rate of adverse effects (Marjoribanks 2010 **Level I** [Cochrane], 73 RCTs, n=5,165). Nonselective NSAIDs are more effective than paracetamol, with no difference between the different nsNSAIDs with regard to efficacy and safety. Nonselective NSAIDs also

reduce bleeding and pain associated with the use of an intrauterine device (Grimes 2006 **Level I** [Cochrane], 15 RCTs, n=2,702).

Vitamin B_1 and magnesium (Proctor 2001 **Level I** [Cochrane], 7 RCTs, n=815), Chinese herbal medicine (Zhu 2008 **Level I** [Cochrane], 39 RCTs, n=3,475), vitamin E (Ziaei 2005 **Level II**, n=278, JS 5), rose tea (Tseng 2005 **Level II**, n=149, JS 2), guava leaf extract (*Psidii guajavae*) (Doubova 2007 **Level II**, n=197, JS 4), aromatherapy (Han 2006 **Level II**, n=67, JS 2; Ayan 2013 **Level III-1**) and fennel (*Foeniculum vulgare*) (Namavar Jahromi 2003 **Level III-2**) show analgesic effects in primary dysmenorrhoea.

High-frequency TENS is effective in primary dysmenorrhoea (Proctor 2002 **Level I** [Cochrane], 7 RCTs, n=164). Acupuncture, acupressure (Smith 2011 **Level I** [Cochrane], 10 RCTs, n=944) and acupoint stimulation (Chung 2012 **Level I**, 25 RCTs, n=3,109) may reduce pain in primary dysmenorrhoea but the quality of studies is poor.

8.6.1.6 Recurrent abdominal pain (abdominal migraine)

Recurrent abdominal pain or abdominal migraine presents to primary care and EDs and is functional and a diagnosis of exclusion. It occurs usually in male school-aged children, sometimes adolescents, rarely in adults. Recurrent abdominal pain is characterised by recurrent attacks of acute abdominal pain, nausea, vomiting and often headaches. There is currently no good evidence for the efficacy of any pharmacological treatment (Huertas-Ceballos 2008a **Level I** [Cochrane], 3 RCTs, n=83) or dietary intervention (Huertas-Ceballos 2009 **Level I** [Cochrane], 7 RCTs, n=341). There is some evidence that cognitive-behavioural therapy may be a useful intervention, "although most children … will improve with reassurance and time" (Huertas-Ceballos 2008b **Level I** [Cochrane], 6 RCTs, n=167).

Key messages

1. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).
2. NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**U**) (**Level I** [Cochrane Review]).
3. NSAIDs given for renal colic reduce requirements for rescue analgesia and produce less vomiting compared with opioids, particularly pethidine (meperidine) (**U**) (**Level I** [Cochrane Review]).
4. Alpha blockers as expulsive therapy for ureteral stones reduce the number of pain episodes and analgesic requirements (**N**) (**Level I** [Cochrane Review]).
5. The onset of analgesia is faster when NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
6. Antispasmodics and tricyclic antidepressants, but not bulking agents, are effective for the treatment of acute pain in irritable bowel syndrome (**S**) (**Level I** [Cochrane Review]).
7. NSAIDs are effective in primary dysmenorrhoea and superior to paracetamol (**S**) (**Level I** [Cochrane Review]).
8. High-frequency TENS, magnesium, Vitamin B_1, Chinese herbal medicines and possibly acupuncture/acupressure are effective in the treatment of primary dysmenorrhoea (**S**) (**Level I** [Cochrane Review]).
9. The smooth muscle relaxant buscopan did not add further analgesic benefit when combined with metamizole (dipyrone) (**N**) (**Level I** [Cochrane Review]), opioids or NSAIDS to treat pain of renal colic (**N**) (**Level II**).
10. NSAIDS are superior to placebo and spasmolytics and as effective as opioids in the treatment of biliary colic, while reducing complications including progression to cholecystitis (**S**) (**Level I** [PRISMA])

11. The perioperative use of rectal indomethacin for endoscopic retrograde cholangiopancreatography (ERCP) reduces the risk of post ERCP pancreatitis (**N**) (**Level I**).
12. Intravenous paracetamol is as effective as intravenous morphine and superior to intramuscular piroxicam for analgesia in renal colic (**N**) (**Level II**).
13. There is no difference between pethidine and morphine for analgesia in renal colic (**U**) (**Level II**).

8.6.2 Herpes zoster-associated pain

Herpes zoster (shingles) is caused by reactivation of the varicella-zoster virus (VZV), which lies dormant in dorsal root and cranial nerve ganglia following primary infection with chickenpox (varicella), usually in childhood (Yawn 2013 **NR**). There is a marked increase in the risk of herpes zoster with increasing age and with diseases and drugs that impair immunity: the lifetime risk is estimated at 30% and 68% of cases occur in those aged ≥50 y.

Herpes zoster-associated pain occurs in up to 80% of those affected and may occur before onset of the characteristic rash (during the prodrome), with onset of the rash or following its resolution. The pain varies in intensity and may be described as "burning", "throbbing" or "shooting"; itching, dysaesthesias, and allodynia may also be present (Dworkin 2008 **NR**). In the majority of cases, herpes zoster is an acute self-limiting disease, although it may progress to postherpetic neuralgia (pain that persists for >3 mth after the onset of herpes zoster). The incidence of postherpetic neuralgia increases with age (>50 y), occurring in up to 75% of patients aged ≥70 y who had herpes zoster (Johnson 2004 **NR**). Early, aggressive treatment of herpes zoster infection and pain may reduce the incidence of postherpetic neuralgia, although data on preventive strategies are limited (see Section 8.6.2.3).

8.6.2.1 Prevention of herpes zoster

A live attenuated VZV vaccine (Zostavax®) is effective in the prevention of herpes zoster (and thereby postherpetic neuralgia) in individuals aged >60 y (Gagliardi 2012 **Level I**, 8 RCTs, n=52,269). A large, multicentre, randomised placebo-controlled trial (The Shingles Prevention Study) demonstrated the vaccine's efficacy, with the incidence of herpes zoster reduced by 51.3%, that of postherpetic neuralgia by 66.5 % and herpes zoster-associated "burden of illness" by 61.1% (Oxman 2005 **Level II**, n=38,546, JS 4). The estimated number needed to vaccinate to prevent a case was 11 (95%CI 10 to 13) for herpes zoster and 43 (95%CI 33 to 53) for postherpetic neuralgia (Brisson 2008 **Level III-3**). The Advisory Committee for Immunization Practices of the USA Centers for Disease Control and Prevention recommends vaccination with live, attenuated VZV for all persons aged ≥60 y even if they have had a previous episode of herpes zoster (Harpaz 2008).

8.6.2.2 Treatment of herpes zoster-associated pain

Antiviral agents

Acyclovir (Wood 1996 **Level I**, 4 RCTs, n=691), valaciclovir (Beutner 1995 **Level II**, n=1,141, JS 5) or famciclovir (Tyring 2000 **Level II**, n=597, JS 5), given within 72 h of rash onset, accelerated the resolution of acute herpes zoster pain. Famciclovir, in various doses and frequencies, was as effective as acyclovir for herpes zoster-related outcomes including acute pain, with fewer adverse effects (Shafran 2004 **Level II**, n=559, JS 5; Shen 2004 **Level II**, n=55, JS 5; Gopal 2013 **Level II**, n=100, JS 2). Famciclovir or valaciclovir have replaced acyclovir as the drugs of choice in the treatment of herpes zoster because of more favourable pharmacokinetics and simpler dosing profiles (Cunningham 2008 **NR**).

Opioids, tramadol and paracetamol

Herpes zoster-associated pain may be severe, so early and effective treatment is essential. Multimodal analgesia with regular paracetamol, in addition to an opioid such as oxycodone (Dworkin 2007 **NR;** Cunningham 2008 **NR;** Dwyer 2002 **NR**) or tramadol as required, has been recommended.

Oxycodone CR, but not gabapentin, was effective in significantly reducing the average worst pain during the first 14 d of herpes zoster compared with placebo, although the oxycodone-treated patients had higher withdrawal rates from the trial, primarily because of constipation (Dworkin 2009 **Level II**, n=87, JS 5).

Corticosteroids

Prednisolone added to acyclovir for acute herpes zoster minimally reduced pain intensity but improved the rate of skin lesion healing for up to 14 d, with no effect on the overall recovery rate at 3 wk (Wood 1994 **Level II**, n=400, JS 4). A later trial showed prednisolone, either as monotherapy or in combination with acyclovir, increased the likelihood of being "pain-free" at 1 mth by a factor of 2.3 (95%CI 1.4 to 3.5), with no difference in the rate of skin healing, compared with placebo (Whitley 1996 **Level II**, n=208, JS 4).

Anticonvulsants

A single dose of gabapentin (900 mg) during herpes zoster reduced acute pain intensity by 66% (33% for placebo) and also reduced the area and severity of allodynia, for up to 6 h (Berry 2005 **Level II**, n=26, JS 5). This was also found with pregabalin (150 mg) (Jensen-Dahm 2011 **Level II**, n=8, JS 5). However, no analgesic benefit was found when gabapentin up to 1,800 mg daily was administered for 28 d (Dworkin 2009 **Level II**, n=87, JS 5) or with pregabalin 150–300 mg daily for 3 wk (Krcevski Skvarc 2010 **Level II**, n=29, JS 3).

Topical lignocaine

Topical lignocaine patches (5%) applied for 12 h twice daily (on intact skin) during herpes zoster reduced pain intensity and improved patients' global impression of pain relief, compared with a vehicle patch: the incidence and severity of adverse effects was low (Lin 2008 **Level II**, n=46, JS 5).

Aspirin

Topical aspirin, in either moisturiser or diethyl ether, was an effective analgesic in herpes zoster, compared with similar preparations containing indomethacin, diclofenac or placebo (De Benedittis 1996 **Level II**, n=37; JS 3) or oral aspirin (Balakrishnan 2001 **Level II**, n=45, JS 3).

Neuraxial or sympathetic block

A systematic review of neuraxial (including sympathetic) block for the treatment of acute herpes zoster-associated pain found that around 80% of studies (Kumar 2004 **Level IV SR**, 15 studies [acute herpes zoster pain], n unspecified), only one of which was an RCT (Pasqualucci 2000 **Level II**, n=600, JS 2), reported a reduction in either the incidence or severity of herpes zoster-associated pain to 1 mth. In a subsequent RCT, there was a significant difference in the incidence (and to a lesser extent the intensity) of acute herpes zoster pain in patients who received a single epidural methylprednisolone and bupivacaine injection, compared with those who received antiviral therapy and analgesia as "standard care" (van Wijck 2006 **Level II**, n=598, JS 3); the NNT for complete resolution of herpes zoster pain at 1 mth with the epidural injection was 10. However, given the modest clinical effects on acute pain and no effect on the incidence of postherpetic neuralgia, the routine use of epidural local anaesthetic and steroid injection during herpes zoster was not supported. Evidence of benefit for sympathetic block in the treatment of herpes zoster-associated pain was limited (Kumar 2004 **Level IV SR**, 15 studies [acute herpes zoster pain], n unspecified).

8.6.2.3 Prevention of postherpetic neuralgia

Immunisation of persons aged ≥60 y with live attenuated VZV vaccine reduces the incidence of herpes zoster and thereby the incidence of postherpetic neuralgia; however there is no evidence that the immunisation prevents postherpetic neuralgia beyond this effect (Chen 2011 **Level I** [Cochrane], 1 RCT; 38,546).

In line with a previous meta-analysis, the use of acyclovir does not significantly reduce the incidence of postherpetic neuralgia at 6 mth (Chen 2014 **Level I** [Cochrane], 6 RCTs, n=1,211). There is insufficient evidence to determine the preventive effect of other antiviral agents.

Similarly, systemic corticosteroids (Han 2013 **Level I** [Cochrane], 5 RCTs, n=787) were ineffective preventive strategies.

During acute herpes zoster, the early administration of amitriptyline (25 mg for 90 d) significantly reduced the incidence of postherpetic neuralgia at 6 mth (Bowsher 1997 **Level II**, n=80, JS 4).

In a systematic review, five of eight studies looked at prevention of postherpetic neuralgia and suggested that neuraxial block during herpes zoster reduced the incidence of postherpetic neuralgia at 6 mth (Kumar 2004 **Level IV SR**, 8 studies [prevention], n unspecified). The only RCT found that local anaesthetic and steroid injections via an epidural catheter, for up to 21 d during herpes zoster, significantly reduced the incidence (but not the intensity) of pain for 1–6 mth, compared with systemic antiviral therapy plus prednisolone (Pasqualucci 2000 **Level II**, n=600, JS 2); however, there are no further RCTs addressing this approach, which has obviously limited practical application. A single epidural injection with methylprednisolone and bupivacaine had no preventive effect (van Wijck 2006 **Level II**, n=598, JS 3).

Key messages

1. Antiviral agents started within 72 hours of onset of the herpes zoster rash accelerate the resolution of acute pain (**U**) (**Level I**) but do not reduce the incidence, severity and duration of postherpetic neuralgia (**S**) (**Level I** [Cochrane]).
2. Immunisation of persons aged 60 years or older with VZV vaccine reduces the incidence of herpes zoster and postherpetic neuralgia (**S**) (**Level I** [Cochrane]).
3. Amitriptyline (used in low doses for 90 days from onset of the herpes zoster rash) reduces the incidence of postherpetic neuralgia (**U**) (**Level II**).
4. Topical aspirin, topical lignocaine patch or controlled-release oxycodone provide analgesia in acute pain due to herpes zoster (**U**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Provision of early and appropriate analgesia is an important component of the management of herpes zoster and may have benefits in reducing the incidence of postherpetic neuralgia (**U**).

8.6.3 Acute cardiac pain

Acute coronary syndrome refers to a range of acute myocardial ischaemic states including unstable angina and myocardial infarction. Typically, myocardial ischaemia causes central chest pain, which may radiate into the arm, neck or jaw; nontypical presentations can occur, particularly in the elderly patient (see Section 10.2). Reducing ischaemia by optimising myocardial delivery, reducing myocardial oxygen consumption and restoring coronary blood flow will reduce ischaemic pain and limit myocardial tissue damage. The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation as outlined above.

However, the routine use of high-flow oxygen in uncomplicated myocardial infarction may result in a greater infarct size and possibly increase the risk of mortality (Wijesinghe 2009 **Level I** [QUOROM], 2 studies, n=250). A further meta-analysis found no benefit from the use of supplemental oxygen in patients with suspected or proven acute MI with a nonsignificant trend to increased mortality (RR 2.05; 95%CI 0.75 to 5.58) (Cabello 2013 **Level I** [Cochrane], 4 studies, n=430). Current guidelines by NICE (NICE 2010 **GL**) and the Australian and New Zealand Cardiology Society (Chew 2011b **GL**) state that the use of supplemental oxygen is not recommended unless hypoxia (oxygen saturation [SaO_2] <94%) is present. In acute coronary syndrome, hyperbaric oxygen therapy reduced time to relief of ischaemic pain, although insufficient evidence exists to recommend routine use (Bennett 2011a **Level I**, 6 studies, n=665).

Nitroglycerine (glyceryl trinitrate) was effective in relieving acute ischaemic chest pain; however, the analgesic response did not predict the diagnosis of coronary artery disease (Henrikson 2003 **Level IV**).

In patients with suspected acute coronary syndrome, IV morphine significantly reduced pain within 20 min of administration (Everts 1998 **Level IV**); morphine doses were low (average of 7 mg over 3 d) and 52% of patients required no morphine at all. Independent predictors of increased morphine requirements included suspicion or confirmation of infarction, ST segment changes on the admission electrocardiogram, male sex and a history of angina or cardiac failure.

After an initial dose of IV metoprolol, IV morphine provided better analgesia than further IV metoprolol (Everts 1999 **Level II**, n=265, JS 4) and was associated with better cardiovascular outcomes during acute hospital admission and later follow-up, when compared with a fentanyl/droperidol mixture administered early in the treatment of patients with acute ischaemic chest pain (Burduk 2000 **Level II**, n=112, JS 2). However a large retrospective audit (n=57,039) reported increased mortality in patients treated with morphine (OR 1.48; 95%CI 1.33 to 1.64), either alone or in combination with nitroglycerine (independent of other confounders), in non-ST segment elevation acute coronary syndrome (Meine 2005 **Level III-2**). IV bolus doses of morphine and alfentanil were equally effective in relieving acute ischaemic chest pain but the onset of analgesia was faster with alfentanil (Silfvast 2001 **Level II**, n=40, JS 2). Morphine was similar to buprenorphine (Weiss 1988 **Level II**, n=76, JS 3) and pethidine (Nielsen 1984 **Level II**, n=275, JS 4) in terms of analgesia and adverse effects. IN fentanyl and IV morphine were equally effective in reducing acute cardiac chest pain during prehospital transfer (Rickard 2007 **Level II**, n=258, JS 3).

In patients with chest pain due to cocaine-induced acute coronary syndrome, the addition of IV diazepam or lorazepam to treatment with SL nitroglycerine has been shown to be beneficial (Honderick 2003 **Level II**, n=36, JS 3) or to make no difference to chest pain resolution or cardiac performance (Baumann 2000 **Level II**, n=43, JS 5).

N_2O in oxygen was effective in relieving acute ischaemic chest pain, with a significant reduction in betaendorphin levels (O'Leary 1987 **Level II**, n=12, JS 2).

NSAIDs may be useful in the treatment of acute pain in pericarditis (Schifferdecker 2003 **NR**).

Key messages

1. Morphine is an effective and appropriate analgesic for acute cardiac pain (**U**) (**Level II**).
2. Nitroglycerine is an effective and appropriate agent in the treatment of acute ischaemic chest pain (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, nitroglycerine, beta blockers and strategies to improve coronary vascular perfusion (**U**).

☑ The routine use of supplemental oxygen in acute myocardial infarction may not be beneficial (**N**).

8.6.4 Acute pain associated with haematological disorders

8.6.4.1 Sickle cell disease

Sickle cell disease includes a group of inherited disorders of haemoglobin production. Haemoglobin S polymerises when deoxygenated, causing rigidity of the erythrocytes, blood hyperviscosity and occlusion of the microcirculation with resultant tissue ischaemia and infarction (Niscola 2009 **NR**).

Sickle cell disease is a systemic multiorgan disease that most commonly presents with painful vaso-occlusive crises, occurring either spontaneously or due to factors such as dehydration, infection, hypothermia and low oxygen tension. There is great interindividual variability in the frequency and severity of crises. Pain during an acute crisis is typically severe, in multiple sites and most frequently reported in the arm, shoulder, upper back, sternum, clavicle, chest

or pelvis and may last from hours to weeks (McClish 2009 **Level IV**). Sickle cell crises involving abdominal organs can mimic an acute surgical abdomen. Acute chest syndrome secondary to sickle cell disease may present with chest pain, cough, dyspnoea and fever (Niscola 2009 **NR**).

An evidence-based approach to the management of sickle cell crisis is published (Glassberg 2011 **GL**).

Treatment of pain

Biopsychosocial assessment and multidisciplinary pain management may be required when treating patients with frequent, painful sickle cell crises. A pain management plan in the form of a letter, card or portfolio carried by the patient is also recommended (Rees 2003 **GL**). Detailed consensus guidelines for managing acute painful crises in sickle cell disease are available (Mousa 2010 **GL**). The implementation of clinical practice guidelines (Morrissey 2009 **Level III-3**) or a clinical pathway (Ender 2014 **Level III-3**) for acute pain treatment in sickle cell crisis leads to more timely and more effective analgesia preparation of individualised pain management plans are resulting in improved pain control and a high level of patient satisfaction in the ED and reduced hospitalisations (Krishnamurti 2014 **Level III-2**).

Opioids

In the hospital setting IV opioids are recommended for severe pain (NICE 2012b **GL**).

When treating acute pain during a sickle cell crisis, IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy (Rees 2003 **GL**). A continuous IV morphine infusion shortened the duration of severe pain compared with intermittent parenteral opioids (Robieux 1992 **Level II**, n=66, JS 2) and PCA with morphine reduced opioid dose and related adverse effects (with a tendency to reduced length of hospital stay) compared with continuous infusion (van Beers 2007 **Level II**, n=19, JS 2). A comparative trial of PCA with higher demand dose with low constant infusion or lower demand dose and higher constant infusion did not lead to any conclusions due to early termination of the trial (Dampier 2011 **Level II**, n=38, JS 5). The use of inpatient morphine PCA rapidly converted to oral sustained-release morphine for use at home, reduced the length of hospital stay by 23% and subsequent ED visits and readmissions by approximately 50%, compared with IM pethidine (Brookoff 1992 **Level III-3**).

Although IV opioid PCA is widely accepted in the management of acute pain in sickle cell disease, oral opioids are also effective. One trial in paediatric patients showed that oral sustained-release morphine for acute pain was just as effective as a continuous IV morphine infusion (Jacobson 1997 **Level II**, n=56, JS 5). The use of oral opioids at home reduced the number of ED visits and hospital admissions for sickle cell pain (Conti 1996 **Level III-3**; Friedman 1986 **Level III-3**). However in children, the incidence of acute sickle chest syndrome (a severe complication in sickle cell crisis) and plasma levels of morphine and M6G, were significantly higher with oral morphine compared with IV infusion (Kopecky 2004 **Level II**, n=50, JS 4).

Care must be taken when using opioids in the treatment of pain in sickle cell disease. In a review of 35 patients who died in hospital following an exacerbation of sickle cell disease, 9 received excessive opioids and "overdose" directly contributed to death in 5 patients (NCEPOD 2008 **Level IV**). In two-thirds of patients, there were inadequate observations of sedation and respiratory rates after opioid administration and IM pethidine administration was prevalent.

NSAIDs

Single-dose parenteral ketorolac did not reduce opioid requirements in painful vaso-occlusive crisis (Wright 1992 **Level II**, n=24, JS 5; Hardwick 1999 **Level II**, n=41, JS 5).

Corticosteroids

Parenteral corticosteroids reduce the duration of severe pain and analgesia requirements and length of hospital stay, without major adverse effects, during sickle cell crises (Dunlop 2006 **Level I** [Cochrane], 9 RCTs, n unspecified). In children, a short course of high dose IV methylprednisolone decreased the duration of severe pain associated with acute sickle cell

crises but patients who received methylprednisolone had more rebound attacks after therapy was discontinued (Griffin 1994 **Level II**, n=36, JS 5).

Ketamine

A case series reported improved analgesia and reduced opioid requirements with use of a low-dose ketamine infusion in 14 of 17 cases (Uprety 2014 **Level IV**); this was confirmed in a subsequent case series (n=9) using a low-dose midazolam/ketamine infusion (Tawfic 2014 **Level IV**). This approach is also suggested for paediatric patients (Neri 2013a **NR**).

Inhaled nitric oxide

Nitric oxide deficiency or defective nitric oxide-dependent mechanisms may underlie many of the processes leading to vaso-occlusion. Inhaled nitric oxide may be of benefit in painful acute vaso-occlusive crises in children; however, further studies are required (Weiner 2003 **Level II**, n=25, JS 4).

Inhaled nitrous oxide

Inhaled N_2O in 50% oxygen used for limited periods may provide analgesia for acute sickle cell pain in the primary-care setting (Rees 2003 **GL**).

Oxygen

Although oxygen supplementation is often prescribed during acute sickle cell crises, there was no difference in pain duration, number of pain sites or opioid consumption in patients treated with either air or oxygen (Robieux 1992 **Level II**, n=66, JS 2; Zipursky 1992 **Level II**, n=28, JS 3). However, nocturnal oxygen desaturation was associated with a significantly higher rate of painful sickle cell crises in children (Hargrave 2003 **Level IV**). Hyperbaric oxygen therapy was effective in reducing pain of sickle cell crisis rapidly (Stirnemann 2012 **Level III-3**).

Rehydration

While commonly practiced, there is no evidence to support fluid replacement therapy to reduce pain associated with sickle cell crises (Okomo 2007 **Level I** [Cochrane], 0 RCTs, n=0).

Epidural analgesia

In severe crises, where pain is unresponsive to other measures, epidural analgesia has been used effectively (Yaster 1994 **Level IV**); this has also been described in a pregnant patient with poorly responsive pain (Winder 2011).

Prevention of painful sickle cell crises

Hydroxyurea increases fetal haemoglobin levels, thereby reducing the frequency of acute crises, blood transfusions and life-threatening complications (including acute chest syndrome) in adults with severe disease who are homozygous for the sickle cell gene (Davies 2001 **Level I** [Cochrane], 2 RCTs, n=324).

Zinc, but not the selective calcium-activated potassium ("Gardos") channel blocker senicapoc reduces the incidence of painful sickle cell crises (Nagalla 2012 **Level I** [Cochrane], 3 RCT, n=524). Niprisan (an antisickling agent) reduces the frequency of crises with severe pain (Wambebe 2001 **Level II**, n=82, JS 4), while the evidence for pircetam is insufficient to support its use (Al Hajeri 2007 **Level I** [Cochrane], 3 studies, n=169).

8.6.4.2 Haemophilia

Deficiency of Factor VIII (haemophilia A) and deficiency of Factor IX (haemophilia B) are inherited disorders of coagulation characterised by spontaneous and post-traumatic haemorrhages, the frequency and severity of which are proportional to the degree of clotting factor deficiency. Bleeding into joints and muscle is common, although other sites such as abdominal organs may also be involved. In haemophilic arthropathy, the most frequent sites of pain are the ankle joints (45%), knee joints (39%), spine (14%) and elbow joints (7%) (Wallny 2001 **Level IV**). Haemophilia patients may also have pain syndromes associated with HIV/AIDS (see Section 8.6.8). Recurrent acute pain may have a significant adverse impact on mood,

mobility and QoL in haemophilia patients; biopsychosocial assessment and treatment should be considered (Wallny 2001 **Level IV**).

Many haemophilia patients use Factor VIII to decrease pain associated with a bleeding episode (Wallny 2001 **Level IV**). Higher-dose Factor VIII replacement reduced the number of patients with restricted joint movement after an acute haemarthrosis (Aronstam 1983 **Level II**, n=114, JS 4). Joint aspiration may reduce pain and improve joint function (Baker 1992 **NR**).

Although there is no good evidence available, opioids, simple analgesics, cold therapy and bandaging have been used in treating acute pain associated with haemophilia. In a Europe-wide survey, the preferred first-line drug was paracetamol for children and paracetamol or NSAIDs for adults (Holstein 2012 **Level IV**). There are no data on NSAID use in acute haemarthrosis; coxibs may be of benefit due to a lack of platelet inhibitory effects (see Section 4.3.2.2). IM analgesics should be avoided due to the risk of bleeding.

8.6.4.3 The porphyrias

The acute porphyrias are a group of inherited disorders of haem biosynthesis. The most common autosomal dominant forms are acute intermittent porphyria, variegate porphyria and hereditary coproporphyria. The disorder of haem biosynthesis leads to accumulation of neurotoxic aminolaevulinic acid and porphyrin metabolites, which can result in peripheral, visceral and autonomic neuropathies (eg clinical features might include motor weakness, abdominal pain and tachycardia) as well as CNS toxicity (neuropsychiatric symptoms, seizures, brainstem and pituitary dysfunction); some patients may have a cutaneous photosensitivity (Visser 2008 **NR**).

Pain management in acute porphyria is based on treatment of the disease, including resuscitation and supportive care, ceasing "triggers", the early administration of haematin (Herrick 1989 **Level II**, n=12, JS 4) and possibly high-dose IV dextrose or cimetidine administration ("disease modifying agents") (Rogers 1997 **NR**).

Specific evidence for pain management in acute porphyria is limited. Analgesia is based largely on the use of IV and (later) oral opioids (Anderson 2005 **NR;** Herrick 2005 **NR**). Analgesics that lower seizure threshold such as pethidine (Deeg 1990 **CR**) or tramadol and others (such as TCAs) should be avoided in acute porphyria because of increased seizure risk.

The safety of NSAIDs or coxibs in acute porphyria has not been established; paracetamol, buscopan (for colic) or N_2O in oxygen are considered safe (Stoelting 1993 **NR**; Anderson 2005 **NR**).

There may be a place for low-dose IV ketamine or regional analgesia, although the safety of these approaches has not been established in acute porphyria. Ketamine does not induce aminolaevulinic acid synthetase in rats (Harrison 1985 **BS**) and has been used for anaesthesia in porphyria patients without apparent problems (Capouet 1987 **CR**). However, one case report noted increased porphyrin levels in a patient after induction with ketamine (Kanbak 1997 **CR**).

As metoclopramide is contraindicated and the safety of $5HT_3$ antagonists is as yet unclear, droperidol has been suggested as the antiemetic of choice in acute porphyria (Anderson 2005 **NR**).

Key messages

1. Parenteral corticosteroids reduce the duration of severe pain, analgesia requirements and length of hospital stay, without major adverse effects, during sickle cell crises (**S**) (**Level I** [Cochrane Review]).
2. There is no evidence that fluid replacement therapy reduces pain associated with sickle cell crises (**U**) (**Level I** [Cochrane Review]).
3. Hydroxyurea decreases the frequency of acute crises, life-threatening complications and transfusion requirements in sickle cell disease (**U**) (**Level I** [Cochrane Review]).
4. Zinc reduces the incidence of painful sickle cell crises (**N**) (**Level I** [Cochrane Review]).

5. Intravenous opioid loading optimises analgesia in the early stages of an acute sickle cell crisis. Effective analgesia may be continued with intravenous opioid therapy, optimally as PCA, or as oral opioids (**S**) (**Level II**).
6. Oxygen supplementation does not decrease pain during a sickle cell crisis (**U**) (**Level II**) but hyperbaric oxygen may be effective (**N**) (**Level III-3)**.

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Pethidine should be avoided for the treatment of acute pain in sickle cell disease or acute porphyria, with increased seizure risk being a potential problem (**U**).

8.6.5 Acute headache

Headaches are a common cause of acute pain. Headaches may be primary or secondary. There are many causes of acute headache, some of which involve structures other than the head (eg the neck). Before treating acute headache, it is vital to exclude serious cranial pathologies such as tumour, infection, cerebrovascular abnormalities, acute glaucoma and temporal arteritis (Silberstein 2000 **GL**; Steiner 2002 **NR**).

The most frequent causes of acute primary headache are episodic TTH and migraine (Headache Classification Committee 2013). Less common primary headaches are trigeminal autonomic cephalalgias (episodic cluster headache, episodic paroxysmal hemicrania and Short lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing [SUNCT]) or "secondary headaches", such as acute posttraumatic headache, postdural puncture headache (PDPH), headache attributed to substance use or its withdrawal and cervicogenic headache (Headache Classification Committee 2013).

Comprehensive guidelines for the evaluation and treatment of acute headaches including migraine have been promulgated (Evers 2009 **GL**; Evers 2011 **GL**; Pringsheim 2012 **GL**; Beithon 2013 **GL**; Worthington 2013 **GL**), including for children and adolescents (see Section 9.9).

8.6.5.1 Tension-type headache

TTHs may be episodic (frequent or infrequent) or chronic in nature. The lifetime prevalence of TTH in the general population is between 30 and 78%. Episodic TTH is usually bilateral and is often described as mild to moderate "pressing" or "tight" pain (sometimes with pericranial tenderness) not worsened by movement and not associated with nausea or vomiting. Photophobia or phonophobia may occasionally be present but not both (Headache Classification Committee 2013).

The symptoms and pathogenesis of TTH may overlap with migraine and particularly with chronic daily headache, medication overuse headache and cervicogenic headache (NICE 2012a **GL**). Psychological, physical and environmental factors are important in TTH and should be addressed during assessment and treatment (Bendtsen 2010 **GL**; NICE 2012a **GL**; Bougea 2013 **Level II**, n=35, JS 3).

TTHs are frequently self-limiting with total duration under 12 h in many cases. Therefore, the efficacy of various treatments should be assessed against the background of natural history. The acute adverse effects and the propensity for analgesic medications to transform intermittent headaches to a chronic daily pattern must be considered in relation to choice of agents (Barbanti 2014 **NR**). Evidence-based guidelines for TTH treatment are published (Bendtsen 2010 **GL**).

Treatment

The NNTs for patients with TTH being pain free at 2 h compared with placebo are similar for all oral analgesics and in the range of 8.7–9.8 for paracetamol 1,000 mg, ibuprofen 400 mg and ketoprofen 25 mg (Moore 2014 **Level I** [PRISMA], 55 RCTs, n=12,143). A paracetamol/ aspirin/ caffeine combination is superior to paracetamol alone (Diener 2014 **Level I**, 4 RCTs, n=1,900).

Parenteral medications are more effective in TTH than oral ones; metoclopramide IV has an NNT of 2 and metamizole IV and chlorpromazine IV have an NNT of 4 (Weinman 2014 **Level I** [PRISMA], 8 RCTs, n=486).

IV magnesium was ineffective in treating acute TTH in the ED (Frank 2004 **Level II**, n=42, JS 5).

8.6.5.2 Migraine

Migraine is common, with a prevalence of 6–8% in males and 12–14% in females (Evers 2009 **GL**). Migraine headache is usually unilateral and is often severe, disabling and often worsened by movement. Either nausea/vomiting or photophobia/phonophobia must be present and 20% of migraineurs experience an aura.

Most migraines are successfully managed by the patient and their family doctor, with up to 57% of patients not seeking medical attention for significant attacks (Mitchell 1998 **Level IV**). However, a small number of patients fail to respond and present for treatment at EDs; approximately 80% of patients have tried their usual medications including simple analgesics or triptans before presentation (see Section 8.9.2).

Treatment

The management of migraine includes avoidance of triggers such as sleep deprivation, stress, sensory stimulation such as bright lights, exercise, alcohol, foods etc. Management of associated symptoms, particularly nausea and vomiting is important, as is the prevention of acute recurrence.

Environmental modification (quiet dark room) and particularly sleep is integral to successful migraine treatment (Steiner 2007 **NR**).

Analgesia outcomes in migraine trials are usually listed as the proportion of patients who either:

- are pain free at 2 h;
- report significant pain relief at 2 h (no headache or mild headache); or
- report a sustained response over 24 h (migraine stays away for at least 1 d).

Many trials fail to document associated outcomes such as improvement in nausea, vomiting or disability (Moore 2003 **NR**).

Strategies for the use of migraine medications

There are three major strategies for the use of analgesics in the treatment of acute migraine (Lipton 2000 **Level II**, n=930, JS 5):

- *stratified care* — where for each attack, the severity and disability caused by the migraine is assessed and the patient uses simple analgesia for a mild attack and a triptan for a severe attack;
- *step-up during an attack* — for each attack a simple analgesic is always tried first but the patient "steps up" to a triptan if there is no relief in 2 h; and
- *step-up across attacks* — a patient tries simple analgesics exclusively for the first three attacks; if there has been no benefit from simple analgesia over the trial period then a triptan is used for all further attacks.

The US Headache Consortium (Silberstein 2000 **GL**) and European Federation of Neurological Societies (Evers 2009 **GL**) have recommended a "stratified care" approach; Canadian guidelines recommend this as the most effective and cost-effective approach but also describe the two other approaches as suitable in selected patients (Worthington 2013 **GL**).

Placebo

A significant placebo effect has been observed in migraine trials, particularly if the treatment was administered by injection (Macedo 2006 **Level I** [QUOROM], 98 RCTs, n=35,481) and it may be more common in children and adolescents (Evers 2009 **Level I**, 27 RCTs, n unspecified).

Accordingly, the beneficial effect of specific analgesic mechanisms may be underestimated by prominent placebo responses (Lund 2014 **Level II**, n=48, JS 5).

Simple analgesics

Patients who experience mild migraine-related headache and disability may be effectively treated with simple analgesics, either alone or in combination with an antiemetic. European consensus guidelines recommend the routine, early use of metoclopramide in adults (or domperidone in children) (Evers 2009 **GL**).

Paracetamol 1,000 mg is superior to placebo in the treatment of migraine but has a lower efficacy than other analgesics (NNT 12 for pain free at 2 h) (Derry 2013a **Level I** [Cochrane], 11 RCTs, n=2,942). The efficacy of the combination with 10 mg metoclopramide was comparable to oral sumatriptan 100 mg. Serious adverse effects occurred only with sumatriptan (NNH 32).

Aspirin 1,000 mg is of similar efficacy to sumatriptan 50 or 100 mg orally (NNT 8.1 for pain free at 2 h) with slightly fewer adverse effects (Kirthi 2013 **Level I** [Cochrane], 13 RCTs, n=4,222); adding 10 mg metoclopramide improves nausea and vomiting.

Ibuprofen is also effective here (NNT 7.2 for pain free at 2 h [400 mg]; NNT 9.7 [200 mg]) and soluble preparations provide faster onset of effect (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473). Adverse effects are similar to placebo.

Diclofenac has similar efficacy (NNT 6.2 for pain free at 2 h) and low rates of adverse effects in this indication (Derry 2013b **Level I** [Cochrane], 5 RCTs, n-=1,356).

Dipyrone is also effective for the treatment of migraine and episodic TTHs (Ramacciotti 2007 **Level I** [Cochrane], 4 RCTs, n=636).

Parecoxib IV was similarly effective compared with oral rizatriptan and SC sumitriptan with no placebo arm (Muller 2011 **Level II**, n=57, JS 2).

Triptans

All triptans are more effective in the treatment of acute migraine than placebo (Thorlund 2014 **Level I**, 74 RCTs, n unspecified), particularly in the presence of severe pain and disability where simple analgesia has failed to provide adequate relief in the past. This must be placed in the context of a high placebo response rate and interindividual differences in response to the different triptans, with recommendations for patients to trial a variety of drugs and doses until the most suitable regimen is found (Worthington 2013 **GL**; Pringsheim 2014 **NR**).

In a review of trials with an eletriptan arm, 30–40% of migraine sufferers do not respond to triptan treatments (Diener 2008 **Level I**, 10 RCTs, n=8,473). The three clinical variables that predict poor therapeutic response are: severe pain, photophobia or phonophobia, and nausea; while time of dosing following onset of headache has no effect on 2-h pain-free response.

The route of administration of a triptan may affect its efficacy, speed of onset and tolerability. For sumatriptan, a comparison of different routes of administration showed that SC administration (in comparison to oral, IN and rectal administration) had the highest efficacy and speed of onset but also the highest rate of adverse effects (Derry 2014 **Level I** [Cochrane], 4 Cochrane Reviews, n=52,236). Most effective doses for each route of administration were oral 100 mg, SC 6 mg, IN 20 mg and rectal 25 mg.

Zolmitriptan is effective in acute migraine with oral doses of 2.5 and 5 mg being comparable in efficacy to oral sumatriptan 50 mg (Bird 2014 **Level I** [Cochrane], 25 RCTs, n=20,162).

As most RCTs have compared a single triptan with placebo, it is difficult to determine the relative efficacy of different triptans. A multiple treatment comparison meta-analysis combining available head-to-head and placebo-controlled trials has been published (Thorlund 2014 **Level I**, 74 RCTs, n unspecified). It shows eletriptan followed by rizatriptan, zolmitriptan and sumatriptan having the highest efficacy at 2 h and eletriptan followed by zolmitriptan and sumatriptan at 24 h.

The combination of sumatriptan/naproxen provides a greater headache reduction in the acute treatment of migraine headaches than the same dose of either agent alone, but the difference

in efficacy is small in comparison to sumatriptan alone (Law 2013a **Level I** [Cochrane], 12 RCTs, n=9,291). The combination and sumatriptan alone causes more adverse effects than naproxen or placebo.

The most frequent adverse effects associated with triptans are dizziness, fatigue, sleepiness, nausea, chest tightness and paraesthesiae (Johnston 2010 **NR**). Triptans may cause an increase in light touch-evoked allodynia and thermal sensitivity (Linde 2004 **Level III-2**). Concerns about an increase in cardiovascular events with the use of triptans could not be confirmed (Roberto 2015 **Level III-2 SR**, 4 studies, n≈131,000); the pooled OR of serious ischaemic events was 0.86 (95%CI 0.52 to 1.43).

Frequent use of triptans may lead to triptan-induced rebound headaches (medication-overuse headache), often described as chronic migraine (Tepper 2012 **NR**). This risk increases with increasing days of triptan use, in particular with use on >10 d/mth (Lipton 2013 **Level IV**).

Ergot derivatives

Ergotamine and dihydroergotamine preparations have been used for many years to treat migraine, although they have been superseded by the triptans, as they are less effective and have more adverse effects (Tfelt-Hansen 2008 **NR**). In particular, oral triptans are superior to oral ergotamine, because the bioavailability of oral ergotamine is extremely low (<1%).

IN dihydroergotamine (2 mg) has a NNT of 2.5 for 2-h headache response in migraine (Oldman 2002 **Level I**, 1 RCT [ergotamine], n=203). As a single agent, parenteral dihydroergotamine may not be as effective as other migraine treatments (Colman 2005 **Level I**, 3 RCTs [ergotamine alone], n=423). However, when dihydroergotamine was combined with an antiemetic such as metoclopramide, the efficacy of this combination was similar to valproate, ketorolac and opioids (Colman 2005 **Level I**, 8 RCTs [ergotamine/antiemetic], n=384).

Importantly, in contrast to the data for triptans, ergot derivatives caused an increased rate of ischaemic events (OR 2.51; 95%CI 1.10 to 5.71) (Roberto 2015 **Level III-2 SR**, 4 studies, n≈131,000).

Opioids and tramadol

Opioids are of limited benefit in the treatment of migraine and should not be used (Tepper 2012 **NR;** Casucci 2013 **NR**). Opioid use for migraine was associated with more severe headache-related disability, symptomology, comorbidities (depression, anxiety and cardiovascular disease and events), and greater healthcare utilisation than no use (Buse 2012 **Level III-2**). Among current opioid users for migraine, 16.6% met criteria for probable dependence. Opioids induce migraine progression with a dose-dependent effect beyond approximately 8 d exposure/mth (Bigal 2009 **NR;** Tepper 2012 **NR**).

Despite these disadvantages and recommendations, opioids continue to be used in more than half of all patients attending EDs in the USA for migraine (Friedman 2014 **Level IV**). However, when other migraine treatments are contraindicated, use of opioids may have to be considered as a last resort (Finocchi 2013 **NR**).

Pethidine in particular is not recommended for the treatment of migraine, due to lack of evidence of efficacy, neurotoxicity of its metabolite norpethidine (epileptogenic) and the high risk of developing dependency. Pethidine is less effective than dihydroergotamine or antiemetics for the treatment of migraine; however, it is of similar efficacy to ketorolac (Friedman 2008b **Level I**, 11 RCTS, n=625).

Overall, the most commonly trialled opioids in migraine (pethidine, tramadol and nalbuphine) are more effective in reducing migraine pain than placebo (Kelley 2012 **Level I**, 23 RCTs, n unspecified). Morphine without an antiemetic was no more effective than placebo (Nicolodi 1996 **Level III-1**). Butorphanol was effective when given by the IN or IM route (Elenbaas 1991 **Level III-1**; Hoffert 1995 **Level II**, n=157, JS 3).

Antiemetics and major tranquillisers

Parenteral metoclopramide, as monotherapy or in combination, is effective for the treatment of headache and nausea in acute migraine (Colman 2004 **Level I**, 13 RCTs, n=728).

Parenteral droperidol is also effective in this indication; the minimum effective dose is 2.5 mg IM or IV (Thomas 2014 **Level I**, 5 RCTS, n=685).

IV prochlorperazine was as effective (Friedman 2008a **Level II**, n=77, JS 4) or more effective than IV metoclopramide (Coppola 1995 **Level II**, n=70, JS 4) or IV promethazine for initial ED treatment of migraine (Callan 2008 **Level II**, n=70, JS 4). Buccal prochlorperazine was superior to an oral ergotamine/caffeine combination or placebo (Sharma 2002 **Level II**, n=45, JS 5). A combination of indomethacin/prochlorperazine/caffeine (Di Monda 2003 **Level II**, n=112, JS 3) and a combination of prochlorperazine/diphenhydramine were more effective than SC sumatriptan (Thomas 2014 **Level II**, n=68, JS 5). Parenteral chlorpromazine (Bigal 2002 **Level II**, n=128, JS 4) was also effective.

Other drug treatments

Steroids were similar to placebo in the treatment of migraine; however, parenteral dexamethasone reduced the rate of moderate or severe headache recurrence after 24–72 h (RR 0.71; 95%CI 0.59 to 0.86) (Huang 2013 **Level I**, 8 RCTs, n=905). There were no differences in efficacy between oral and parenteral steroids.

The efficacy of lignocaine in the treatment of migraine is unclear. Analgesia provided by IV lignocaine was similar to dihydroergotamine but not as effective as chlorpromazine (Bell 1990 **Level II**, n=76, JS 2) and, in another trial, no better than placebo (Reutens 1991 **Level II**, n=25, JS 3). IN lignocaine was more effective than placebo (Maizels 1996 **Level II**, n=91, JS 4).

IV magnesium has no benefit compared to placebo for analgesic effect and need for rescue analgesia in acute migraine treatment but causes more adverse effects (Choi 2014 **Level I**, 5 RCTs, n=295).

IV sodium valproate was ineffective in treating acute migraine (Frazee 2008 **Level IV SR** including 3 RCTs). This was contradicted by a subsequent case series (Shahien 2011 **Level VI**), but confirmed in an RCT, which found sodium valproate inferior to ketorolac and metoclopramide (Friedman 2014 **Level II**, n=330, JS 5).

Propofol in 30–40 mg IV bolus doses was more effective than sumatriptan 6 mg SC at 30 min with less need for antiemetics and lower rate of recurrence (Moshtaghion 2014 **Level II**, n=91, JS 5). Propofol in 10 mg IV bolus doses up to 80 mg was also superior to dexamethasone (IV 0.15 mg/kg to a maximum of 16 mg) (Soleimanpour 2012a **Level II**, n=90, JS 5). The efficacy was also confirmed in a number of case series (Soleimanpour 2012c **Level IV**; Mosier 2013 **Level IV**; Ward 2013 **Level IV**), including one in paediatric patients (Sheridan 2012 **Level IV**). However, guidelines give a weak recommendation against the use of propofol (Orr 2015 **GL**).

Sublingual ginger (*Zingiber officinale*)/feverfew (*Tanacetum parthenium*) extract was more effective than placebo in aborting acute migraine when used in early mild headache (Cady 2011 **Level II**, n=60, JS 5).

Pramipexole has been linked with a significant reduction in migraine, particularly the morning headaches in patients with concomitant restless legs syndrome (Suzuki 2013 **Level VI**).

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy was effective in relieving migraine headaches compared to sham therapy (RR 5.97; 95%CI 1.46 to 24.38) but there was no effect on nausea and vomiting, rescue analgesic requirements or migraine prevention (Bennett 2008 **Level I** [Cochrane], 9 RCTs, n=201).

8.6.5.3 Menstruation-related migraine

Management of acute migraine during menstruation does not differ from treatment at other phases of the menstrual cycle. Prophylaxis is based on modifying hormone fluctuations, usually by intake of oestrodiol-containing oral contraceptive preparations (MacGregor 2010 **NR**).

Sumatriptan, zolmitriptan, rizatriptan and mefenamic acid are more effective than placebo for acute treatment (Pringsheim 2008 **Level I**, 10 RCTs [acute abortive treatment], n=3,255). Eletriptan was as effective to achieve 2 h pain relief in females in and outside of the menstrual period

but with higher rate of recurrence and less sustained suppression of nausea in the menstrual period (Bhambri 2014 **Level I**, 5 RCTs, n=3,217).

8.6.5.4 Migraine in pregnancy and breastfeeding

Migraine can occur for the first time during pregnancy and pre-existing migraine may worsen, particularly during the first trimester or may improve in later pregnancy with the patient becoming headache-free (MacGregor 2014 **NR**). Approximately 60–70% of migraineurs improve during pregnancy (frequency, duration) with a sharp rise in the incidence after delivery (Kvisvik 2011 **Level IV**, n=2,126). Breastfeeding is protective (David 2014 **NR**).

Migraine in pregnancy is a risk factor for gestational hypertension and preeclampsia (OR=2.3; 95%CI 2.1 to 2.5) and is also associated with ischemic stroke (OR 30.7; 95%CI 11.1 to 22.5), myocardial infarction (OR 4.9; 95%CI 1.7 to 14.2), deep vein thrombosis (OR 2.4; 95%CI 1.3 to 4.2) and thrombophilia (OR 3.6; 95%CI 2.1 to 6.1) (Bushnell 2009 **Level III-2**).

The major concerns in the management of migraine in pregnancy are the effects of medication and the disease itself on the fetus. Medication use should ideally be limited. Paracetamol, metoclopramide, caffeine, codeine (or perhaps other opioids) can be used during pregnancy, while aspirin, NSAIDs or coxibs should not be used during the third trimester (David 2014 **NR**) (see also Section 10.1 and Tables 10.1 and 10.2).

There is contradictory information on the safety of triptan therapy during pregnancy. While there are human data suggesting potential teratogenicity (David 2014 **NR**), a large Scandinavian population study (n=181,124) has shown no significant risk of congenital malformation but a small risk of uterine atony and haemorrhage with use during the second and third trimesters (Nezvalova-Henriksen 2013 **Level III-2**).

Ergot alkaloids during pregnancy may disrupt fetoplacental blood supply and cause uterine contractions, which can result in low birth weight and preterm birth (Banhidy 2007 **Level IV**). Birth defects and stillbirths due to vascular spasm have been reported and it is recommended that ergotamines be avoided in pregnancy (Acs 2006 **NR**). However, dihydroergotamine has significantly fewer vasoconstrictor and uterotonic effects compared with other ergotamines: dihydroergotamine use in pregnancy (n=59,707) did not increase risk for major malformations but increased the risk of prematurity and resulted in a risk of spontaneous abortion similar to that of triptan and NSAID use (Berard 2012 **Level III-2**).

Low-dose acetylsalicylic acid, ibuprofen, sumatriptan, paracetamol, caffeine and metoclopramide are considered safe for the treatment of acute migraine in mothers who are breastfeeding (Hutchinson 2013 **NR;** David 2014 **NR;** Davanzo 2014 **Level IV SR**). Acute migraine medications that should be avoided include high-dose acetylicsalicylic acid, dihydroergotamine, ergotamine and opioids. (See also Section 10.1 and Tables 10.1 and 10.2.)

8.6.5.5 Cluster headache and other trigeminal autonomic cephalalgias

Cluster headache is a rare primary headache disorder, presenting almost exclusively in males with recurrent acute episodes of brief severe unilateral periorbital pain associated with autonomic phenomena such as conjunctival injection and tearing.

Guidelines for the treatment of cluster headache attacks propose as first-line treatments sumatriptan 6 mg SC, zolmitriptan 5 mg and 10 mg IN, and 100% oxygen 6–12 L/min (Francis 2010 **GL**).

Oxygen

Although high-flow oxygen is recommended as a first-line treatment (Francis 2010), this recommendation is only supported by a meta-analysis of two small RCTs (Bennett 2008 **Level I** [Cochrane], 2 RCTs [cluster headache], n=69) and one subsequent larger RCT (Cohen 2009 **Level II**, n=109, JS 5). The presence of nausea/vomiting and "restlessness" was predictive of a poor response to oxygen (Schurks 2007 **Level IV**).

Hyperbaric oxygen is statistically no more effective than sham hyperbaric treatment in reducing the frequency or duration of cluster headaches (Bennett 2008 **Level I** [Cochrane], 1 RCT [cluster headache], n=13).

High-flow oxygen treatment had a superior effect to high-flow room air in all types of headaches in an ED setting (Ozkurt 2012 **Level II**, n=204, JS 5).

Triptans

Triptans are effective to treat cluster headaches; sumatriptan 6 mg SC is superior to zolmitriptan 5 mg or 10 mg IN for rapid response at 15 min, while oral routes of administration are not appropriate for this condition (Law 2013b **Level I** [Cochrane], 6 RCTs, n=1,180).

Other treatments

IN (Dahlof 2002 **NR**) or IV (May 2006 **GL**) lignocaine may be effective, although good evidence is lacking.

The efficacy of cannabis in cluster headaches is limited and it should only be used in clinical trials (Leroux 2013b **Level IV**).

In attacks of high frequency, short courses of high-dose oral corticosteroids, dihydroergotamine and occipital nerve blocks with local anaesthetic and steroids are recommended with limited evidence (Becker 2013 **NR**). Here, occipital nerve blocks have been shown to be effective in multiple case series and two RCTs but the mechanism is uncertain and the role of additional steroids unclear (Leroux 2013a **Level IV SR**, 12 studies, n unspecified).

While bilateral occipital nerve stimulation has been used successfully as a prophylaxis (Blumenfeld 2013 **NR;** Pedersen 2013 **NR**), sphenopalatine ganglion stimulation has an abortive effect on acute attacks (Ansarinia 2010 **Level IV**; Schoenen 2013 **Level II**, n=32, JS 5).

8.6.5.6 Paroxysmal hemicrania and SUNCT

Paroxysmal hemicrania and SUNCT are rarer forms of trigeminal autonomic cephalalgia. Paroxysmal hemicrania is similar to cluster headache except that it is more common in females, episodes are shorter but more frequent and diagnosis requires the complete abolition of symptoms with indomethacin (Headache Classification Committee 2013), which is the suggested treatment of choice (May 2006 **GL**). There is no high-level evidence to guide the treatment of SUNCT, however consensus guidelines based on case-series data suggest that IV lignocaine for acute treatment and lamotrigine, possibly topiramate and gabapentin may be useful prophylactics (May 2006 **GL**). Occipital nerve stimulation may be a potential effective treatment for SUNCT and hemicrania continua (Young 2012b **Level IV**; Lambru 2014 **Level IV**).

8.6.5.7 Postdural puncture headache

PDPH, usually following spinal anaesthesia, inadvertent dural puncture with an epidural needle, diagnostic or therapeutic lumbar puncture or neurosurgery, occurs with an incidence of approximately 0.7–50% (Bezov 2010a **NR;** Bezov 2010b **NR)**. Up to 85% of cases improve spontaneously within 6 wk.

Risk factors are younger age, female gender, low BMI, history of prior PDPH and history of chronic headache. Children who undergo lumbar puncture may present a special group (Janssens 2003 **NR**) (see Section 9.4).

Spinal needle size, type and lumbar puncture technique

Data from the anaesthesiology and neurology literature indicate that needle calibre, bevel type and lumbar puncture technique affects the incidence of PDPH. The incidence of PDPH following spinal anaesthesia was reduced significantly by using a smaller gauge needle (26gauge or less NNT 3) or a needle with a “noncutting” bevel (eg “pencil point” NNT 27) (Halpern 1994 **Level I**, 16 RCTs, n=3,593).

Subsequent studies support these findings for noncutting bevel needles (Schmittner 2011 **Level II**, n=363, JS 3) but could not find a difference between 23- and 25-gauge needles in patients >60 y (Kim 2011b **Level II**, n=53, JS 5) or between cutting 22- and 25-gauge needles in children aged 4–15 y (Crock 2014 **Level II**, n=93 [341 punctures], JS 5).-

The incidence of PDPH was also reduced by orientating the cutting bevel parallel to the spinal sagittal plane (dural fibres) (Richman 2006 **Level I**, 5 RCTs, n=521) or by replacing the stylette

prior to withdrawing a noncutting needle (Strupp 1998 **Level II**, n=600, JS 3); these techniques presumably reduce CSF loss. However, a subsequent study could not confirm the benefit of replacing the stylette in a 25-guage Quincke needle (Sinikoglu 2013 **Level II**, n=630).

Similarly, for diagnostic lumbar punctures, noncutting (pencil point) needles significantly reduced the incidence of PDPH compared with cutting needles (Quincke) (Lavi 2006 **Level II**, n=58, JS 4; Strupp 2001 **Level II**, n=306, JS 5), leading to a recommendation to use noncutting needles routinely in neurology practice (Arendt 2009 **NR**).

During epidural catheter insertion in labour the incidence of accidental dural puncture was not reduced when using an 18-gauge epidural Sprotte (pencil point) needle compared with a 17-gauge epidural Tuohy needle (Morley-Forster 2006 **Level II**, n=1,077, JS 5). However the incidence of PDPH was significantly lower with the Sprotte needle.

Epidural blood patch

The use of an epidural blood patch (EPB) for the treatment of PDPH has been recommended as first-line therapy (Bezov 2010a **NR**), especially in obstetric patients (Thew 2008 **NR**) and following inadvertent dural puncture with an epidural needle (Gaiser 2006 **NR**). EPB is more effective than conservative treatment (OR 0.18; 95%CI 0.04 to 0.76, 1 RCT) and a sham procedure (OR 0.04, 95%CI 0.00 to 0.39, 1 RCT) (Boonmak 2010 **Level I** [Cochrane], 9 RCTs, n=379).

The most effective blood volume for EBP administration is not known. Data vary significantly from 7.5–30 mL. There was no difference in the severity of PDPH at 3 d in patients who received either a 7.5 or 15 mL EBP, except for a lower incidence of nerve-root irritation during injection with the lower volume (Chen 2007 **Level II**, n=33, JS 3). EBP volumes in the range of 10–20 mL were effective in relieving PDPH in 98% of patients, following spinal or epidural anaesthesia (Wu 1994 **Level IV**). There was no difference in the frequency of PDPH resolution (approximately 91%) with either 10 or 15 mL blood volumes randomised according to patient height (Taivainen 1993 **Level III-1**). Significant relief of PDPH was obtained in 93% of patients, who received a mean EBP volume of 23 (+/-5) mL (Safa-Tisseront 2001 **Level IV**). With use of volumes of 15, 20 and 30 mL, permanent or partial relief of headache was achieved in 61%, 73%, and 67% respectively and complete relief in 10%, 32%, and 26% without a difference in backache (Paech 2011 **Level II**, n=121, JS 5); the authors recommended 20 mL as the "optimal" target volume.

EBP is sometimes performed prophylactically to prevent PDPH after an inadvertent dural puncture (eg by an epidural needle) (Bezov 2010a **NR**). However, there is conflicting evidence of benefit with prophylactic EBP administration; there is improvement compared to no treatment (OR 0.11; 95%CI 0.02 to 0.64, 1 RCT), conservative treatment (OR 0.06; 95%CI 0.03 to 0.14, 2 RCTs) and epidural saline patch (OR 0.16; 95%CI 0.04 to 0.55, 1 RCT) but not compared to a sham procedure (1 RCT) (Boonmak 2010 **Level I** [Cochrane], 9 RCTs, n=379). The authors of this Cochrane Review do not recommend prophylactic EPB due to concerns about inconclusive findings in small studies. However, a subsequent RCT showed benefit with reduction of incidence of PDPH from 79.6–18.3% by a prophylactic blood patch (Stein 2014 **Level II**, n=60, JS 3).

The use of autologous blood patch may be contraindicated in patients with coagulopathy, cancer, leukaemia or infection, including HIV, although some of these are debated in the literature (Tom 1992 **Level IV**).

Bed rest and hydration

There is no evidence of benefit with bed rest or fluid supplementation in the treatment or prevention of PDPH (Arevalo-Rodriguez 2013 **Level I** [Cochrane], 23 RCTs, n=2,477). However, patients with PDPH may have difficulty in mobilising and the headache subsides with bed rest.

Other treatments

PDPH is successfully treated with morphine, cosyntropin and aminophylline, while dexamethasone increased PDPH and there were inconclusive data for fentanyl, caffeine and indomethacin (Basurto Ona 2013b **Level I** [Cochrane], 10 RCTs, n=1,611). These findings are based on studies of limited quality with small sample size.

A number of other treatments investigated were not considered in the above Cochrane Review.

- IV theophylline reduced the severity of PDPH (Ergun 2008 **Level II**, n= 33, JS 0) and was more effective than paracetamol in this indication (Mahoori 2013 **Level II**, n=60, JS 2).
- The addition of IV hydrocortisone to conventional therapy (bed rest and analgesia) for 48 h decreased the intensity of PDPH following spinal anaesthesia for general surgery (Alam 2012b **Level II**, n=60, JS 4) and for Caesarean delivery (Rucklidge 2004 **Level II**, n= 18, JS 5; Noyan Ashraf 2007 **Level II**, n=60, JS 1).
- Gabapentin (Erol 2011 **Level II**, n=42, JS 2; Vahabi 2014 **Level II**, n=120, JS 3) and pregabalin (Huseyinoglu 2011 **Level II**, n=40, JS 2; Wagner 2012 **Level IV**) reduced the intensity and duration of PDPH; both were superior to paracetamol (Mahoori 2014 **Level II**, n=90, JS 5). Preoperative gabapentin before spinal anaesthesia for elective Caesarean delivery did not reduce PDPH incidence but did reduce severity (Nofal 2014 **Level II**, n=88, JS 5).
- Sumatriptan was ineffective in PDPH (Connelly 2000 **Level III-1**), although frovatriptan has been reported to have sufficient benefit to warrant further evaluation (Bussone 2007 **Level III-2)**.
- IT administration of 5 mL normal saline reduced the overall incidence of PDPH from 24–2% (Faridi Tazeh-Kand 2014 **Level II**, n=100, JS 4).

Low CSF pressure headache may result from disruption of the dural integrity, often in cervical or thoracic levels with persisting headaches of identical character to PDPH. Management requires careful evaluation of the potential site of CSF leak. Extra dural spinal fluid may be apparent on careful MRI and a clue to the site of leak may come from the clinical history. Management is similar to that of PDPH (Mokri 2003 **NR;** Mokri 2013 **NR**).

8.6.5.8 Other headaches

There is little evidence to guide the treatment of acute cervicogenic headache, post-traumatic headache or acute headache attributed to substance use or its withdrawal, although general principles of evaluation of headache and management of acute pain must apply (Silberstein 2000 **GL**).

Giant cell arteritis

The treatment of giant cell arteritis is with high-dose steroids but there are no evidence-based guidelines and the steroid dose and route of administration are empirical. Because of the potential devastating effect on vision in this common vasculitic disorder, high-dose steroid is recommended: IV methylprednisolone 15 mg/kg/d showed more rapid and sustained remission compared with oral prednisone 40 mg/d (Mazlumzadeh 2006 **Level II**, n=27, JS 5).

Headache attributed to substance withdrawal (severe analgesic "rebound" headache)

Patients may present with severe acute-on-chronic headache due to the overuse and/or withdrawal of antimigrainal (triptans or ergot alkaloids) or analgesics. Inpatient treatment is often required to manage this chronic pain condition and may include cessation of analgesics, IV hydration, steroids, NSAIDs, antiemetics and benzodiazepines (Kristoffersen 2014 **NR**).

Key messages

Tension-type headache

1. Acupuncture is possibly effective in the treatment of tension-type headache (**W**) (**Level I** [Cochrane Review]).
2. Simple analgesics such as paracetamol or NSAIDs, either alone or combined, are effective in the treatment of episodic tension-type headache (**S**) (**Level I** [PRISMA]).
3. Metoclopramide, metamizole and chlorpromazine as parenteral treatments of tension-type headache have high efficacy (**N**) (**Level I** [PRISMA]).

4. The combination of caffeine/aspirin/paracetamol is superior to paracetamol in the treatment of episodic tension-type headache (**Q**) (**Level I**).

Migraine

5. Paracetamol is effective in the treatment of migraine, however less than other analgesics; the efficacy is increased when combined with metoclopramide (**S**) (**Level I** [Cochrane Review]).
6. Aspirin, ibuprofen, diclofenac and dipyrone are effective in the treatment of migraine; soluble preparations of ibuprofen provide a faster onset (**S**) (**Level I** [Cochrane Review]).
7. For sumatriptan, subcutaneous administration achieves the fastest onset of effect and highest efficacy (**N**) (**Level I** [Cochrane Review]).
8. Hyperbaric oxygen therapy is effective in controlling pain in migraine, but no other symptoms and outcomes (**N**) (**Level I** [Cochrane Review]).
9. A significant placebo effect occurs in migraine treatment (**N**) (**Level I** [QUOROM]), which leads to an underestimation of treatment effects of analgesic compounds (**Level II**).
10. All triptans are more effective than placebo in the treatment of severe migraine (**S**) (**Level I**), however 30–40% of patients may not respond (**N**) (**Level I**).
11. Parenteral antiemetics (metoclopramide or droperidol) are effective in the treatment of migraine (**S**) (**Level I**).
12. Triptans and mefenamic acid are effective in treatment of menstruation-related migraine (**N**) (**Level I**).
13. Some opioids are more effective than placebo in the treatment of acute migraine (**N**) (**Level I**), but their use in this setting is associated with significant adverse effects and poor outcomes (**N**) (**Level III-2**).
14. Pethidine is less effective than most other migraine treatments and should not be used (**U**) (**Level I**).
15. Magnesium IV has no analgesic effect compared to placebo in migraine (**N**) (**Level I**).
16. Parenteral prochlorperazine, chlorpromazine or droperidol are effective in the treatment of migraine, especially in the emergency department (**U**) (**Level II**).
17. A "stratified care strategy" is effective in treating migraine (**U**) (**Level II**).
18. Ergotamine derivatives, but not triptans, increase the rate of severe myocardial ischaemic events (**N**) (**Level III-2 SR**).
19. Migraine in pregnancy is a risk factor for gestational hypertension, preeclampsia and cardiovascular complications (**N**) (**Level III-2**).

Cluster headache

20. Parenteral triptans (sumatriptan or zolmitriptan) or high-flow oxygen therapy are effective treatments for cluster headache attacks (**S**) (**Level I** [Cochrane Review]).

Postdural puncture headache

21. There is no evidence that bed rest or fluid supplementation are beneficial in the treatment and prevention of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).
22. Epidural blood patch administration is more effective than conservative treatment or a sham procedure in the treatment of postdural puncture headache (**S**) (**Level I** [Cochrane Review]).

23. Morphine, cosyntropin and aminophylline are successful treatments for postdural puncture headache; dexamethasone is not, with inconclusive data for fentanyl, caffeine and indomethacin (N) (**Level I** [Cochrane Review]).
24. The incidence of postdural puncture headache is reduced by using smaller-gauge spinal or non-cutting bevel needles or by orientating the cutting bevel parallel to the spinal sagittal plane (**S**) (**Level I**).
25. IV theophylline, IV hydrocortisone, gabapentin and pregabalin are effective in the treatment of postdural puncture headache (N) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Opioids should be used with extreme caution in the treatment of headache; pethidine should not be used (**S**).

☑ Frequent use (>8–10 days/month) of analgesics, triptans and ergot derivatives in the treatment of recurrent acute headache may lead to medication overuse headache (**U**).

8.6.6 Acute pain associated with neurological disorders

Pain associated with neurological disorders is usually neuropathic in nature, although nociceptive pain due to problems such as muscle spasms may also occur. Neuropathic pain may be acute or chronic and may be due to a lesion or disease of the somatosensory system, either in the periphery or centrally (Jensen 2011 **NR**). Treatment of acute neuropathic pain is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain disorders. Effective treatments for neuropathic pain include TCAs, anticonvulsants, membrane stabilisers, NMDA-receptor antagonists, opioids or tramadol (see Sections 4.1 and 4.3.2 to 4.3.6).

Associated psychosocial problems and physical disabilities must also be managed within a multidisciplinary framework.

8.6.6.1 Multiple sclerosis

Chronic pain is experienced by 26–86% of patients with multiple sclerosis (Truini 2013 **NR**). These data are confirmed in a systematic review, which finds a prevalence of 63% (95%CI 55 to 70%) (Foley 2013 **Level IV SR**, 17 studies, n=5,319).

A new mechanism-based classification distinguishes the following types of pain related to multiple sclerosis (Truini 2013 **NR**):

- trigeminal neuralgia and Lhermitte's phenomenon (paroxysmal neuropathic pain due to ectopic impulse generation along primary afferents);
- ongoing extremity pain (deafferentation pain secondary to lesion in the spinothalamocortical pathways);
- painful tonic spasms and spasticity pain (mixed pains secondary to lesions in the central motor pathways but mediated by muscle nociceptors);
- pain associated with optic neuritis (nerve trunk pain originating from nervi nervorum);
- musculoskeletal pains (nociceptive pain arising from postural abnormalities secondary to motor disorders);
- migraine (nociceptive pain favoured by predisposing factors or secondary to midbrain lesions); and
- treatment-induced pains.

The prevalence of headache (43%; 95%CI 33 to 52%), neuropathic extremity pain (26%; 95%CI 7 to 53%), back pain (20%; 95%CI 13 to 28%), painful spasms (15%; 95%CI 8.5 to 23%), Lhermitte's sign (16%; 95%CI 10 to 25%) and trigeminal neuralgia (3.8%; 95%CI 2 to 6%) is reported (Foley 2013 **Level IV SR**, 17 studies, n=5,319). Treatment approaches need to be targeted

to the wide variety of different pain types occurring in multiple sclerosis balanced with adverse-effect profiles.

A systematic review of pharmacological management of pain in multiple sclerosis identified only two treatment approaches amenable to meta-analysis (Jawahar 2013 **Level I** [PRISMA], 15 RCTS, n unspecified). Various anticonvulsants have a pooled effect size of -1.88 (95%CI: -3.13 to 0.64) and thereby the only statistically significant effect (Jawahar 2013 **Level I** [PRISMA], 4 RCTs [anticonvulsants], n=78).

In contrast, the pooled effect size for cannabinoids of 0.08 (95%CI: -0.74 to 0.89) suggests no effect (Jawahar 2013 **Level I** [PRISMA], 3 RCTs [cannabinoids], n=565). In spasticity due to multiple sclerosis, the treatment difference compared to placebo is -0.32/10 on an NRS (95%CI -0.61 to -0.04) for nabiximols (Sativex®; containing THC:cannabidiol=approx. 1:1), with high numbers of subjects experiencing at least one adverse effect (Wade 2010 **Level I**, 3 RCTs, n=666). Oral cannabis extract specifically shows some efficacy in treating spasticity and central pain in patients with multiple sclerosis and nabiximols and THC show probable efficacy in these conditions (Koppel 2014 **Level I**, 34 RCTS [in multiple neurological conditions and for multiple indications], n unspecified). The authors advise weighing of the risks and benefits of cannabinoid use in this indication carefully, particularly in view of a near 1% incidence of serious adverse psychopathological effects (see also Section 4.3.8).

8.6.6.2 Parkinson's disease

Pain is a common distressing symptom in Parkinson's disease; between 30 and 50% of patients with Parkinson's disease have pain (Fil 2013 **NR**).

Acute pain management is empirical; conventional analgesics, TCAs, atypical neuroleptics and possibly opioids should be considered (Ford 2010 **NR;** Sophie 2012 **NR**).

8.6.6.3 Central poststroke pain

Central pain develops in 8–35% of stroke patients (Kumar 2009 **NR**). It is not only a consequence of thalamic stroke but also lateral medullar and parietal cortical stroke or ischaemic events affecting the spinothalamic or trigeminothalamic pathways (Flaster 2013 **NR**).

IV lignocaine (Attal 2000 **Level II**, n=6 [poststroke], JS 5) and IV propofol in subhypnotic doses (Canavero 2004 **Level II**, n=44, JS 5) may provide short-term relief in central poststroke pain. Amitriptyline was more effective than placebo and carbamazepine (which were equivalent) (Leijon 1989 **Level II**, n=15, JS 4). Lamotrigine was moderately effective and well tolerated in central poststroke pain (Vestergaard 2001 **Level II**, n=30, JS 5). Pregabalin in poststroke pain did not result in significant pain relief at the endpoint of the trial but there was a profound placebo response and pain relief at other time points and secondary outcomes were in favour of pregabalin (Kim 2011a **Level II**, n=219, JS 5).

The SSRI fluvoxamine showed benefit in poststroke pain (Shimodozono 2002 **Level IV**).

On the basis of the limited data available, a practical guide to treatment recommends trials of amitriptyline, lamotrigine, gabapentin or pregabalin or a combination of these to treat central poststroke pain (Kim 2014b **GL**).

8.6.6.4 Trigeminal neuralgia

Exacerbations of trigeminal neuralgia can present as acute neuropathic pain.

Topiramate is as effective as carbamazepine at 1 mth after treatment commencement and slightly more effective at the 2-mth endpoint (RR 1.20; 95%CI 1.04 to 1.39) (Wang 2011 **Level I**, 6 RCTs, n=354). All included RCTs were of poor methodological quality; this is also an issue for carbamazepine trials, which show probable effectiveness over placebo (Wiffen 2014 **Level I** [Cochrane], 10 RCTs, n=480). Lamotrigine had no analgesic benefit in neuropathic pain in large, high-quality, long-duration studies in comparison with placebo (Wiffen 2013 **Level I** [Cochrane] 12 RCTs, n=1,511).

There is insufficient evidence to support the use of any nonantiepileptic medications (tizanidine, pimozide, tocainide) in trigeminal neuralgia (Zhang 2013c **Level I** [Cochrane] 3 RCTs [systemic medications], n=92).

IV infusion of magnesium/lignocaine once/wk for 3 wk resulted in reduction of pain in patients with trigeminal neuralgia not responding to previous treatments (Arai 2013a **Level IV**). Duloxetine has been shown to have an effect in trigeminal neuralgia (Anand 2011 **Level IV**).

Topical ophthalmic anaesthesia has been studied with varying results. Proparacaine hydrochloride 0.5% was not superior to placebo (Zhang 2013c **Level I** [Cochrane] 1 RCT [proparacaine hydrochloride], n=47). Amethocaine 1% eye drops reduced paroxysms of pain in trigeminal neuralgia in a small open-label study (n=40) (Brill 2010 **Level IV**). Intraoral lignocaine 8% was also effective in a similar study (Niki 2014 **Level IV**).

Published guidelines identified insufficient evidence for the effectiveness of any IV medication in this setting (Cruccu 2008 **GL**). The same guidelines rate carbamazepine as effective and oxcarbazepine as probably effective and suggest that baclofen, oxcarbazepine, gabapentin, lamotrigine, tizanidine and pimozide may be considered, if the first-line medications are ineffective. An updated review of the evidence supports carbamazepine and oxcarbazepine with insufficient data to support baclofen, lamotrigine and gabapentin (Zakrzewska 2014 **NR**).

Key messages

1. Various anticonvulsants have an effect in the treatment of neuropathic pain associated with multiple sclerosis (**N**) (**Level I** [PRISMA]).
2. Cannabinoids have a clinically small effect on spasticity caused by multiple sclerosis; the effect on neuropathic pain associated with multiple sclerosis is unclear and may depend on the preparation used (**N**) (**Level I**).
3. With cannabinoid use in multiple sclerosis, serious adverse psychopathological effects occur in nearly 1% of patients (**N**) (**Level I**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Treatment of acute pain associated with neurological disorders is based largely on evidence from trials for the treatment of a variety of chronic neuropathic pain states.

8.6.7 Orofacial pain

Acute orofacial pain may be caused by infective, traumatic, neuropathic, vascular, neoplastic and other pathologies (Hegarty 2011 **NR**; Zakrzewska 2013 **NR**). Most commonly, acute orofacial pain is due to either dental or sinus disease. It may also be associated with flare-ups of more chronic orofacial pain syndromes eg TMDs, trigeminal neuralgia and migraine headaches. Pain may also be referred from adjacent structures such as the cervical spine and ear.

Post-traumatic neuropathic orofacial pain (post-traumatic trigeminal neuropathy) may be caused by nerve injury secondary to dental surgical procedures eg extraction of teeth, root canal therapy, local anaesthetic injections or placement of dental implants. Such orofacial pain conditions may be exacerbated by repeated procedures, incorrect treatment and comorbid psychological factors.

A thorough medical/dental history and clinical examination (particularly of the mouth, jaw and cranial nerves) are essential components of the assessment of acute orofacial pain (Hegarty 2011 **NR;** Zakrzewska 2013 **NR**).

Recurrent or persistent orofacial pain may require additional biopsychosocial assessment and appropriate multidisciplinary management (Vickers 2000 **NR**).

8.6.7.1 Acute dental pain

In general, patients suffering acute oral and dental pain should be referred to a dentist for appropriate diagnosis and management. NSAIDs and emergency pulpectomy reduces

pain in patients with acute apical periodontitis (Sutherland 2003 **Level I**, 8 RCTs, n=531) but there is insufficient evidence to determine if the addition of antibiotics reduces pain due to irreversible pulpitis (Fedorowicz 2013 **Level I** [Cochrane], 1 RCT, n=40) or apical periodontitis (Cope 2014 **Level I** [Cochrane], 2 RCTs, n=62). Unless it has been established that infection is the cause, it is inappropriate for antibiotics to be prescribed, even though they may provide some symptomatic relief (Abbott 2007 **NR**). Pulpitis due to extension of caries into the pulp, or pulp exposure may lead to pulp necrosis and acute periapical periodontitis.

The use of local anaesthetics to permit dental treatment is beyond the scope of this document and has not been dealt with.

8.6.7.2 Acute postoperative dental pain

Paracetamol and NSAIDs

Acute pain after third molar extraction is the most extensively studied model for testing postoperative analgesics in single-dose investigations. Nonselective NSAIDs or coxibs are recommended as "first-line" analgesics following third molar extraction (Derry 2011 **Level I**, 155 RCTs, n=16,104), however paracetamol is also safe and effective with a dose of 1,000 mg providing better pain relief than lower doses (Weil 2007 **Level I** [Cochrane], 21 RCTs, n=1,968).

Nonselective NSAIDs are more effective than paracetamol or codeine (either alone or in combination) (Ahmad 1997 **Level I**, 33 RCTs, n=5,171). Ibuprofen (200–512 mg) specifically is superior to paracetamol (600–1,000 mg) in this setting and combining these two drugs improves analgesia further (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241). The combination of paracetamol 1,000 mg with ketoprofen 100 mg was more effective than either drug given alone (Akural 2009 **Level II**, n=76, JS 5). Ketorolac (30 IM/IV mg) provided better analgesia with fewer adverse effects than pethidine (100 mg IM) (Fricke 1992 **Level II**, n=145, JS 5) or tramadol (50 mg IV) (Ong 2004 **Level II**, n=64, JS 3).

Coxibs are of similar efficacy to nsNSAIDs in acute postoperative dental pain. Single-dose celecoxib 200 mg is less effective than ibuprofen 400 mg (Chen 2004 **Level I**, 18 RCTs, n=2,783); however celecoxib 400 mg provided similar analgesia to ibuprofen 400 mg with increased time to rescue analgesia following dental surgery (Cheung 2007 **Level II**, n=171, JS 5). Single daily doses of etoricoxib 90 mg and 120 mg were similar in analgesic efficacy to ibuprofen 600 mg every 6 h but longer lasting as well as superior to a paracetamol/codeine (600/60 mg) combination (Brown 2013 **Level II**, n=588, JS 5). A combination of oxycodone/ibuprofen (5/400 mg) was more effective than other combinations of paracetamol, ibuprofen, oxycodone or hydrocodone or placebo for analgesia following dental surgery (Litkowski 2005 **Level II**, n=249, JS 5).

A systematic review to investigate the influence of pain models revealed that the placebo response for analgesia was significantly lower post third molar extraction pain than in other acute pain models (Barden 2004a **Level I**, 160 RCTs, n=14,410).

Tramadol

Tramadol 100 mg had a similar efficacy to aspirin/weak opioid or paracetamol/weak opioid combinations in treating acute dental pain (Moore 1997 **Level I**, 18 RCTs, n=3,453) but was significantly less effective than naproxen 500 mg (Mehrvarzfar 2012 **Level II**, n=100, JS 5).

A tramadol/paracetamol combination is superior to tramadol alone with fewer adverse effects due to a reduced tramadol dose (Edwards 2002a **Level I**, 7 RCTs, n=1,376); Fricke 2004 **Level II**, n=456, JS 5) and was comparable to a codeine/acetaminophen/ibuprofen combination preparation (Jung 2004 **Level II**, n=128, JS 5).

Steroids

Perioperative steroid administration reduced swelling and trismus but not pain following third molar extraction (Markiewicz 2008 **Level I**, 12 RCTs, n=287). However, two subsequent studies suggested there might be an analgesic benefit from dexamethasone (Klongnoi 2012 **Level II**, n=20, JS 2) with dexamethasone 4 mg being similarly effective to 120 mg etoricoxib (Sotto-Maior 2011 **Level II**, n=50, JS 3).

A submucosal injection of dexamethasone immediately before surgery led to reduced postoperative facial swelling but not a significant reduction of either pain or trismus, compared with placebo at 48 h; no difference was found between 4 mg and 8 mg dose (Grossi 2007 **Level II**, n=72, JS 5). A single 40 mg injection of methylprednisolone into the masseter muscle following third molar extraction reduced pain, swelling and trismus (Vegas-Bustamante 2008 **Level II**, n=35, JS 5).

Pregabalin

Postoperative administration of oral pregabalin 75 mg provided better analgesic effects than administration before third molar extraction surgery (Cheung 2012 **Level II**, n=34, JS 5).

Nonpharmacological treatment

Cryotherapy (ice packs) following third molar extraction showed inconsistent results with regard to facial pain (Laureano Filho 2005 **Level III-2**; van der Westhuijzen 2005 **Level II**, n=60, JS 5). Facial compression reduced pain for up to 3 d with no additional benefit from coapplication of ice packs (Forouzanfar 2008 **Level II**, n=95, JS 5).

Acupuncture may have a beneficial effect on acute dental pain but the quality of evidence is limited (Ernst 1998 **Level III-1 SR**, 16 studies, n=941).

Low-level laser energy irradiation fails to reduce either pain or swelling after removal of third molar teeth (Brignardello-Petersen 2012 **Level I**, 10 RCTs, n=581).

8.6.7.3 Acute post-tonsillectomy pain

Paracetamol, NSAIDs and opioids

A systematic review of analgesia for tonsillectomy in children was unable to generate clear conclusions due to heterogeneity of the trials (Hamunen 2005 **Level I**, 36 RCTs, n=1,798). However, no single prophylactic dose of an analgesic provided adequate pain relief for the entire postoperative d 1; orally administered paracetamol was more effective than rectal, and prophylactic NSAIDs were at least as effective as opioids in reducing post-tonsillectomy pain.

Single doses of diclofenac, either orally (Romsing 2000 **Level II**, n=48, JS 5) or rectally (Schmidt 2001 **Level II**, n=90, JS 5) or IV ketorolac (Rusy 1995 **Level II**, n=50, JS 5) were no more effective than paracetamol in providing analgesia in children post tonsillectomy. Paracetamol IV administered every 6 h on first postoperative day reduced pain and rescue analgesia requirements in adults following tonsillectomy (Atef 2008) **Level II**, n=76, JS 5).

In meta-analyses of tonsillectomy in both adult and paediatric patients, nsNSAIDs were found to increase the risk of reoperation for bleeding (NNH 29–60) (Marret 2003 **Level I**, 7 RCTs, n=505; Moiniche 2003 **Level I**, 25 RCTs, n=970) but surgical blood loss was not significantly increased (Moiniche 2003 **Level I**, 25 RCTs, n=970) (see also Section 4.3). Aspirin (OR 1.94; 95%CI 1.09 to 3.42) (Krishna 2003 **Level I**, 7 RCTs, n=1,368) and ketorolac (RR 2.04; 95%CI 1.32 to 3.15) (Chan 2014 **Level I**, 10 RCTs, n unspecified) specifically increased the risk of bleeding; however for ketorolac, this was found only in adults (RR 5.64; 95%CI 2.08 to 15.27; p<.001) and not in children (RR 1.39; 95%CI 0.84 to 2.30).

In children, there was a nonsignificant increase in the risk of bleeding requiring surgical intervention with nsNSAID analgesia (OR 1.69; 95%CI 0.71 to 4.01) (Lewis 2013 **Level I** [Cochrane], 15 RCTs, n=1,101). The authors conclude that there is insufficient evidence to exclude an increased risk of bleeding when NSAIDs are used in paediatric tonsillectomy (see also Section 9.4.3.2).

Death or OIVI has occurred after codeine treatment. Although rare, the risk is highest in children who are ultrarapid metabolisers, after they have undergone tonsillectomy, adenoidectomy, or both, as many of these have sleep-disordered breathing and are therefore more sensitive to opioids (Racoosin 2013 **NR**). The FDA now requires a boxed warning of the risk posed by codeine after a child has undergone tonsillectomy or adenoidectomy (FDA 2013) (see also Sections 1.7 and 9.4.4.5).

Gabapentin and pregabalin

Gabapentin reduced analgesia requirements for up to 24 h and pain on swallowing for up to 4 h following tonsillectomy in adults (Jeon 2009 **Level II**, n=58, JS 3). Gabapentin and diclofenac were equally effective analgesics with a longer duration of action for gabapentin (Yeganeh Mogadam 2012 **Level II**, n=90, JS 5). Pregabalin and pregabalin/dexamethasone improved pain control after tonsillectomy compared to placebo (Mathiesen 2011 **Level II**, n=131, JS 5).

Steroids

A single intraoperative dose of dexamethasone in children reduces postoperative pain, nausea and vomiting and time to resumption of oral intake after tonsillectomy with no increase in adverse effects (Steward 2011 **Level I** [Cochrane], 19 RCTs, n=1,756).

Note: reversal of conclusion

This reverses the Level II key message in the previous edition of this document; a single RCT had reported an increased bleeding risk with dexamethasone.

Antibiotics

Perioperative antibiotics show no benefit in decreasing post-tonsillectomy pain, need for analgesia and secondary haemorrhage rates; adverse effects were more common with their use (Dhiwakar 2012 **Level I**, 10 RCTs, n=1,035).

Local anaesthesia

Peritonsillar injection or topical application of local anaesthetics produce equally modest reductions in post-tonsillectomy pain for up to 24 h (Grainger 2008 **Level I**, 13 RCTs, n=777). Ropivacaine 1.0% with adrenaline resulted in better pain relief up to 4 d after tonsillectomy than either bupivacaine 0.25% with adrenaline or placebo (Arikan 2008 **Level II**, n=58, JS 5). Peritonsillar infiltration with bupivacaine provided pain relief comparable to rectal paracetamol (Dahi-Taleghani 2011 **Level II**, n=110, JS 2). The addition of magnesium to levobupivacaine reduced analgesic requirements compared with levobupivacaine alone or saline control (Karaaslan 2008 **Level II**, n=75, JS 4).

Infiltration of the tonsillar bed with tramadol (Atef 2008 **Level II**, n=40, JS 5) as well as an equivalent IM tramadol dose reduced pain and analgesic requirements in the first few hours after tonsillectomy compared to placebo (Ugur 2008 **Level II**, n=45, JS 5) (see also Section 9.4.4.8).

Topical administration

There is poor and inconsistent evidence on the analgesic effects of oral rinses, mouthwashes and sprays after tonsillectomy, although lignocaine spray appeared to be more effective than saline spray (Fedorowicz 2011 **Level I** [Cochrane], 6 RCTs, n=528).

8.6.7.4 Acute pain associated with temporomandibular disorders

TMDs are a group of musculoskeletal pains affecting the masticatory muscles and/or temporomandibular joints (TMJs) and are the most common cause of orofacial pain apart from the teeth (Hegarty 2011 **NR;** Zakrzewska 2013 **NR**). The common TMDs include masticatory myalgia, myofascial pain, TMJ disc interference disorders and TMJ degenerative joint disease. The primary TMD symptoms include painful limitation of mouth opening and/or deviation of the mandible on opening, TMJ tenderness, TMJ crepitus and/or clicking noise and masticatory muscle pain or tenderness. Headaches are often an associated feature.

There is limited evidence for the successful pharmacological management of TMD pain (Mujakperuo 2010 **Level I** [Cochrane], 11 RCTs, n=496). The best evidence exists for naproxen 1,000 mg/d, which was more effective than celecoxib 200 mg/d and placebo (Ta 2004 **Level II**, n=68, JS 5).

8.6.7.5 Acute pain associated with pharyngitis

Systemic analgesics

Paracetamol, nsNSAIDs, coxibs and opioids, administered as monotherapy or in combination, were effective in the treatment of pain associated with acute pharyngitis (Thomas 2000 **Level I**, 17 RCTs, n=3,259).

Corticosteroids

Corticosteroids provide relief of pain, in particular in patients with severe or exudative sore throat (Hayward 2012b **Level I** [Cochrane], 8 RCTs, n=743). Here, corticosteroids in combination with analgesics and antibiotics tripled the likelihood of complete resolution of pain at 24 h and the time to onset of pain relief. In acute pharyngitis potentially caused by group A beta-haemolytic Streptococcus, corticosteroids reduced the time to clinically meaningful pain relief, however provided only a small reduction in pain scores at 24 h (Wing 2010 **Level I**, 10 RCTs, n=1,096). Following drainage and antibiotics for peritonsillar abscess, a single dose of IV corticosteroid reduced pain, trismus and fever (Ozbek 2004 **Level II**, n=62, JS 2).

Antibiotics

Antibiotics for sore throat reduced pain, headache and fever by 50% on d 3; this effect was more pronounced if throat swabs were positive for Streptococcus (Spinks 2013 **Level I** [Cochrane], 27 RCTs, n=12,835). Antibiotics also shortened the duration of symptoms by 16 h, although the absolute benefits are modest.

Topical analgesics

Topical analgesics such as benzydamine spray (Thomas 2000 **Level I**, 17 RCTs, n=3,259) or benzydamine/chlorhexidine spray (Cingi 2010 **Level II**, n=164, JS 5), lozenges containing flurbiprofen (Watson 2000 **Level II**, n=301, JS 5), amylmetacresol/2,4-dichlorobenzyl alcohol with lignocaine or hexylresorcinol (McNally 2012 **Level II**, n=190, JS 5) and benzocaine (Chrubasik 2012 **Level II**, n=50, JS 3) provide analgesia superior to placebo in acute sore throat with minimal adverse effects. Ambroxol, a mucolytic substance with local anaesthetic properties, reduced pain of pharyngitis significantly (but with questionable clinical relevance) in comparison to placebo (mint lozenges) (Chenot 2014 **Level I**, 3 RCTs, n=1,772).

Nonpharmacological treatment

A single-point acupuncture treatment at large intestine meridian for pain of acute pharyngitis and tonsillitis was not more effective than sham laser acupuncture (Fleckenstein 2009 **Level II**, n=60, JS 5).

8.6.7.6 Acute pain associated with sinusitis and otitis media

Treatment is primarily symptomatic using analgesics and antipyretics; it may be appropriate to use nsNSAIDs, coxibs, paracetamol, weak opioids or tramadol, based on evidence for treatment of dental pain. Antihistamines and/or decongestants have no clinically relevant benefit in acute otitis media (Coleman 2008 **Level I** [Cochrane], 15 RCTs, n=2,695).

Antibiotics

Antibiotic treatment of acute otitis media leads to significant pain reduction at 2–7 d but with a NNT of 20 (Venekamp 2013 **Level I** [Cochrane], 12 RCTs, n=3,317). As the effects on pain are limited and adverse effects are common, for most children with mild disease antibiotic use might not be justified.

Steroids

Oral corticosteroids as a monotherapy are not effective and in combination with antibiotics may be modestly beneficial for symptoms of acute sinusitis (Venekamp 2014 **Level I** [Cochrane] 5 RCTs, n=1,193).

Topical treatment

For sinusitis, IN corticosteroids have consistently significant benefits for facial pain (Hayward 2012a **Level I**, 6 RCTs, n=2,495). For acute rhinosinusitis and uncomplicated presumed viral rhinosinusitis, nasal irrigation with physiological saline and decongestants provided symptomatic relief (Rabago 2002 **Level** II, n=76, JS 5). A phytotherapeutic nasal spray containing *Cyclamen europaeum* provided better facial pain relief than placebo in sinusitis (Pfaar 2012 **Level** II, n=99, JS 3).

The evidence for the effectiveness of eardrops in acute otitis media is insufficient (Foxlee 2006 **Level I** [Cochrane]**,** 4 RCTs, n=328). However, local anaesthetic eardrops reduced pain in otitis media in children (Bolt 2008 **Level II**, n=63 patients, JS 5).

Clinical practice guidelines for the diagnosis and treatment of sinusitis (Meltzer 2011 **GL**; Chandran 2013 **GL**) and otitis media are published (Rosenfeld 2014 **GL**).

8.6.7.7 Acute pain associated with oral ulceration, including mucositis

Acute oral ulceration due to trauma (physical, chemical, thermal), infection (eg herpes simplex), drugs, radiation or chemotherapy (mucositis) may be extremely painful and debilitating. Mucosal analgesia may be achieved by topical application of EMLA® cream and 5% lignocaine (Vickers 1992 **Level II**, n=60, JS 5), although a subsequent trial in children found no increased oral intake following viscous lignocaine solution applied topically (Hopper 2014 **Level II**, n=101, JS 5).

Mucositis is a common adverse effect of high-dose chemo- and radiotherapy for malignancies affecting the head and neck and for conditioning prior to bone marrow transplants. It may be complicated by opportunistic infections including herpes simplex and candidiasis. Quality of life and nutrition can be greatly impaired by the pain of cancer-related acute mucositis. In this indication, there was no significant difference in analgesia between PCA and continuous opioid infusion, except that PCA was associated with reduced opioid requirements and pain duration (Clarkson 2007 **Level I** [Cochrane] 26 RCTs, n=1,353). IV ketamine "burst therapy" may be effective in mucositis pain that is refractory to opioid analgesia (Jackson 2005 **NR**).

There is weak evidence that allopurinol mouthwash, granulocyte macrophage-colony stimulating factor (GM-CSF), immunoglobulin or human placental extract either improve or eradicate mucositis (Clarkson 2007 **Level I** [Cochrane] 26 RCTs, n=1,353). Ineffective treatments were benzydamine hydrochloride, sucralfate, tetrachlorodecaoxide, chlorhexidine, lignocaine solution, diphenhydramine hydrochloride and aluminium hydroxide suspensions (Clarkson 2007 **Level I** [Cochrane] 26 RCTs, n=1,353) and a supersaturated calcium phosphate mouth rinse (Lambrecht 2013 **Level II**, n=60, JS 5). Povidone-iodine mouthwash significantly reduced the severity of oral mucositis compared with sterile water, however chlorhexidine was ineffective (Potting 2006 **Level I**, 7 RCTs, n=863).

Polymyxin E, tobramycin and amphotericin B (PTA), GM-CSF, oral cooling and amifostine had a preventive effect by significantly reducing the incidence and severity of oral mucositis (Stokman 2006 **Level** I, 45 RCTs, n=4,145). Preventive strategies for mucositis such as palifermin (Bensinger 2008 **GL**) or oral cryotherapy (Tayyem 2014 **NR;** Batlle 2014 **Level III-2**) may be effective in specific circumstances.

Several topical measures have been postulated to treat the pain of oral mucositis. Two different formulation of 200 mcg dose transmucosal fentanyl citrate were equal in efficacy, tolerability and adverse-effect profile, but no better than placebo for analgesia in radiation-induced mucositis (Shaiova 2004 **Level II**, n=14, JS 5). Topical doxepin as an oral rinse provided better pain relief than placebo rinse (Epstein 2001 **Level IV**; Epstein 2006 **Level IV**; Epstein 2007 **Level IV;** Leenstra 2014 **Level II**, n=155, JS 5).

Topical morphine (Cerchietti 2002 **Level II**, n=26, JS 3; Cerchietti 2003 **Level III-1**; Vayne-Bossert 2010 **Level II**, n=11, JS 5), and ketamine (Slatkin 2003 **CR**) may also provide analgesia.

Oral low-level laser therapy reduced pain and mucositis progression in two small low-quality studies (Abramoff 2008 **Level II**, n=11, JS 2; Arora 2008 **Level II**, n=28, JS 2).

Evidence-based clinical practice guidelines for the prevention and treatment of mucositis in cancer patients have been published (Alvarino-Martin 2014 **GL**; Lalla 2014 **GL**) (for paediatrics see Section 9.8.3.1).

Key messages

Acute dental pain

1. NSAIDs and emergency pulpectomy reduce pain in patients with acute apical periodontitis (**N**) (**Level I**) with insufficient evidence to support analgesic benefit from adding antibiotics (**N**) (**Level I** [Cochrane]).

Dental extraction

2. Paracetamol, nonselective NSAIDs and coxibs provide safe and effective analgesia with minimal adverse effects following dental extraction (**S**) (**Level I** [Cochrane Review]).
3. Nonselective NSAIDs and coxibs provide similar analgesia, which is superior to paracetamol, codeine, combinations of paracetamol/codeine (**N**) (**Level I**) and pethidine/tramadol (**N**) (**Level II**) after dental extraction.
4. Combinations of paracetamol with ibuprofen (**N**) (**Level I** [Cochrane Review]) and other nonselective NSAIDs (**N**) (**Level I**) provide superior analgesia to either drug alone after dental extraction.
5. Tramadol provides equal analgesia to paracetamol/weak opioid and aspirin/weak opioid combinations (**N**) (**Level I** [Cochrane Review]) and tramadol/paracetamol combinations provide superior analgesia to tramadol alone after dental extraction (**N**) (**Level I**).
6. Perioperative corticosteroid administration reduces swelling, but not pain (**U**) (**Level I**), and reduces postoperative nausea (**U**) (**Level II**) following third molar extraction.

Tonsillectomy

7. Paracetamol and NSAIDs are effective analgesics after tonsillectomy (**N**) (**Level I**); paracetamol may be comparable to nsNSAIDs in this setting (**N**) (**Level II**)
8. Nonselective NSAIDs (**U**) (**Level I**), in particular aspirin and ketorolac (**U**) (**Level II**), increase the risk of reoperation for bleeding after tonsillectomy in adults, but not in children (**U**) (**Level I** [Cochrane Review]).
9. Intraoperative dexamethasone administration reduces postoperative pain, nausea and vomiting and time to resumption of oral intake post-tonsillectomy (**S**) (**Level I** [Cochrane Review]), with no increase in adverse effects (**R**) (**Level I** [Cochrane Review]).
10. Peritonsillar infiltration or topical application of local anaesthetics produces a modest reduction in acute post-tonsillectomy pain with topical application and infiltration being equally effective (**U**) (**Level I**).
11. Perioperative antibiotics show no benefit in post-tonsillectomy pain, but increase adverse effects (**N**) (**Level I**).
12. Preoperative gabapentinoids improve analgesia after tonsillectomy (**N**) (**Level II**).
13. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements but was no more effective than equivalent doses administered parenterally (**U**) (**Level II**).

Pharyngitis

14. Corticosteroids (**S**) (**Level I** [Cochrane Review]) and antibiotics (**N**) (**Level I** [Cochrane Review]) improve analgesia and reduce duration of pain in pharyngitis.
15. Paracetamol, NSAIDs (nonselective NSAIDs or coxibs) and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**U**) (**Level I**).

16. Benzydamine spray (**N**) (**Level I)** and other topical analgesics (**N**) (**Level II**) provide analgesia superior to placebo in acute sore throat with minimal adverse effects.
17. Corticosteroids reduce acute pain associated with peritonsillar abscess (following drainage and antibiotics) (**U**) (**Level II**).

Sinusitis

18. Oral corticosteroids have no analgesic effect in sinusitis (**N**) (**Level I** [Cochrane Review]), but intranasal corticosteroids reduce facial pain (**N**) (**Level I**).

Oral mucositis

19. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis; PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
20. Topical treatments (**U**) (**Level I**), including povidone-iodine (**U**) (**Level I**), doxepin mouthwash (**N**) (**Level II**) and morphine (**N**) (**Level II**), provide analgesia in mucositis.
21. There is limited evidence that oral laser light therapy reduces mucositis pain and progression (**U**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**N**).

☑ Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches (**U**).

☑ Neuropathic orofacial pain, which is often post-traumatic (iatrogenic), may be exacerbated by repeated dental procedures, incorrect drug therapy or psychosocial factors (**S**).

8.6.8 Acute pain in patients with HIV infection

Pain is common in people infected with HIV (Breitbart 1996 **NR;** Larue 1997 **Level IV**; Vogl 1999 **Level IV**; Frich 2000 **Level IV**; Simmonds 2005 **Level IV**; Namisango 2012 **Level IV**; Ebirim 2013 **Level IV**) and may have diverse aetiologies, including HIV itself (which is a neurotropic virus), opportunistic infections and malignancies, and unrelated comorbidities (O'Neill 1993 **NR;** Hewitt 1997 **Level IV**; Glare 2001 **NR**). In untreated HIV infection, pain becomes more common as disease progresses and is almost universal among those with advanced acquired immunodeficiency syndrome (AIDS) (O'Neill 1993 **NR;** Kimball 1996 **Level IV**). Even among relatively well individuals, pain is prevalent and associated with depression and impaired function (Singer 1993 **Level IV**; Vogl 1999 **Level IV**).

Adults diagnosed with HIV today can have a near normal life expectancy with access to antiretroviral therapy, both in well-resourced and resource-limited settings (Mills 2011 **Level IV**; van Sighem 2010 **Level IV**). This improvement in HIV prognosis, however, has been associated with an ageing HIV-infected population with increasing numbers of comorbidities and an ongoing high prevalence of pain (Balderson 2013 **Level IV**). Pain continues to be associated with poorer quality of life and impaired function among people living with HIV (Simmonds 2005 **Level IV**; Namisango 2012 **Level IV**; Ebirim 2013 **Level IV**; Merlin 2013 **Level IV**). Several studies have found that pain is undertreated in those with HIV infection, with both physician and patient barriers suggested (Breitbart 1996 **NR;** Larue 1997 **Level IV**; Breitbart 1998 **Level IV**; Breitbart 1999 **NR;** Frich 2000 **Level IV**; Ebirim 2013 **Level IV**). An unmet need for analgesia is one of the commonest reasons people with HIV use complementary therapies (Tsao 2005 **Level IV**; Peltzer 2008 **Level IV**). HIV/AIDS patients with diagnosed mood/anxiety or substance-use disorders report much higher levels of pain than HIV/AIDS patients without these comorbidities or the general population (Tsao 2009 **Level III-2**).

8.6.8.1 Treatment of pain in people infected with HIV

The optimal management of pain in an individual with HIV will depend on the cause of the pain. The general principles of treating the underlying cause where possible and providing adequate analgesia are the same as for any other individual with the same injury or illness. Some special considerations (particularly drug interactions) may be important and are set out below.

Opioids have utility for managing severe pain due to a variety of conditions in those with AIDS, with limited or manageable adverse effects (Kaplan 1996 **Level IV**; Kaplan 2000 **Level IV**). TD fentanyl provided better pain relief and improved daily functioning in patients with severe AIDS-related pain previously taking oral morphine or equivalent (Newshan 2001 **Level IV**). Around 15–20% of patients require parenteral opioid therapy in the terminal phase of HIV disease (Dixon 1991 **Level III-3**; Kimball 1996 **Level IV**; Frich 2000 **Level IV**).

HIV and its treatment are frequently complicated by a distal, small-fibre, sensory neuropathy that is typically painful (painful HIV-associated sensory neuropathy) (Cherry 2012 **NR**). Prevalence rates >50% are described in cohorts exposed to stavudine (a potentially neurotoxic antiretroviral agent) (Wadley 2011 **Level IV**). Although stavudine use is being phased out, many patients living with HIV have previously been exposed to this drug. Further, a large, USA-based prospective survey found that 15% of adults with HIV who had never used stavudine are affected by painful sensory neuropathy, with older patients at higher risk (Ellis 2010 **Level IV**).

Neuropathic pain is particularly difficult to treat in HIV. Despite anecdotal reports of individual patients responding well to each of the pain-modifying agents typically used in other small-fibre neuropathies, only smoking of cannabis, topical capsaicin and recombinant human nerve growth factor have been shown to be more effective than placebo for HIV neuropathy pain (Phillips 2010 **Level I** [PRISMA], 14 RCTs, n=1,764). With regard to smoked cannabis, the authors caution that there is a risk of bias due to difficulties in blinding patient exposure; in one trial 92% guessed treatment allocation correctly. This meta-analysis shows no benefit of lamotrigine in this setting.

Note: reversal of conclusions
This reverses the Level II conclusion in the previous edition of this document; a single RCT had previously shown benefit of lamotrigine in treatment of HIV-related neuropathic pain.

A meta-analysis of data on high-dose capsaicin found limited efficacy with NNT of 11 (Derry 2013c) **Level I** [Cochrane], 2 RCTs, n=801). In a pilot study of hypnosis for managing HIV-neuropathy pain 26 of 36 patients were responders with a mean 44% reduction in pain scores 7 wk after the intervention (Dorfman 2013 **Level IV**). These data together with the large placebo responses in several HIV-neuropathy analgesia trials suggest that nonpharmacological interventions may be useful in this difficult pain syndrome and warrant further study.

The chronic nature of HIV disease as well as the many possible causes of pain in those infected mandate a holistic approach to managing HIV-associated pain. Ideally, disease-specific therapy, psychosocial interventions and physical modalities should accompany standard analgesic treatment (Glare 2001 **NR**)

8.6.8.2 Special considerations in treating pain in patients with HIV infection

Drug interactions

Antiretroviral agents (notably non-nucleoside reverse transcriptase inhibitors and protease inhibitors) may cause important drug interactions by inducing and inhibiting various enzymes in the cytochrome P450 family. Several antiretroviral agents are also hepatically metabolised with potential for drug interactions. Predicting clinically relevant interactions is made extremely complex, both by the fact that antiretroviral drugs are used in combinations and because most interactions have not been formally studied. Updated tables of likely interactions between individual antiretroviral agents and medications used to treat common comorbidities (including an analgesic chart) are provided by The University of Liverpool HIV Pharmacology Group at: http://www.hiv-druginteractions.org/PrintableCharts.aspx.

Ritonavir (an HIV protease inhibitor) is a potent inhibitor of cytochrome P450 3A4. This results in clinically relevant inhibition of fentanyl metabolism (Olkkola 1999 **Level II**, n=12, JS 3), increased concentrations of the toxic metabolite norpethidine (normeperidine) if used with pethidine (potentially important in high doses or longer-term use) (Piscitelli 2000 **Level III-2**), but no clinically meaningful interaction with methadone or buprenorphine (McCance-Katz 2003 **Level III-2**)**.** Conversely, both nevirapine (a non-nucleoside reverse transcriptase inhibitor) (Arroyo 2007 **Level III-3**) and lopinavir (a protease inhibitor) (McCance-Katz 2003 **Level III-2**) significantly induce methadone metabolism and may lead to withdrawal in patients on maintenance doses.

Some medications used to treat opportunistic infections in HIV patients may also interact with analgesics. For example, both rifampicin and rifabutin may increase opioid metabolism (particularly methadone) (Finch 2002 **NR**) and fluconazole may potentiate adverse effects of methadone (Tarumi 2002 **CR**).

Patients with a history of substance abuse

Pain may be more common in those with HIV with a history of injecting drugs (Martin 1999 **Level IV**; Vogl 1999 **Level IV**) and is more likely to be inadequately treated in this group (Breitbart 1997 **Level IV**; Breitbart 1996 **Level IV)**. Two cohort studies showed that that even though HIV-positive patients with a history of problematic drug use report higher ongoing use of prescription analgesics specifically for pain, these patients continue to experience persistently higher levels of pain, relative to nonproblematic users (Passik 2006 **Level III-2**; Tsao 2007 **Level III-2**). Importantly, opioid analgesia was similarly effective for treating severe pain in those with AIDS who had previously injected drugs as in those who were opioid naïve, although higher doses were required (Kaplan 2000 **Level IV**). Similarly, patients in a methadone-maintenance program, who also suffered from HIV/AIDS-related pain, gained improved analgesia without adverse effects with use of additional methadone (Blinderman 2009 **Level IV**).

The principles of pain management in patients with a history of substance abuse are outlined in Sections 10.6 and 10.7.

Key messages

1. High-concentration capsaicin patches have limited efficacy in treating neuropathic pain in patients with HIV/AIDS **(S)** (**Level I** [Cochrane]).
2. Smoking cannabis is effective in treating neuropathic pain in patients with HIV/AIDS, although potential study bias and legal constraints mean that this is not recommended as routine treatment **(S)** (**Level I** [PRISMA])**.**
3. Lamotrigine is not effective in treating neuropathic pain in patients with HIV/AIDS (**R**) (**Level I** [PRISMA]).
4. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use but also more intense pain (**U**) (**Level III-2**).
5. Pain, and notably neuropathic pain, is common in patients with HIV (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ HIV/AIDS has become a chronic, manageable condition; in view of limited specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of acute, cancer and chronic pain in the general population (**N**).
- ☑ Interactions between antiretroviral and antibiotic medications and analgesics should be considered in this population (**U**).

8.7 Acute cancer pain

8.7.1 Assessment of acute cancer pain

Acute pain in the cancer patient may signify an acute oncological event including pathological fracture or microfracture, spinal cord or nerve compression, visceral obstruction or cutaneous ulceration due to tumour. Cancer pain may become acute in the presence of infection, and during diagnostic or therapeutic interventions. Anticancer therapies, including surgery, chemotherapy, hormonal therapy and radiotherapy, may be associated with both acute and chronic pain of a nociceptive or neuropathic nature. In progressive cancer, there is increasing potential for acute clinical change.

Acute pain requires urgent assessment to exclude cancer recurrence or an oncological emergency requiring rapid treatment in addition to acute pain management (NCCN 2014 **GL**). Where malignancy is advanced, there is urgency in differentiating an acute pain crisis, which is readily reversible, from an intractable painful condition (Moryl 2008 **NR**). Standardised assessment tools for the comprehensive assessment of cancer pain are advantageous, and required for quality research trials (Caraceni 2002 **GL**). There is no consensus on the ideal multidimensional pain-assessment tool for cancer pain, with electronic tools and a standard prognostic classification system for cancer pain under development (Burton 2014 **NR**). Palliative-care physicians identified the most important dimension to assess was pain intensity with unidimensional tools (eg NRS, VRS) followed by documentation of temporal pattern, treatments, exacerbating or relieving factors, location, pain interference, pain quality, pain affect, duration, pain beliefs and previous pain history (Holen 2006 **NR**). The revised Edmonton Staging System, the MPQ and the Brief Pain Inventory are well validated in many settings (Fainsinger 2005 **Level IV**; Bennett 2009 **Level IV**; Wu 2010 **Level IV**; Ngamkham 2012 **NR**; Nekolaichuk 2013 **Level IV**; Gauthier 2014 **Level IV**).

8.7.2 Principles of management of acute cancer pain

Comprehensive consensus best-practice guidelines relating to cancer pain management have been developed by several agencies worldwide with online access (SIGN 2008 **GL**; Green 2010 **GL**; Ripamonti 2011 **GL**; NCCN 2014 **GL**). The WHO Analgesic Ladder (WHO 1996 **GL**) underpins these guidelines but was determined to provide inadequate pain relief in 12% of patients (Zech 1995 **Level IV**, n=2,118). Hence the WHO ladder has undergone considerable scrutiny over the last decade with more flexibility proposed in some cancer-pain settings (Forbes 2011 **NR**). Where pain is moderate to severe, a jump from Step I (simple analgesics) direct to Step III (strong opioids) reduces the time to pain control relative to staged progression through Step II (weak opioids) (Maltoni 2005 **Level II**, n=54 [prematurely terminated], JS 2). Simple analgesics, adjuvants and specific targeted therapies, such as anticonvulsant medicines for neuropathic pain and radiotherapy and bone-modifying agents for metastatic bone pain, should be considered at every step of the ladder. Despite availability of numerous consensus guidelines, a survey of Australian palliative care physicians identified barriers to best practice, notably access to nonpharmacological interventions, patient-educational resources, and optimal care coordination (Lovell 2013 **Level IV**). Patient education about cancer pain is a key factor in optimising pain management (Marie 2013 **Level I**, 15 RCTs, n unspecified; Lovell 2014 **NR**; Martinez 2014 **Level III-2 SR** 16 RCTs and 3 studies, n unspecified; Lee 2014 **Level III-3 SR**, 17 RCTs and 7 studies, n unspecified). Despite this, a patient-centred approach is often overlooked in guidelines (Luckett 2013 **Level IV SR**, 70 studies, n unspecified).

There is similar urgency in managing an acute pain crisis in the patient with cancer as there is when managing any other medical crisis. Acute pain, particularly in patients with terminal cancer, causes immense distress in the patient, the family and the care team (Moryl 2008 **NR**). In such a crisis, consider hospital admission to evaluate the patient, assess and manage the aetiology of pain and achieve patient-specific pain goals (NCCN 2014 **GL**). Treatment of the underlying cause of pain may be urgent.

8.7.3 Medicines for acute cancer pain

8.7.3.1 Opioids

Rapid analgesic control of acute pain or persisting pain exacerbations may be achieved with a regular dose schedule of a parenteral opioid with frequent reassessment and dose adjustment, or by use of IV PCA technique. A single randomised, but small and unblinded trial, demonstrated more rapid pain control with IV than oral morphine for severe cancer pain (Harris 2003 **Level II**, n=62, JS 2). IV and SC bolus dosing and infusions have similar tolerability and efficacy but IV route provides faster relief (Anderson 2004 **NR**; Elsner 2005 **Level II**, n=39, JS 2; Radbruch 2011 **Level III-2 SR**, 18 studies, n=674). Consensus clinical practical guidelines and systematic reviews are available to guide the administration of short-acting opioids including IV, SC and rectal morphine in exacerbations of pain (Klepstad 2011 **GL**; Caraceni 2012 **GL**; NCCN 2014 **GL**). As opioid-naïve patients are more vulnerable to opioid adverse effects, pre-emptive plans for aggressive management of adverse effects need to be clearly documented, including for prophylaxis against constipation from the onset of opioid therapy. Once acute pain control is achieved, maintain analgesia with ER opioids. There is a lack of good evidence in the patient with cancer pain for differences in efficacy or safety with various ER opioids (Mesgarpour 2014 **Level III-2 SR**, 5 RCTs and 4 studies, n unspecified). Morphine's efficacy and toxicity are related to morphine and morphine-metabolite concentrations. Higher morphine and metabolite concentrations are associated with severe central adverse effects, including drowsiness, confusion or hallucinations, particularly with higher metabolite:morphine ratios in plasma. Myoclonus occurs unpredictably at morphine doses >400 mg/d, with higher morphine and metabolite concentrations in adults with moderate to severe cancer pain (Gretton 2013 **Level III-2**).

Wide interindividual variability in opioid response mandates close monitoring and review of the opioid care plan. Clinical trials have indicated no significant difference in analgesia or tolerability between oxycodone and morphine or hydromorphone when used for moderate to severe cancer pain. Methadone also has similar efficacy but requires considerable care in dose estimation, titration and monitoring, due to complex pharmacokinetics/pharmacodynamics and marked variability in response (Good 2014 **Level I**, 4 RCTs, n=272).

The TD route of administration is inappropriate for unstable acute pain due to its slow titratability. Studies of TD fentanyl for chemoradiation-induced mucositis indicated only gradual reduction in pain intensity over several days (Guo 2015 **Level III-3**; Xing 2014 **Level III-3**). In cancer patients, TD fentanyl significantly reduces risk of constipation compared to oral morphine (RR 0.61; 95%CI 0.47 to 0.78) (Hadley 2013 **Level I** [Cochrane], 9 RCTs, n=1,382). There is insufficient evidence to determine the roles of SC, SL or TD buprenorphine in cancer pain (Naing 2014 **Level I** [PRISMA], 16 RCTs, n=1,329). There are limited data to support a role for tapentadol in cancer pain, with insufficient numbers to pool RCTs; efficacy and safety were comparable to morphine and oxycodone (Wiffen 2015 **Level I** [Cochrane] 4 RCTs, n=1,029). A small study (n=25) identified an analgesic benefit of tapentadol ER for moderate to severe bone pain in opioid-naïve myeloma patients (Coluzzi 2015 **Level III-3**). A small prospective, observational cohort study (n=30) demonstrated that opioid-tolerant cancer patients taking the equivalent of at least 60 mg oral morphine daily could be rotated to tapentadol (oral conversion ratio morphine:tapentadol=1:3.3) with significant improvement in pain intensity within the first week and few withdrawals due to uncontrolled pain (5/30), adverse effects (2/30) or other reasons (3/30) (Mercadante 2014 **Level III-3**) (see also Section 4.1).

Combination opioid therapy for poorly controlled cancer pain has little evidence to support the practice despite encouraging preclinical scientific studies, and well-designed studies are needed (Fallon 2011 **Level III-2 SR**, 2 studies, n=36).

Opioid switching, due to preference, uncontrolled pain or intolerable adverse effects, may improve opioid response and reduce adverse effects (Mercadante 2011 **Level III-2 SR**, 31 studies, n unspecified). Opioid conversion should be carefully individualised, as conversion ratios may be influenced by multiple factors including relative potency, prior doses, tolerance and reason

for switch. Conversion ratios are less predictable at higher opioid doses. Conversion tools of which there are many should be used with caution.

There is no evidence that opioids used for pain control in terminal cancer have any adverse impact on patient survival (Lopez-Saca 2013 **Level III-3 SR**, 10 studies, n unspecified). Optimising patient comfort, function and safety should be the goal of care. All management options should be fully discussed with the treating and palliative care teams, to meet the physical, psychosocial and existential needs of the patient and family, with consideration of an end-of-life care pathway when cancer is advanced. Opioids have immunoregulatory actions that vary with mode and timing of administration. Concern regarding the potential impact of opioids on immune tumour surveillance is increasing. Overall, there is currently inadequate evidence to guide opioid selection in cancer patients, based on immune function, as no studies have measured any clinical endpoints or outcomes, including cancer progression or disease-free survival (Boland 2014 **Level III-3 SR**, 5 studies, n unspecified).

8.7.3.2 Paracetamol and NSAIDs

Any addition of NSAIDs or paracetamol to strong opioids should be justified on the basis of individual improved analgesia or reduction of opioid-related adverse effects, recognising the NSAID-associated risks of gastrointestinal bleeding and relative contraindications in patients with renal, hepatic and cardiac failure. An evaluation of the role of NSAIDs and paracetamol in cancer pain management concluded that these simple analgesics are more effective than placebo for cancer pain, with no clear evidence to support the superiority of any one NSAID (McNicol 2005 **Level III-2 SR** [Cochrane], 42 studies, n=3,084). A systematic review of simple analgesics combined with strong opioids weakly supported the combined use of NSAIDs and opioids to improve pain control or reduce opioid doses but found insufficient evidence to support the addition of paracetamol to Step III opioids (Nabal 2012 **Level III-2 SR**, 12 studies, n unspecified).

8.7.3.3 Ketamine

Despite extensive evidence to support the use of ketamine for acute perioperative pain and analgesic sedation, very limited evidence guides its use for cancer-related pain (Bell 2012 [Cochrane] 2 RCTs, n=30; Bredlau 2013 **Level IV SR**, 5 RCTs and 6 studies, n=483). The largest multicentre RCT included in the latter systematic review concluded that ketamine had no therapeutic benefit with an adverse safety profile in cancer patients (Hardy 2012 **Level II**, n=187, JS 5). Despite relating to chronic moderate to severe pain in a palliative setting and a broad patient population, this trial has negatively influenced the use of ketamine for all cancer-related pain, including acute exacerbations, with resultant debate and calls for further controlled studies targeting more specific cancer pain populations (MacKintosh 2012 **Level IV**; Jackson 2013 **NR**; Leppert 2013 **NR**; Hardy 2014 **Level IV**). Certain types of cancer pain, including mucositis, bone and neuropathic pain, may be "good responders" to ketamine and merit more focussed, higher quality controlled studies (Jackson 2005 **NR**).

Larger case series and individual reports have highlighted the wide range of clinical situations, routes of administration and dose schedules for ketamine in the cancer setting. Ketamine has been used successfully for morphine-resistant pain (Mercadante 2000 **Level II**, n=10 [cross over], JS 3), acute incident pain (Mercadante 2009 **Level IV**) and for cancer patients in the perioperative period, where ketamine can be morphine-sparing, lower pain scores and promote earlier return of function (Kollender 2008 **Level II**, n=60, JS 5; Nesher 2009 **Level II**, n=44, JS 3). Oral and topical use of ketamine resulting in effective analgesia has been described in case series (Soto 2012 **Level IV**; Amin 2014 **Level IV**; Okamoto 2013 **Level IV**; Uzaraga 2012 **Level IV**). Analgesia was successfully maintained when continuous ketamine infusion was converted to oral ketamine (Benitez-Rosario 2011 **Level III-2**). Topical ketamine-amitriptyline did not reduce chemotherapy-induced peripheral neuropathic pain (Gewandter 2014 **Level II**, n=462, JS 5).

8.7.3.4 Glucocorticoids

Common indications for glucocorticoids in cancer include spinal cord compression, superior vena cava compression, raised intracranial pressure, bowel obstruction, anorexia and pain

related to inflammation, bone tumour or neuropathy. Despite good evidence for many of these clinical scenarios, only weak evidence supports glucocorticoids for cancer pain (Leppert 2012 **NR**; Paulsen 2013 **Level I** [PRISMA], 4 RCTs, n=667). Methylprednisolone provided no significant analgesic benefit but improved fatigue, appetite and patient satisfaction (Paulsen 2014 **Level II**, n=50, JS 5). A meta-analysis of studies comparing corticosteroids, notably dexamethasone, to standard therapy did suggest a statistically significant, but clinically limited, reduction in cancer pain at 1 wk (MD -0.84/10; 95%CI -1.38 to -0.30); however, data were flawed by attrition, potential bias, small sample size and infrequent indication of adverse effect rates (Haywood 2015 **Level III-2 SR** [Cochrane], 15 studies, n=1,926). Consequently, no recommendation could be made regarding selection of glucocorticoid, dose, route or duration of administration, and adverse-effect profile. Dexamethasone is often preferred due to high potency, long duration of action and minimal mineralocorticoid effect. Immediate adverse effects include immunosuppression, hyperglycaemia and psychiatric disorders, whereas longer-term use increases risk of proximal myopathy, peptic ulceration, osteoporosis and Cushing's syndrome (Leppert 2012 **NR**). Steroid/nsNSAID combination therapy in a large population of general hospitalised patients resulted in a 15-fold increase in gastrointestinal bleed, reinforcing the need for gastroprotective therapy (Piper 1991 **Level III-2**, n=7,478). If glucocorticoids are used in the acute setting for >3 wk, a schedule of dose reduction must precede cessation.

8.7.4 Breakthrough pain

The term "breakthrough pain" typically refers to a transitory acute flare-up of pain in the setting of chronic cancer pain managed with a fixed opioid drug schedule. Despite stable therapy, breakthrough pain is common, heterogeneous, frequently severe or excruciating, often paroxysmal, and may occur several times daily for seconds to hours in duration (Portenoy 1990 **Level IV**; Deandrea 2014 **Level IV SR**, 33 studies, n unspecified). Some episodes of breakthrough pain may be an end-of-dose failure of maintenance opioids. In contrast, incident pain is predictably precipitated by some movement or action. Assessment should elucidate the severity, duration, pattern and cause of breakthrough pain.

Conventional management guidelines dictated that the opioid breakthrough dose should be a proportion (one-sixth to one-tenth) of the daily dose; for example, an oral breakthrough dose of morphine would be equivalent to a 4-hourly dose, or one-sixth the oral morphine equivalent daily dose. However, there is little evidence to support the standard practice of utilising the same opioid for breakthrough pain as for maintenance analgesia, and most recent studies indicate a poor relationship between rescue and maintenance doses (Zeppetella 2011 **Level I**, 8 RCTs, n unspecified). "Rescue medication" used for breakthrough pain should ideally have a pharmacokinetic profile that mirrors the time-course of that pain and ideally have high potency, rapid onset and fast offset. Meta-analyses of emerging evidence support the rapid efficacy and safety of several transmucosal formulations of fentanyl for breakthrough pain (Vissers 2010 **Level I**, 6 RCTs, n=594; Hansen 2012 **Level I** [PRISMA], 3 RCTs, n=301; Zeppetella 2013 **Level I** [Cochrane] 15 RCTs, n=1,699; Jandhyala 2013 **Level I**, 5 RCTs, n=415) (see also Section 5.5.3.1). These transmucosal fentanyl products are superior to placebo at 15 min and require individual titration to effect. The titrated rescue dose is largely independent of background opioid dosing (Portenoy 1999 **Level IV**). The slower onset of oral morphine (45 min) limits its suitability to more gradual-onset pain or for pre-emptive anticipation of incident pain (Zeppetella 2014 **Level I**, 4 RCTs [network meta-analysis], n unspecified). Notably, not all breakthrough pain may be opioid responsive. A large observational study identified 23% of patients who found nothing to relieve their breakthrough pain (Davies 2013 **Level IV**, n=1,000), indicating further investigations are required in this area.

8.7.5 Acute neuropathic cancer pain

8.7.5.1 Incidence and diagnosis of neuropathic cancer pain

Neuropathic pain or mixed nociceptive-neuropathic pain has an estimated frequency of 40% in patients with cancer (Bennett 2012 **Level IV SR**, 22 studies, n=13,683). Diagnosis was largely based on clinical judgement rather than objective criteria, and most studies

predated the updated IASP definition of neuropathic pain as pain due to a disease or lesion in the somatosensory system. Peripheral or central neuropathic pain may result from disease progression, cancer treatment, a comorbid condition or be multifactorial. No clear standardised approach or taxonomy has been used to assess neuropathic pain in cancer or to guide treatment. Improvements in the classification, assessment and diagnosis of neuropathic cancer-pain conditions are required to address gaps in understanding of this diverse condition (Lema 2010 **NR**). The neuropathic grading scale of the Neuropathic Pain Special Interest Group of the IASP is recommended for use in cancer patients to facilitate recognition, management and study of neuropathic cancer pain (Mulvey 2014 **GL**).

8.7.5.2 Treatment of neuropathic cancer pain

Adjuvant medications may be needed for acute or persistent neuropathic cancer pain that is poorly responsive to opioids, or where opioid intolerance limits further dose escalation. Acute neuropathic cancer pain may also be associated with inflammation and require specific targeted therapy. A systematic review of European clinical practice guidelines for management of cancer-associated neuropathic pain highlighted a lack of evidence. Extrapolation of data from individuals without cancer to a population with neuropathic cancer pain may not provide optimal care. Only 11% of references supporting European clinical practice guidelines came from patients with cancer (Piano 2014 **NR**). All of the guidelines included recommendations for TCAs as first-line treatment, despite the lack of high-level evidence. Imipramine (to 75 mg; 1 RCT) and amitriptyline (to 50 mg; 1 RCT) in small RCTs in patients with advanced cancer or chemotherapy-induced painful neuropathy has resulted in only a small analgesic benefit, with increased adverse effects including sedation, confusion and dry mouth (Bennett 2011b **Level I**, 2 RCTs [TCAs], n=85). A further review including two additional amitriptyline RCTs (to 100 mg), one venlafaxine and one trazodone RCT has calculated weighted mean absolute relative benefit for antidepressants overall as 0.55 (95%CI 0.40 to 0.69) (Jongen 2013 **Level III-2 SR**, 6 RCTs [antidepressants], n=189 [analysed]). Gabapentin, pregabalin and alpha-2 adrenergic agonists were also recommended as first line agents with relatively low-level supportive evidence (see below). Future clinical practice guidelines need to provide an improved evidence base and information relating to adverse effects and altered kinetics.

Antiepileptic medications added to opioids for control of neuropathic pain caused by cancer have also only a small effect (Bennett 2011b **Level III-2 SR**, 3 RCTs and 3 studies [anticonvulsants], n=380). Anticonvulsants (gabapentin 2 RCTs and 2 studies; sodium valproate 1 study; phenytoin 1 RCT) provided limited improved analgesia within 4–8 d, after which benefits did not further increase. The addition of an adjuvant to a stable opioid dose resulted in only modest pain reduction at the expense of increased adverse effects, whereas when opioid dose was lowered after the introduction of the adjuvant, pain intensity was maintained or reduced, and adverse effects decreased. A further review overlapping by two RCTs and three studies calculated a mean absolute relative benefit of 0.57 (0.43 to 0.70) for anticonvulsants (Jongen 2013 **Level III-2 SR**, 14 RCTs and 16 studies, n=2,267); gabapentin is the most studied. A systematic review of pregabalin for neuropathic pain in cancer was unable to make any clear recommendations due to limitations in the study methodology and data (Bennett 2013 **Level IV SR**, 1 RCT and 3 studies and 1 CR, n= 761). A single RCT (included in both reviews) compared the efficacy of amitriptyline, pregabalin and gabapentin for severe neuropathic cancer pain and reported efficacy of all treatments but superiority of pregabalin.

Beneficial effects of antidepressants and anticonvulsants were found overall to outweigh harms in neuropathic cancer pain (Jongen 2013 **Level III-2 SR**, 14 RCTs and 16 studies, n=2,267). Benefits did not differ for neuropathic and mixed nociceptive-neuropathic pain states. Lack of data precluded conclusions regarding opioids alone. A firm diagnosis of neuropathic cancer pain should be made prior to use of these adjuvants.

8.7.5.3 Painful chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is resistant to treatment and remains poorly understood. Acute severe CIPN may adversely limit cancer treatment and hence survival, while chronic CIPN is a major cause of pain and poor QoL in survivors.

Chemotherapies causing painful CIPN include vinca alkaloids (vincristine), platins (cisplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), the proteasome inhibitor bortezomib and immunomodulatory agent thalidomide. Each class of agent has a distinct neuropathology, site of toxicity in the peripheral nerves and risk profile (Park 2013b **NR**). CIPN is dependent on dose and duration of treatment. CIPN is a predominantly sensory neuropathy, with many agents also causing myalgia and myopathy (taxanes), muscle cramps (oxaliplatin, vincristine, thalidomide) and autonomic neuropathy (vincristine, bortezomib) at higher doses. Paclitaxel and oxaliplatin have distinct acute and chronic CIPN syndromes. Significant acute neurotoxicity complicates oxaliplatin infusion in 90% of patients for up to 1 wk and is exacerbated by exposure to cold. Paclitaxel-induced acute pain syndrome with painful paraesthesias and numbness, poor motor skills, myalgias and arthralgias may persist up for up to 4 d. Bortezomib-induced CIPN is a common small-fibre neuropathy characterised by severe, sharp, burning pain in the feet that resolves by 3 mth in most affected patients. The severity of acute neuropathy and pain (paclitaxel, oxaliplatin) and the use of combination chemotherapies promoting neurotoxicity may be predictors of chronic CIPN.

There is a lack of evidence to support any agent for prevention of CIPN. Current protective strategies include dose modification or cessation of the causative chemotherapy. Risk stratification should include identification of individuals with pre-existing conditions predisposing to peripheral neuropathy. Trials of antioxidants including glutathione, glutamine and N-acetylcysteine have provided contradictory outcomes (Hershman 2014 **GL**).

There is limited specific evidence to guide treatment of established CIPN. Duloxetine (30 mg titrated to 60 mg/d over 5 wk) resulted in a modest reduction in pain severity relative to placebo (MD -1.06/10; 95%CI 0.72 to 1.40); additional benefits included improved QoL and reduced numbness and tingling of the feet (Smith 2013 **Level II**, n=231, JS 5). The analgesic benefit of duloxetine was greater in patients with oxaliplatin-induced CIPN.

Venlafaxine may be effective in acute oxaliplatin-induced CIPN but additional supportive evidence is recommended prior to any routine use in clinical practice (Hershman 2014 **GL**). Trials of amitriptyline (to 50 mg/d) and nortriptyline (to 100 mg/d), and gabapentin (2,700 mg/d) were inconclusive, while lamotrigine (300 mg/d) provided no benefit for CIPN.

8.7.6 Procedural pain in cancer patients

Both adults and children with cancer may undergo multiple painful diagnostic and therapeutic procedures. Few trials have evaluated procedural pain in adults with cancer. Attention to adequate analgesia and anxiolysis is imperative to reduce anticipatory stress with repeat interventions. Simple techniques include premedication, administration of prophylactic breakthrough analgesia, application of topical local anaesthetic, inhalational analgesia including methoxyflurane via the Penthrox Inhaler and N_2O-oxygen as Entonox (see Section 4.5), and sedation (midazolam, ketamine, propofol) by appropriately trained personnel (see respective sections of Chapter 4).

Few interventions decrease acute pain during mammography, including provision of prior information about the procedure, some degree of self-control over the extent of breast compression and the use of breast cushions; in contrast, pre-emptive paracetamol was of no benefit (Miller 2008 **Level I**, 7 RCTs, n=1,671).

For procedural pain in children with cancer see Sections 9.7.2 and 9.8.2.

8.7.7 Acute pain due to bone cancer

Refractory severe pain with acute incident pain is commonly caused by primary and metastatic bone cancers, notably prostate, breast, lung, bladder, renal and thyroid cancers, and multiple myeloma. Bone pain may also be precipitated during some cancer treatments eg granulocyte-colony stimulating factor (G-CSF) for febrile neutropenia prophylaxis. Malignant bone pain often has mixed nociceptive, inflammatory and neuropathic components. Preclinical studies have highlighted the pathophysiology of malignant bone pain (Currie 2013 **BS**; Mantyh 2014b **BS**; Mantyh 2014a **BS**; Falk 2014 **BS**).

8.7.7.1 Diagnosis of bone cancer pain

In the setting of known or potential bone primary or metastatic cancer, any new onset constant aching, gnawing pain over bone, or acute incident pain precipitated by movement or weight-bearing, requires prompt evaluation to pre-empt or exclude critical bone-related events, with assessment for pathological fracture, neurological deficit or hypercalcaemia. Many studies and reviews have informed guidelines to predict, expedite diagnosis and appropriately treat bone metastases. A systematic approach to assessment of spinal metastases is imperative. For detection of bone metastases, MRI and fludeoxyglucose F 18 PET offer advantages of sensitivity and/or specificity over bone scintigraphy and computer tomography (CT), although tumour type may influence diagnostic performance (Yang 2011 **SR** of diagnostic studies; Liu 2011 **SR** of diagnostic studies; Cheng 2011 **SR** of diagnostic studies). In assessment of new, acute back pain, "red flags" to predict potential cancer have been proposed, yet the only evidence-based predictor of spinal malignancy is "previous history of cancer" (Henschke 2013 **SR** of diagnostic studies; Downie 2013 **SR** of diagnostic studies). "History of cancer" increased the probability of malignancy to between 7% (95%CI 3 to 16) and 33% (95%CI 22 to 46); "older age", "unexplained weight loss", and "failure to improve after 1 mth" increased probability by <3% (Downie 2013 **SR** of diagnostic studies). Diagnostic imaging pathways that advocate larger lists of red flags and promote imaging for a single red flag may lead to "substantial and arguably unwarranted" referrals for imaging. However, there is no data on the diagnostic accuracy of combinations of proposed red flags.

8.7.7.2 Spinal cord compression

Risk of spinal cord compression (SCC) is between 5 and 20% of patients with spinal bone metastases, yet diagnosis and treatment are often delayed until neurological dysfunction is irreversible. Early suspicion and referral improves outcome. SCC risk relates to many factors including the type and characteristics of malignancy, extent of vertebral invasion, thoracic metastases, the number and duration of spinal metastases (Sutcliffe 2013 **Level III-3 SR**, 33 studies, n=5,782). Localised back pain is the most common presenting feature and neurological deficit is a late presentation; MRI is the investigation of choice (Samphao 2010 **SR** of diagnostic studies; Cheng 2011 **SR** of diagnostic studies).

Early referral for surgical assessment is required within 24 h of MRI. In addition to analgesic medications and adjuvants for pain, treatment options include corticosteroids, radiotherapy and decompressive surgery (Samphao 2010 **NR**; Loblaw 2012 **GL**; Ivanishvili 2014 **NR**). The NOMS (neurologic, oncologic, mechanical, and systemic) framework is a recognised decision tree to optimise local tumour control, pain relief, neurological preservation and functional restoration (Laufer 2013 **NR**). A Canadian scoring system (LMNOP) also incorporates a spinal instability neoplastic score into a similar decision framework (Ivanishvili 2014 **NR**).

8.7.7.3 Treatment strategies for bone cancer pain

Treatment strategies for bone cancer pain, including pain of spinal cord compression, should focus on both analgesia, preservation of function and prevention of complications (Kane 2015 **NR**). Rapid analgesia should be provided and advice given regarding nonpharmacological strategies such as rest, avoidance of strenuous activity of painful areas and use of general mobility aids. For acute bone pain, an accepted approach includes omission of Step II of the WHO ladder when simple analgesics are inadequate, with progression directly to strong opioids (Maltoni 2005 **Level II**, n=54 [prematurely terminated], JS 2). For predictable incident pain, pre-emptive treatment with rapid-onset opioids should be charted. Preclinical data indicates a role for NSAIDs for bone pain but there is a lack of clinical evidence to support this. In a systematic review of NSAIDs added to strong opioids for cancer pain, no subgroup analysis of the combination for bone cancer pain was undertaken (Nabal 2012 **Level III-2 SR**, 12 studies, n unspecified). Notably, histamine release is involved in the inflammatory process and generalised bone pain secondary to G-CSF treatment, and pain relief of refractory severe pegfilgrastim-induced bone pain after use of antihistamine loratidine has been described in a case report (Romeo 2015 **CR**).

Management of bone pain, in addition to complications of bone cancers, also includes targeted strategies that may be local (external beam radiotherapy, surgery) or systemic (chemotherapy, bisphosphonates, denosumab, hormonal therapy) (Samphao 2010 **NR;** Kane 2015 **NR**; Poon 2013 **NR**).

8.7.7.4 Surgery

In the case of imminent or actual pathological fracture of long bones and pelvis, surgical intervention with stabilisation may be of considerable benefit to reduce acute pain but has attendant risks. The incidences following surgical management of metastases in the humerus, femur and pelvis/acetabulum are 89–94% for pain relief, 91–93% for maintained or improved function, 17% for morbidity and 4% mortality (Wood 2014 **Level IV SR**, 47 studies, n=807). Placement of catheters for regional nerve or plexus block may eliminate acute incident pain leading up to orthopaedic surgery and during the perioperative period. The high infection rates (10%) after limb salvage surgery for primary bone cancer (Racano 2013 **Level IV SR**, 48 studies, n=4,838) should be considered when evaluating and managing acute pain in the postoperative period. A systematic review of treatment for metastatic SCC (1970 to 2007) that compared surgical stabilisation with or without radiotherapy and radiotherapy alone, concluded that tumour excision and instrumented stabilisation may improve clinical outcomes, with regard to both pain and neurological function (Kim 2012 **Level IV SR**, 33 studies, n=2,495). Radical surgical treatments should be considered where spinal metastases have a favourable prognosis, such as thyroid metastases (Zhang 2013a **Level IV**). Surgery to correct craniocervical instability also may alleviate acute pain, improve QoL and reduce hospitalisations (Kirchner 2014 **Level IV SR**, 9 studies, n=48). Prognosis should be re-evaluated, to ascertain the primary goals of treatment and to undertake risk-benefit assessment of potential treatment (Sutcliffe 2013 **Level III-3 SR**, 33 studies, n=5,782).

8.7.7.5 Radiation therapy

Radiotherapy effectively reduces malignant bone pain and may reduce complications of bone cancer. At 1 mth after radiation therapy, around 25% patients experienced complete pain relief (NNT 4.2; 95%CI 3.7 to 4.9) and 41% experienced 50% pain relief (McQuay 2000 **Level I** [Cochrane] 43 RCTs, n=1,933). An update of this meta-analysis of palliative radiotherapy treatment for uncomplicated bone metastases indicated similar response rates following single-fraction (60%) and multiple-fraction (61%) radiation, including 23 and 24% complete response rates, respectively (Chow 2012 **Level I** 25 RCTs, n=5,263). However, after single-fraction treatment, retreatment rates are higher and there is a trend for higher rates of pathological fracture and spinal cord compression. Multiple-fraction radiotherapy is favoured for borderline complicated metastases, without any high quality supportive evidence. For bone metastases with a neuropathic component to pain, a single randomised study indicated a trend for multiple fraction treatment to provide a longer-term benefit (Roos 2005 **Level II**, n=272, JS 3). Reirradiation of bone metastases improved pain in about 58% patients, with complete response in 16–28%; time to response from 3–5 wk, with duration 15–22 wk (Huisman 2012 **Level IV SR**, 7 studies, n=2,694). For patients with pain due to widespread bone metastases, radiopharmaceuticals may provide complete reduction in pain over 1–6 mth with no increase in analgesic use but with common severe adverse effects of leucopenia and thrombocytopenia (Roque 2011 **Level I**, 15 RCTs, n=1,146). There are limited data comparing the various isotopes used (Strontium-89 [89Sr], Samarium-153 [153Sm], Rhenium-186 [186Re] and Phosphorus-32 [32P]) showing no significant differences.

8.7.7.6 Percutaneous vertebroplasty

Where other measures fail, percutaneous vertebroplasty is a procedure that aims to stabilise vertebral compression fractures, restore function and achieve rapid pain relief by the injection of bone cement (polymethylmethacrylate). A systematic review of vertebroplasty for bone metastases and myeloma, highlighted low-level evidence from heterogeneous studies and identifies pain reduction rates of 47–87%, with no correlation between cement volume and pain relief (Chew 2011a **Level IV SR** 30 studies, n=987). Serious complications may result from the technique and from cement injection or extravasation, including to the epidural space.

Complications were reported in 2–11.5% of patients and may correlate with cement volume. These included haematoma, neuropathic pain, haemothorax and pulmonary embolism of cement, with five related deaths. No good evidence currently supports superiority of kyphoplasty over vertebroplasty. In multiple myeloma, vertebroplasty or kyphoplasty are equally effective resulting in prompt and sustained reduction in pain and reduced analgesic use (Khan 2014 **Level IV SR**, 23 studies, n= 923 patients). Vertebroplasty and kyphoplasty had similar complication rates in these patients, with the most frequent complication being new vertebral fracture at untreated levels. Technical difficulties of percutaneous vertebroplasty for a patient receiving denosumab, believed related to a sclerotic bone response, highlighted the need for further investigation of this issue (Mattei 2014 **CR**).

Cementoplasty, with percutaneous fluoroscopic-guided injection of bone cement into pelvic bone malignancies involving acetabulum, superior and inferior pubic rami, ischium and sacrum, is also a therapeutic option for acute intractable pain from primary or metastatic bone disease (Marcy 2000 **Level IV**; Kelekis 2005; **Level IV**; Harris 2007 **Level IV**; Jakanani 2010 **Level IV**; Kim 2013b **Level IV**). A combined technique of embolisation, radiofrequency ablation and cementoplasty for painful pelvic bone metastasis of renal cell cancer resulted in profound and sustained pain relief and reduction of opioid requirements for up to 6 mth (Pellerin 2014 **Level III-2**, n=52).

8.7.7.7 Bone-modifying agents

Bisphosphonates

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate with affinity for the hydroxyapatite matrix of bone, where they inhibit osteoclast-mediated bone resorption (see also Section 4.10.2). By this action, bisphosphonates reduce bone pain (see below), in addition to the primary role to decrease the risk of, and time to, skeletal-related events consequent to bone cancer, including fracture, SCC and hypercalcaemia. Hypercalcaemia is less frequent since bone-modifying agent use has increased but can still complicate widespread bone cancer and heighten the pain experience (Poon 2013 **Level I**, 20 studies, n unspecified). Later generation bisphosphonates are now most widely used, have considerably greater inhibition of bone resorption, maximal effect by 3 mth, and prolonged residence and duration of action in bone, for up to years for zoledronate (Kennel 2009 **NR**). Potential serious but uncommon problems include renal impairment and osteonecrosis of the jaw (ONJ); other effects include gastrointestinal symptoms, acute phase reaction with pyrexia, myalgia and arthralgia, hypocalcaemia, and idiosyncratic musculoskeletal pain or ocular inflammation. ONJ in cancer patients after bisphosphonates occurred in 6.7% of patients; the incidence is increased with time of exposure, a history of dental procedures, and zoledronate (Bamias 2005 **Level IV**). Clodronate or pamidronate use instead of zoledronate may reduce risk of ONJ but dental extractions remain the main risk factor for ONJ (RR 14.04; 99%CI 10.36 to 19.03) (Kyrgidis 2013 **Level III-2 SR**, 12 studies, n unspecified).

The efficacy of various bisphosphonates has been shown in a number of meta-analyses. In multiple myeloma, bisphosphonates ameliorate pain (RR 0.75; 95%CI 0.60 to 0.95) (Mhaskar 2012 **Level I** [Cochrane], 20 RCTs, n=6,692). Bisphosphonates improve pain control in patients with metastatic bone disease from lung cancer (Lopez-Olivo 2012 **Level I**, 12 RCTs, n=1,767). Zoledronate specifically reduces the likelihood of experiencing a bone-pain event in metastatic bone disease in comparison to placebo (RR 0.83; 95%CI 0.76 to 0.89) (Zhu 2013 **Level I**, 12 RCTs, n=4,450). Analgesic effect is not shown in advanced prostate cancer (OR 1.54; 95%CI 0.97 to 2.44) (Yuen 2006 **Level I** [Cochrane], 10 RCTs, n=1,955).

Denosumab

Activation of osteoclasts is driven by the receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) gradient. Denosumab is a human monoclonal antibody to RANKL that blocks osteoclast development and hence bone resorption. In patients with metastatic and primary bone cancer, denosumab reduces bone pain and slows time to worsening of pain (Prommer 2015 **NR**; Rolfo 2014 **NR**; Iranikhah 2014 **NR**).

In bone metastases from breast cancer (n=2,046), prostate cancer (n=1,901) or other solid tumours (n=1,597), denosumab compared to zoledronate delayed onset of moderate/severe pain by 1.8 mth (median 6.5 vs 4.7 mth; HR 0.83; 95 %CI 0.76 to 0.92) and clinically meaningful increases in overall pain interference by 2.6 mth (median 10.3 vs 7.7 mth; HR 0.83; 95%CI 0.75 to 0.92) (von Moos 2013 **Level I**, 3 RCTs, n=5,544, JS 5). Denosumab also reduced strong opioid use and worsening of health-related QoL. Compared to zoledronate, denosumab delayed time to worsening of pain in patients with skeletal metastases (RR 0.84; 95%CI 0.77 to 0.91) (Peddi 2013 **Level I**, 6 RCTs, n=6,142).

Denosumab can also lead to ONJ (Diz 2012 **NR**). Use of denosumab instead of zoledronate does not reduce the risk of ONJ (RR 0.71; 99%CI 0.41 to 1.24) (Kyrgidis 2013 **Level III-2 SR**, 12 studies, n unspecified) occurring in 1.6% of patients overall (1.3% with zoledronate and 1.8% with denosumab [p=0.13]) (Saad 2012 **Level I**, 3 RCTs, n=5,723).

Calcitonin

Although calcitonin has been used to reduce metastatic bone pain and skeletal events, the limited evidence available does not support the effectiveness of salmon calcitonin in the treatment of acute and persistent metastatic bone pain (Martinez-Zapata 2006 **Level I** [Cochrane], 2 RCTs, n=90) (see also Section 4.10).

8.7.7.8 Treatment of acute malignant extradural spinal cord compression

Comprehensive clinical practice guidelines exist to optimise care and pain control of patients with malignant SCC (Loblaw 2012 **GL**). Corticosteroids are indicated for neurological deficit, particularly if there is to be radiotherapy eg dexamethasone (bolus 8–10 mg; maintenance 16 mg/d; higher doses for dense paraparesis). Early surgical consultation is required, with due consideration of the associated morbidity. Patients unsuitable for surgery should receive radiotherapy. Selected groups suitable for stereotactic radiosurgery, with spinal cord sparing, remain to be clarified. Pain is acute and may be exacerbated during early radiotherapy, with incident pain associated with movement and positioning for treatments.

8.7.8 Other acute cancer pain syndromes

8.7.8.1 Malignant bowel obstruction

Malignant bowel obstruction frequently complicates advanced abdominal cancers, develops over days to months, and presents as generalised abdominal pain or visceral colicky pain. Very little, and heterogeneous, trial data exists to inform guidelines and choice of best medical care, surgery or endoscopic interventions, which may vary according to acuity, degree of obstruction, disease prognosis and objectives of care. Treatment should be individualised. Pharmacological management is based on glucocorticoid, analgesic, antiemetic and antisecretory agents, with attention to adequate hydration (Ripamonti 2008 **NR**; Mittal 2014 **Level IV**). Acute severe pain can be managed with parenteral opioids, which also reduces colicky pain by reducing bowel motility. Oral opioids should not be used due to unpredictable absorption. For exacerbations of colic, the antispasmodic hyoscine butylbromide is of benefit and less sedating than hyoscine hydrobromide. Decompression and reduction in secretions may also assist with pain in patients with inoperable bowel obstruction. Hyoscine butylbromide and the somatostatin analogues octreotide reduce gastrointestinal secretions, slow motility and decrease both continuous and colicky pain intensity (Ripamonti 2000 **Level III-1**). A trend for dexamethasone (6–16 mg IV) to improve bowel obstruction is described (Feuer 2000 **Level I** [Cochrane], 3 RCTs, n=89).

For inoperable bowel obstruction with peritoneal carcinomatosis, a staged protocol with analgesic, antiemetic, anticholinergic and corticosteroid as initial therapy (Stage 1), followed by a somatostatin analogue for persistent vomiting (Stage 2) and then venting gastrostomy (Stage 3) was highly effective in relieving symptoms and avoiding permanent nasogastric tube (Laval 2006 **Level IV**). Fluoroscopic-guided, percutaneous venting gastrostomy tube placement can be technically difficult, with 72 and 77% primary and secondary technical success, and 10% incidence of major complications; prior intraperitoneal catheter to manage ascites may reduce the technical difficulty (Shaw 2013 **Level IV**). Endoscopic stenting may offer effective

and safe palliation or act as a bridging step before surgery (Frago 2014 **Level IV SR**, 59 studies, n unspecified). Complications include perforation (3.76%), stent migration (11.81%) and reobstruction (7.34%) (Sebastian 2004 **Level IV SR**, 54 studies, n=1,198). Reports of no or mild nausea increased from 10% at baseline to 100% after treatment with olanzapine in patients with inoperable and incomplete bowel obstruction (Kaneishi 2012 **Level IV**).

8.7.8.2 Mucositis

Mucositis may be due to adverse effects of chemotherapy and radiation therapy for solid and blood malignancies. For management see Sections 8.6.7 and 9.8.3.4.

8.7.9 Interventional therapies for acute cancer pain

Although pain is adequately controlled in the majority of patients with advanced cancer, patients with severe acute exacerbations of pain may benefit from interventions.

Where pain is prolonged, but opioid-resistant, intractable, and associated with frequent acute exacerbations of pain, including incident pain or paroxysmal neuropathic pain, and adverse effects limit other pharmacological strategies, patients with advanced disease may benefit from longer-term local anaesthetic infusions, including neuraxial infusions, or more destructive neurolytic and other ablative procedures to manage pain.

8.7.9.1 Peripheral nerve blocks

Local anaesthetic nerve or plexus blocks including CPNBs may be used to control pain prior to surgery eg acute or imminent fracture, during painful diagnostic or therapeutic procedures, or while awaiting a response from other therapy such as radiation therapy (Chambers 2008 **NR**; Klepstad 2015 **Level IV SR**, 16 studies, n=79) (see also Section 5.8).

8.7.9.2 Neuraxial techniques

Currently, epidural or IT infusions of several classes of agents by a variety of medication delivery systems may provide effective analgesia to cancer patients with previously refractory pain, poor tolerance of oral or systemic analgesia and poor performance status (see also Sections 5.6 and 5.7). However, consensus guidelines for their use are based largely on weak evidence for cancer pain, despite broad experience in the use of IT opioids, local anaesthetics, clonidine, baclofen and other neuraxial medications (Stearns 2005 **GL**; Deer 2011 **GL**; Kurita 2011 **Level IV SR**, 44 studies, n unspecified). These consensus guidelines and other systematic or practical reviews provide a framework to optimise safety and effectiveness of these techniques that may be used in various and potentially remote palliative settings (Myers 2010 **SR** of 3 SRs, 3 consensus conferences and 12 RCTs; Upadhyay 2012 **NR**; Mercadante 2012 **NR**). Breakthrough analgesia with either SL ketamine or an IT local anaesthetic bolus was used successfully in palliative patients with ongoing IT analgesia (Mercadante 2005 **Level IV**). Although infrequently used, morphine by the intracerebroventricular (ICV) route may offer advantages for patients with head, neck or upper limb malignancy causing intractable pain (Ballantyne 2005 **Level IV SR** [Cochrane], 13 studies [ICV], n=337). This review noted few treatment failures and excellent analgesia reported in 73% after ICV opioids but more reports of respiratory depression, sedation and confusion, and lower incidence of nausea, urinary retention, pruritus and constipation with ICV therapy than with IT and epidural routes.

8.7.9.3 Spinal cord stimulation

Evidence is insufficient to establish any role for spinal cord stimulation for cancer pain in adults. Four case series provide the only evidence base in cancer pain (Lihua 2013 **Level III-3 SR**, 4 studies, n=92).

8.7.9.4 Destructive procedures

For pain due to pancreatic cancer, neurolytic coeliac plexus block has been widely used (Nagels 2013 **NR**) with improved pain scores at 4 wk (-0.42/10; 95%CI -0.70 to -0.13) and at 8 wk (0.44/10; 95%CI -0.89 to -0.01) and reduced opioid requirements (p<0.00001) (Arcidiacono 2011 **Level I** [Cochrane], 6 RCTs, n=358). Similar findings were reported by a systematic review

including additional case series (Nagels 2013 **Level IV SR**, 66 studies, n unspecified), while a subsequent meta-analysis confirmed reduced analgesic requirements with improved pain control only at 4 and not 8 wk (Zhong 2014 **Level I**, 7 RCTs, n=403).

In selected cases, IT neurolytic blocks can be a pain-relieving intervention (Candido 2003 **NR**).

Cordotomies have also been performed successfully to treat cancer pain in highly selected cases (Raslan 2011 **NR**). In pain due to mesothelioma, percutaneous cervical cordotomy (PCC) may be safe and effective (France 2014 **Level IV SR**, 9 studies, n=160). In pain mainly due to malignancies, CT-guided PCC provided pain relief in 98.13% of cases (Kanpolat 2013 **Level IV**, n=210). In another case series, 32 of 45 patients experienced significant pain relief without relevant adverse effects (Bain 2013 **Level IV**).

Pulsed radiofrequency was used to treat pain from infiltration of the brachial plexus by a tumour (Arai 2013b Level IV, n=4; Rana 2013 CR; Magistroni 2014 CR).

Key messages

1. Transmucosal fentanyl formulations are rapidly effective in treating acute breakthrough pain in cancer patients (**S**) (**Level I** [Cochrane Review]).
2. Radiotherapy and bone-targeting agents (bisphosphonates, denosumab) are effective treatments of acute cancer pain due to bone metastases (**S**) (**Level I** [Cochrane Review]).
3. Neurolytic coeliac plexus block in pancreatic cancer lowers pain intensity and opioid analgesic requirements for at least 8 weeks (**N**) (**Level I** [Cochrane Review]).
4. Patient education about cancer pain is a key factor in optimising pain management (**N**) (**Level I**).
5. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects (**S**) (**Level II**).
6. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity (**U**) (**Level III**).
7. Neuropathic pain or mixed nociceptive-neuropathic pain has an estimated frequency of 40% in patients with cancer (**N**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Acute pain in patients with cancer often signals disease progression; sudden severe pain in patients with cancer should be recognised as a medical emergency and immediately assessed and treated (**U**).
- ☑ Prompt assessment and fast coordinated management of spinal metastases with suspected spinal cord compression is required to mitigate against neurological deficit (**N**).
- ☑ Cancer patients receiving controlled-release opioids need access to immediate-release opioids for titration of breakthrough pain; selection of breakthrough medication should consider the time course and aetiology of the pain flare (**S**).
- ☑ If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed (**U**).
- ☑ Transdermal opioids are inappropriate to control acute unstable pain (**N**).
- ☑ High interindividual variability in opioid conversion rates dictates that all opioid rotations should be individualised and monitored, particularly where higher opioid doses are in use (**N**).

8.8 Acute pain management in intensive care

The management of pain in intensive care requires the application of many principles detailed elsewhere in these guidelines. Most critical care patients are likely to experience pain during their stay in ICU. However, many of the patients are unable to self-report pain due to a variety of reasons, such as sedative infusions to tolerate mechanical ventilation, the presence of a traumatic brain injury, paralysis and metabolic causes of altered consciousness. ICU patients also experience pain from a range of painful conditions, for example following surgery and trauma, in association with invasive devices and procedures and acute neuropathic pain. There may also be a need for the intensivist to provide palliative care (Puntillo 2014 **NR**).

8.8.1 Pain assessment in the intensive care unit

Assessment of pain in the ICU is difficult. The most important index of pain is the patient's own subjective experience but it is frequently impossible to quantify this because of the presence of an endotracheal tube or decreased conscious state due to illness or coadministered sedative agents. In 17 trauma patients admitted to an ICU, 95% of doctors and 81% of nurses felt that the patients had adequate analgesia whereas 74% of patients rated their pain as moderate or severe (Whipple 1995 **Level IV**).

Traditional subjective scales including the VAS or NRS are not applicable to the unresponsive patient. Instead, the observation of behavioural and physiological responses may be the only information available to modify pain management (Puntillo 1997 **Level IV**; Puntillo 2002 **Level IV**; Chong 2003 **NR**). The use of such behavioural scales is recommended but only validated, reliable and feasible scales should be used (Gelinas 2013 **NR**)

The BPS has been described and validated for the evaluation of pain in sedated, mechanically ventilated, unresponsive patients (Aissaoui 2005 **Level III-1**; Payen 2001 **Level III-1**; Gelinas 2013 **NR**). A CPOT that is based upon the response to noxious stimuli has been developed and validated for the detection of pain in nonverbal critically ill patients (Gelinas 2006 **Level III-2**; Gelinas 2011 **Level III-2**) The available data support self-rating where possible and, where not, a nurse-administered NRS combined with the BPS (Ahlers 2008 **Level III-3**). In brain-injured adults pain indicators remain poorly described (Roulin 2012 **NR**)

The use of formal pain/ agitation assessment and subsequent treatment decreased the incidence overall of pain (63 vs 42%) and agitation (29 vs 12%) (Chanques 2006 **Level III-1**; Payen 2009 **Level III-2**). These findings were associated with a decrease in the duration of mechanical ventilation. There were similar findings in critically ill trauma patients, where a formalised analgesia-delirium-sedation protocol shortened duration of ventilation, ICU and hospital stay while also decreasing total sedative doses (Robinson 2008 **Level III-3**).

8.8.2 Management of pain, agitation and delirium

It is difficult to separate pain management from sedation in the ICU context; the approaches to sedation and analgesia in ICU patients have changed dramatically as reflected in the recently updated guidelines with a broader-based approach ("care bundle") in this challenging patient group (Barr 2013b **NR**). There is recognition, however, that there remains a dearth of sufficient large-scale randomised ICU pain studies to support evidence-based guidelines.

The use of analgesia-based sedation protocols to preserve consciousness while treating pain appropriately has been associated with decreased duration of mechanical ventilation (De Jonghe 2005 **Level III-3**; Barr 2013a **GL**). The most useful intervention during sedation and analgesia in ICU is the provision of a daily drug "holiday" (daily interruption of sedation [DIS]) to reassess the need for sedation and analgesia. This simple step is associated with significantly shorter periods of mechanical ventilation and shorter stays in the ICU (Kress 2000 **Level II**, n=128, JS 3) but does not cause adverse psychological outcomes and reduces symptoms of post-traumatic stress disorder (Kress 2003 **Level III-2**). Contrary to initial concerns, DIS is not associated with an increased risk of myocardial ischaemia even in high-risk patients (Kress 2007 **Level III-1**). However, the use of a "no-sedation analgesia-only regimen" (morphine) compared to a conventional DIS strategy (morphine/propofol/midazolam) in mechanically ventilated patients with pneumonia is associated with an even shorter duration of ventilation (4.2 d)

coupled with a shorter stay in the ICU (Strom 2010 **Level II**, n=140, JS 5). This strategy may have an associated higher risk of delirium.

A summary of the principal recommendations of evidence-based guidelines includes (Barr 2013a **GL**):

- pain should be routinely monitored in ICU, using the BPS and the CPOT for patients who are unable to self report;
- vitals signs alone should not be used for pain assessment;
- analgesia should be administered prior to painful procedures;
- opioids are recommended as first-line analgesics for non-neuropathic pain;
- sedation levels should be titrated to light-level rather than deep sedation;
- monitoring of depth of sedation using Richmond Agitation-Sedation Scale (RASS) or Sedation-Agitation Scale (SAS) is recommended; and
- use of "care bundle" for managing pain, agitation and delirium:
  - DIS;
  - "analgesia first" sedation strategy;
  - promoting sleep and establishing day-night routine; and
  - interdisciplinary team approach.

Current practice still falls well short of these recommendations. In an Australian and New Zealand point-prevalence study, fewer than half of patients in the 41 participating ICUs had their pain assessed within the 4-h period audited and 22% of those assessed were considered to have moderate or severe pain (Elliott 2013 **Level IV**).

8.8.3 Nonpharmacological measures

Much of the discomfort associated with a prolonged admission to an ICU can be alleviated by holistic nursing care. Attention to detail with positioning, pressure care, comfortable fixation of invasive devices, care in the management of secretions and excretions, minimisation of noise from spurious alarms and unnecessary equipment (such as the uncritical application of high-flow mask oxygen) can substantially lessen the burden of discomfort for the patient (Aaron 1996 **Level IV**; Chong 2003 **Level IV**; Puntillo 2004 **Level III-3**). Maintenance of a day-night routine (lighting and activity) is thought to aid sleep quality (Horsburgh 1995 **NR**). A flexible and liberal visiting policy should decrease the pain of separation from family and friends. Physiotherapy maintains range of movement of joints and slows deconditioning while massage can trigger a relaxation response leading to improved sleep. Listening to music before and during turning of a patient did not reduce discomfort or anxiety for the critically ill patient (Cooke 2010 **Level II**, n=17, JS 4).

8.8.4 Pharmacological treatment

The mainstay of treatment of acute pain in the ICU remains parenteral opioid analgesia (Shapiro 1995 **GL**; Hawryluck 2002 **GL**; Barr 2013a **GL**).

8.8.4.1 Paracetamol, nonselective NSAIDs and coxibs

The use of nonopioids is restricted due to concerns relating to potential organ toxicity (principally renal and hepatic) that may occur with these agents (Jefferies 2012 **NR**). However, they may confer benefit when used in selected patient populations, particularly elective postoperative patients or those after trauma. The addition of paracetamol at a dose of 1 g IV every 6 h to elective cardiac surgical patients improved analgesia and shortened extubation times (Memis 2010 **Level II**, n=40, JS 5). The use of ketorolac in patients with rib fractures was associated with a decrease in the incidence of pneumonia and shorter ventilation times, with no apparent increase in the risk of bleeding or renal failure (Yang 2014 **Level III-2**).

8.8.4.2 Opioids

Morphine is usually the first choice but it is relatively contraindicated in the presence of renal impairment because of possible accumulation of its active metabolites. Pethidine is rarely used in the ICU because of concerns about accumulation of norpethidine, especially in the presence of renal dysfunction or prolonged exposure, and because of its potential interaction with several medicines (eg tramadol, monoamine oxidase inhibitors and SSRIs).

There is little evidence to suggest superiority of one opioid over another in terms of analgesia.

Fentanyl has a short duration of action after a single dose due to redistribution but its long elimination half-life suggests that it may accumulate when given in high doses for long periods. The replacement of a fentanyl infusion with enteral methadone in mechanically ventilated patients was associated with a shorter weaning time (Wanzuita 2012 **Level II**, n=68, JS 4).

The newer opioids, alfentanil and remifentanil, have potentially favourable kinetics for use in patients with organ dysfunction. Alfentanil combined with propofol led to shorter time to extubation and ICU discharge compared with a morphine and midazolam combination (Manley 1997 **Level II**, n=26, JS 3).

Remifentanil exhibits rapid clearance that is independent of renal function (Cohen 2001; Breen 2004 **Level IV**), while remifentanil acid, a weak active metabolite, may accumulate in the presence of renal impairment (Pitsiu 2004 **Level IV**). This has no clinical consequences (Breen 2004 **Level IV**). Remifentanil compared with either another opioid or hypnotic agent has no benefits in mortality, duration of mechanical ventilation, length of ICU stay and risk of agitation (Tan 2009 **Level I**, 11 RCTs, n=1,067). The use of remifentanil is only associated with a reduction in the time to extubation after cessation of sedation (2.04 h; 95%CI 0.39 to 3.69 h).

Note: reversal of conclusions
This reverses the Level II conclusion in the previous edition of this document; a number of RCTs had previously shown some benefits of remifentanil in the ICU setting.

A subsequent study confirmed this by failing to identify superiority of remifentanil over fentanyl in terms of analgesia, duration of ventilation or morbidity (Spies 2011 **Level II**, n=60, JS 5).

There are ongoing concerns about remifentanil with regard to the development of OIH and acute opioid tolerance in the perioperative setting, which may also have implications in the ICU (Kim 2014d **Level IV**, SR of multiple studies, n unspecified).

8.8.4.3 Alpha-2 agonists

Dexmedetomidine is a highly selective alpha-2 agonist sedative, with anxiolytic and analgesic properties. It can cause a temporary increase in blood pressure during administration but the subsequent reductions in heart rate and blood pressure are more noticeable, especially in haemodynamically labile individuals. It has been introduced into ICU practice as an aid to increase tolerance of intubation and mechanical ventilation and to smooth the transition to spontaneous respiration and extubation. Dexmedetomidine is associated with reduction in ICU stay and might reduce time to extubation, when compared with other sedative or hypnotic agents (Pasin 2013 **Level I** [PRISMA], 28 RCTs, n=3,648). One of the trials showed that dexmedetomidine was associated with significantly lower morphine requirements than propofol-based sedation after cardiac surgery (Herr 2003 **Level II**, n=295, JS 5). It is also of note here that dexmedetomidine facilitated patient interaction such as the ability to use a VAS for pain assessment, compared to midazolam and propofol (Ahmed 2013 **Level II**, n=500, JS 5).

8.8.4.4 Local anaesthesia techniques

Regional analgesic modalities are covered elsewhere (see Chapter 5). The ICU patients who may derive benefit are those that receive TEA for abdominal aortic aneurysm surgery (Nishimori 2006 **Level I** [Cochrane], 13 RCTs, n=1,224 patients), traumatic rib fractures (Carrier 2009

Level I, 8 RCTs, n=232) or thoracoabdominal procedures (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044).

8.8.5 Guillain-Barre syndrome

Patients with Guillain-Barre syndrome commonly need treatment in an ICU. They may report significant pain including painful paraesthesiae, backache, sciatica, meningism, muscle and joint pain. The distal to proximal distribution of pain that characterises peripheral neuropathies is not usually seen (van Doorn 2008 **NR**).

Gabapentin and carbamazepine, but not methylprednisolone, have analgesic efficacy in Guillain-Barre syndrome but the evidence is limited and of low quality (Liu 2013 **Level I** [Cochrane], 3 RCTs, n=277). Lignocaine IV may be useful in the treatment of acute neuropathic pain in Guillain-Barre syndrome based on evidence of benefit in other neuropathic pain disorders (Kalso 1998 **Level I**, 17 RCTs, n=450).

Plasma exchange in acute Guillain-Barre syndrome was associated with a shortened duration of disease and improved outcomes, including pain (Raphael 2012 **Level I** [Cochrane], 6 RCTs, n=649). However, corticosteroids do not offer any benefits in this indication and may even delay recovery, while causing adverse effects (Hughes 2012 **Level I** [Cochrane], 6 RCTS, n=587).

8.8.6 Procedure-related pain

There is often an assumption that patients who are intubated and sedated in an ICU will not recall or perceive pain during procedures. Lines and catheters are sometimes inserted without supplementary anaesthesia. A survey suggests that specific treatment of procedure-related pain occurs less than 25% of the time (Payen 2007 **Level IV**). Of patients who have memories of ICU, 54% recall discomfort and 12% overt pain.

Endotracheal tube suctioning and other medical interventions are consistently reported as being uncomfortable or painful (Jeitziner 2012 **Level III-2**). Therefore adequate local and/or parenteral anaesthesia should be provided during any noxious procedure (Puntillo 2004 **Level IV**; Casey 2010 **Level II**, n=60, JS 5). Reliance on dexmedetomidine as the sole agent for painful procedures does not reliably prevent recall or acute stress disorder (MacLaren 2015 **Level II**, n=23, JS 5).

Bolus remifentanil at a dose of 1 or 0.5 mcg/kg prior to removal of chest drains after cardiac surgery was superior to placebo with the higher dose causing more respiratory depression (Casey 2010 **Level II**, n=60, JS 5). In a dose-response study, the 90% effective dose (ED90) of sufentanil was 0.15 mcg/kg for turning patients during the first 5 d of sedation (Chaveron 2012 **Level II**, n=25, JS 5).

Key messages

1. Remifentanil provides no advantages over other opioids in ventilated intensive care unit patients (**R**) (**Level I**).
2. Carbamazepine and gabapentin may reduce the pain associated with Guillain-Barre syndrome, based on limited and low-quality evidence (**W**) (**Level I** [Cochrane Review]).
3. Plasma exchange in acute Guillain-Barre syndrome improves outcome including analgesia (**N**) (**Level I** [Cochrane Review]).
4. NSAIDs and paracetamol improve analgesia in selected intensive care unit patients (**N**) (**Level II**).
5. Daily interruptions of sedative infusions reduce duration of ventilation and ICU stay without causing adverse psychological outcomes (**U**) (**Level II**) or increasing the risk of myocardial ischaemia (**U**) (**Level III-1**).
6. The formal assessment and management of pain and agitation in ventilated intensive care unit patients decreases the incidence of pain and the duration of ventilation (**N**) (**Level III-1**).

7. Procedures such as endotracheal tube suctioning are consistently reported as uncomfortable and painful (**N**)(**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Observation of behavioural and physiological responses permits assessment of pain in unconscious patients (**U**).
- ☑ Routine monitoring for pain in sedated intensive care patients should be performed, using the Behavioural Pain Scale and the Critical-Care Pain Observation Tool (**N**).
- ☑ Intensive care unit patients should be provided with appropriate analgesia prior to and during potentially painful procedures (**S**).
- ☑ Opioids are the recommended first-line analgesic agents in ventilated intensive care patients (**N**).

8.9 Acute pain management in emergency departments

Pain is the most common reason for presentation to the ED and many patients will self-medicate for pain before attending (Kelly 2008 **NR**). There is evidence that, as in many other areas of health care, patients in EDs around the world receive suboptimal pain management (Gueant 2011 **Level IV**), although this has been challenged more recently (Green 2012 **NR**; Cinar 2012 **Level III-3**). Although 70% of patients presenting to an ED rated their analgesia as "good" or "very good", patient satisfaction with analgesia did not correlate with pain scores at presentation or discharge or change in pain scores (Kelly 2000 **Level IV**). This indicates that other factors are involved (Shill 2012 **Level III-2**).

In the ED setting, analgesia should be simple to administer, patient- and condition-specific and, where appropriate, based on local-regional rather than systemic techniques. Systems should be adopted to ensure adequate pain assessment, timely, adequate and appropriate analgesia, frequent monitoring and reassessment of pain and additional analgesia as required. Strategies to improve analgesic administration in the ED include nurse-initiated processes (Shaban 2012 **Level III-3**), however, nurse-initiated analgesia was not associated with high satisfaction (Shill 2012 **Level III-2**). Other strategies include the introduction of a protocol-based opioid titration regimen (Curtis 2007 **Level III-3**) and mandatory pain scoring at triage was also associated with a faster time to analgesia (n=35,628) (Vazirani 2012 **Level III-1**).

8.9.1 Systemic analgesics

8.9.1.1 Paracetamol and NSAIDs

Both paracetamol and NSAIDs are useful for treating mild to moderate trauma pain, musculoskeletal pain, renal and biliary colic and some acute headaches, as discussed elsewhere (see Sections 4.2 and 4.3).

The combination of oral paracetamol and NSAIDs is generally more effective than the use of either agent alone (Ong 2010 **Level I**, 21 RCTS, n=1,909), the combination of paracetamol and ibuprofen specifically (Bailey 2013 **Level I** [Cochrane], 7 RCTs, n=2,241). However, one subsequent RCT in acute traumatic pain, found the combination of oral paracetamol and NSAIDs (ibuprofen) to be no more effective than the use of either agent alone (Bondarsky 2013 **Level II**, n=90, JS 5).

8.9.1.2 Opioids

In the ED, opioids are frequently prescribed for the treatment of severe pain and should preferably be titrated via the IV route, given the wide interindividual variability in dose response and the delayed absorption via the IM or SC routes. Patients require close observation for sedation, respiratory depression and occasionally hypotension (Coman 1999 **Level IV**).

There is no clear consensus on what constitutes the most effective IV opioid and dosing regimen for analgesia in the ED. A comparison of IV opioids to treat severe pain in the ED shows no clinically significant differences in efficacy or adverse effects between all opioids studied (Patanwala 2010 **Level I**, 10 RCTs, n=2,095). Single IV doses below 0.1 mg/kg of morphine, 0.015 mg/kg of hydromorphone or 1 mcg/kg of fentanyl may be inadequate for severe acute pain without subsequent titration. Nurse-initiated or patient-driven protocols provide better and faster analgesia.

Opioid titration is often poorly done, leading to suboptimal dosing and analgesia (Bijur 2012 **Level IV**). The use of PCA is a more effective way of providing pain relief than physician-managed opioids in EDs resulting in greater patient satisfaction (Birnbaum 2012 **Level II**, n=211, JS 3; Rahman 2012 **Level II**, n=96, JS 3).

Higher initial opioid doses may be associated with more rapid onset of analgesia but studies comparing high- vs low-dose titration regimens for IV morphine (Bounes 2008 **Level II**, n=106, JS 3) and hydromorphone (Chang 2013a **Level II**, n=334, JS 3) show similar pain relief by 30 min and a trend towards fewer adverse effects in the lower dose range.

SL buprenorphine (Jalili 2012 **Level II**, n=110, JS 5) and IN sufentanil (Stephen 2012 **Level IV**) were also effective analgesics for extremity injuries in the ED.

In children requiring analgesia in the ED, IN (Borland 2007 **Level II**, n=67, JS 5), inhaled (nebulised) (Furyk 2009 **Level II**, n=73, JS 5) or oral transmucosal (Mahar 2007 **Level II**, n=87, JS 3) fentanyl provided effective analgesia (see Sections 6.6.1 and 10.1.9 for details). The use of IN fentanyl improves the time to analgesia in younger children without adverse effects (Holdgate 2010a **Level III-2**). In a study of patients with post-traumatic thoracic pain, there was no difference in analgesia between nebulised morphine and morphine PCA (Fulda 2005 **Level II**, n=44, JS 5).

In patients with difficult IV access, intraosseous (Von Hoff 2008 **Level II**, n=22, JS 3) and IN (Hansen 2013 **Level I** [PRISMA], 3 RCTs, n=301) opioids have been shown to have similar pharmaokinetic and clinical profiles. Doses should be adjusted for age (see Section 4.1) and titrated to effect. Oral opioids in situations with delayed or difficult IV access are another option (Miner 2008 **Level II**, n=320, JS 3); oral oxycodone 0.125 mg⁄kg in a suspension vs 0.1 mg⁄kg morphine IV resulted in delayed onset of analgesia and lower patient satisfaction but similar efficacy at 30 min.

Opioid-tolerant patients pose a special challenge in the ED and their management is discussed in Section 10.7.

8.9.1.3 Tramadol

In the management of severe trauma pain, IV tramadol had similar analgesic efficacy to morphine in equianalgesic doses (100–200 mg tramadol vs 5–20 mg morphine) (Vergnion 2001 **Level II**, n=105, JS 5). In patients with right lower quadrant pain, presumed to be due to appendicitis, IV tramadol reduced pain and did not affect the clinical examination (Mahadevan 2000 **Level II**, n=68, JS 5). For renal colic, tramadol was less effective than pethidine (Eray 2002 **Level II**, n=47, JS 1). For acute musculoskeletal pain, IM tramadol was similar to ketorolac in efficacy and adverse effects, also when both were combined with oral paracetamol (Lee 2008 **Level II**, n=78, JS 3). They were also equally effective administered SL in children with suspected fractures or dislocations (Neri 2013b **Level II**, n=131, JS 5). However, for musculoskeletal pain in the ED, oral tramadol 100 mg provided inferior analgesia to hydrocodone/paracetamol (5 mg/500 mg) (Turturro 1998 **Level II**, n=68, JS 5). Due to a lack of more specific studies in the ED, tramadol is regarded as having a limited use in this setting (Close 2005 **NR**).

8.9.1.4 Inhalational analgesics

N_2O in oxygen (see Section 4.5.1) provided effective analgesia and anxiolysis for minor procedures in both adults and children (Gamis 1989 **Level II**, n=30, JS 5; Gregory 1996 **Level II**, n=28, JS 3; Burton 1998 **Level II**, n=30, JS 5; Gerhardt 2001 **Level II**, n=11, JS 5) and may be useful as a temporising measure while definitive analgesia is instituted (eg insertion of a digital nerve block for finger injury).

Methoxyflurane (see Section 4.5.2) is used to provide analgesia most commonly in prehospital emergency care. In ED patients aged ≥12 y, methoxyflurane was significantly more analgesic than placebo, with only mild transient adverse effects such as dizziness (Coffey 2014 **Level II**, n=300, JS 4). Onset of analgesia was rapid at 4 min; peak analgesia was at 18.5 min. Safety was assessed over 14 d following administration and no significant adverse effects, including renal toxicity, were found (see also Sections 4.5 and 8.10).

8.9.1.5 Ketamine

There is increasing evidence regarding the use of ketamine as an analgesic in the ED.

Ketamine IV (0.5 mg/kg) was comparable to morphine IV (0.1 mg/kg) for treatment of acute pain due to long bone fractures in the ED (Majidinejad 2014 **Level II**, n=126, JS 4).

Ketamine boluses IV produced a significant morphine-sparing effect (without a change in pain scores) when used to treat severe trauma pain in the ED (Galinski 2007 **Level II**, n=73, JS 5). When treating acute musculoskeletal trauma pain, a low-dose SC ketamine infusion provided better analgesia with less nausea, vomiting and sedation, and improved respiratory function than intermittent SC morphine (Gurnani 1996 **Level II**, n=40, JS 3). Ketamine-midazolam was more effective and had fewer adverse effects than fentanyl-midazolam or fentanyl-propofol for fracture reduction in children in the ED (Migita 2006 **Level I**, 8 RCTs, n=1,086). Ketamine IN (0.5–1 mg/kg) was an effective analgesic in the ED (Andolfatto 2013 **Level IV**; Yeaman 2013 **Level IV**) (see also Section 4.6.1.1).

8.9.2 Analgesia in specific conditions

8.9.2.1 Abdominal pain

Patients and physicians differ in their assessment of the intensity of acute abdominal pain in the ED (Marinsek 2007 **Level IV**), with physician estimates of severity of abdominal pain being significantly lower than patient reports. Administration of analgesia correlated with the physician's assessment of a pain score greater than 60/100 mm on VAS. A patient's satisfaction with analgesia correlated with a reduction in pain of at least 20/100 mm on VAS and titration of analgesia to the patient's pain reports. Nevertheless, 60% of patients presenting to the ED with abdominal pain were satisfied with their analgesia on discharge. It is therefore reassuring that in patients presenting with abdominal pain to an ED, over a 10-y period analgesia administration increased and time to administration decreased (Cinar 2013 **Level IV**).

In the past, clinicians were concerned that administering analgesia may mask the signs and symptoms of abdominal pathology resulting in a delay in diagnosis and definitive treatment. Pain relief (usually in the form of opioids) does not interfere with the diagnostic process in acute abdominal pain in adults (Manterola 2011 **Level I**, 8 RCTs, n=922) or in children (Kim 2002 **Level II**, n=60, JS 5; Green 2005 **Level II**, n=108, JS 5) and does not lead to increased errors in clinical management (Ranji 2006 **Level I**, 12 RCTs, n=1,389).

8.9.2.2 Renal colic

Although it has previously been recommended that pethidine be used in preference to morphine, particularly for renal and biliary colic due to the theoretical risk of smooth muscle spasm, there is no difference in clinical efficacy between morphine and pethidine in the ED (O'Connor 2000 **Level II**, n=103, JS 5).

Nonopioids such as paracetamol and NSAIDs are effective in treating the pain of renal colic (see Section 8.6.1.2).

8.9.2.3 Biliary colic and acute pancreatitis

See Section 8.6.1.3.

8.9.2.4 Acute cardiac chest pain

See Section 8.6.3.

8.9.2.5 Acute pain and sickle cell disease

See Section 8.6.4.1.

8.9.2.6 Migraine

While a number of different classes of medicines are effective in the treatment of acute migraine, other more serious causes of headache, particularly subarachnoid haemorrhage and CNS infection, should always be considered during clinical assessment. Clinical improvement with medication directed at migraine relief is not specific and does not rule out alternative causes of headache (Pfadenhauer 2006 **Level IV**).

Simple treatment with oral NSAIDs, especially aspirin, is effective in patients who are not vomiting (Kirthi 2010 **Level I** [Cochrane], 13 RCTs, n=4,222). In patients unable to tolerate oral therapy, phenothiazines such as chlorpromazine and prochlorperazine (Kelly 2009 **Level I**, 13 RCTs, n=917), selective serotonin agonists especially sumatriptan (Derry 2012 **Level I** [Cochrane], 35 RCTs, n=9,365) and butyrophenones (however with significant adverse effects) (Leong 2011 **Level I**, 6 RCTs, n=574) provide effective analgesia in up to 80% of patients. A systematic review of treatment of migraine pain in ED settings supports these results with strong evidence in favour of prochlorperazine and moderate evidence for chlorpromazine, metoclopramide, sumatriptan and IV lysine acetylic acid (Orr 2015 **Level I** [PRISMA], 44 RCTs, n unspecified). These medicines provide superior analgesia compared with opioids with fewer adverse effects; thus opioids are not recommended in the treatment of migraine (Worthington 2013 **GL**; Orr 2015 **GL**).

Evidence-based recommendations for the treatment of migraine in ED settings are published (Orr 2015 **GL**); see Section 8.6.5 for a more detailed review of the treatment of migraine and other acute headache syndromes.

8.9.2.7 Fractured neck of femur

Nerve blocks reduce pain in comparison to placebo and had a sparing effect on parenteral or oral analgesia administered to control pain from a fractured neck of femur. However the data were insufficient to show superiority over other analgesic techniques (Abou-Setta 2011 **Level I**, 29 RCTs, n unspecified). The effects are significant for epidural, femoral nerve, psoas compartment, fascia iliaca and combined nerve blocks, but not for 3-in-1 blocks. In a subsequent RCT, nerve stimulator-guided FNB was more effective than landmark-guided fascia iliaca block (Newman 2013 **Level II**, n=107, JS 4). The effective dose to achieve ≥20/100 pain reduction (VAS) in 95% of patients (ED95) with 30 mL levobupivacaine for a US-guided FNB was 0.036% (95%CI 0.027 to 0.047) found by sequential up-down titration (Watson 2014 **Level IV**).

Although opioids alone are not particularly effective in providing analgesia and have the potential for significant adverse effects such as respiratory depression and delirium in this older patient cohort, regional nerve blocks are underutilised in Australian ED (Holdgate 2010b **Level IV**).

8.9.2.8 Shoulder dislocation

Intra-articular lignocaine (injected via landmark technique) for anterior shoulder dislocations provided analgesia comparable to systemic analgesics with fewer adverse effects (Ng 2009 **Level I**, 6 RCTs, n=263).

8.9.2.9 Wounds

Local anaesthesia is frequently required for the treatment of wounds in the ED. Agents most commonly used for local infiltration are lignocaine or the longer acting bupivacaine, ropivacaine or levobupivacaine, depending on the duration of anaesthesia required and whether analgesia following the procedure is desirable.

It is less painful to infiltrate local anaesthesia by injection through the wound rather than in the tissues surrounding it (Bartfield 1998 **Level II**, n=63, JS 4). Buffering of lignocaine with

bicarbonate reduces the pain of infiltration, particularly when using lignocaine with adrenaline (Cepeda 2010 **Level I**, [Cochrane], 23 RCTs, n=1,067).

Digital nerve block with 0.75% ropivacaine significantly prolonged analgesia and reduced rescue analgesia requirements to 24 h, without a clinically significant increase in time to block onset, compared with 2% lignocaine (Keramidas 2007 **Level II**, n=70, JS 2).

Topical local anaesthetic preparations are also used, particularly for wound care in children. Topical tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lignocaine are as effective as EMLA® cream for dermal instrumentation (eg cannulation) analgesia in the ED (Eidelman 2005 **Level I**, 25 RCTS, n=2,096). For simple lacerations in children, topical anaesthetic preparations such as ALA (adrenaline, lignocaine, amethocaine) are effective alternatives to infiltration with local anaesthesia without the pain of local injection (Ferguson 2005 **Level I**, 7 RCTs, n=1,260). Topical lignocaine and adrenaline applied to a wound in sequential layers significantly reduced reports of pain during initial application compared with a 2% lignocaine injection but with no difference in pain scores during suturing (Gaufberg 2007 **Level II**, n=100, JS 3). A topical gel dressing containing morphine was no more effective than other gel dressings in reducing burns injury pain in the ED (Welling 2007 **Level II**, n= 49, JS 3).

8.9.3 Nonpharmacological management of pain

Although analgesic agents may be required to treat pain in the ED setting, the importance of nonpharmacological treatments should not be forgotten. These include ice, elevation and splinting for injuries and explanation of the cause of pain and its likely outcome to allay anxiety. Psychological techniques such as distraction, imagery or hypnosis may also be of value (see Sections 7.1 and 9.7).

In young children, interventions such as distraction, positioning, sucrose and cold application may be helpful to manage pain in the ED (Wente 2013 **Level IV**, SR of 14 studies, n=1,459).

Key messages

1. Appropriate doses of intravenous opioids are effective in treating acute severe pain in the emergency department and ideally should be titrated according to nurse-initiated and patient-driven protocols; there is no preference for a specific opioid (**N**) (**Level I**).

Abdominal pain

2. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain and does not increase the risk of errors in clinical management (**U**) (**Level I** [Cochrane Review]).

Migraine (see also Section 8.6.5)

3. NSAIDs, triptans, phenothiazines (prochlorperazine, chlorpromazine) and metoclopramide are effective to treat migraine in the emergency department (**S**) (**Level I**).

Fractured neck of femur

4. Nerve blocks with local anaesthetics reduce pain and analgesia requirements in fractured neck of femur (**N**) (**Level I**).
5. Femoral nerve blocks in combination with intravenous opioids are superior to intravenous opioids alone in the treatment of pain from a fractured neck of femur (**U**) (**Level II**).

Local anaesthesia

6. Buffering of lignocaine with bicarbonate reduces the pain of infiltration, particularly when using lignocaine with adrenaline (**N**) (**Level I** [Cochrane Review]).
7. Topical local anaesthetic agents (including those in liposomal formulations) (**U**) (**Level I**) or topical local anaesthetic-adrenaline agents (**U**) (**Level II**) provide effective analgesia for wound care in the emergency department.

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ To ensure optimal management of acute pain, emergency departments should adopt systems to ensure adequate assessment of pain, provision of timely, adequate and appropriate analgesia, frequent monitoring and reassessment of pain (**U**).

8.10 Prehospital analgesia

The above section considered management of acute pain in patients admitted to EDs. However, many of these patients will also have required prehospital pain relief when under the care of paramedic or medical retrieval teams. While the term "prehospital" is also used to cover a greater variety of prehospital locations, it is beyond the scope of this document to look at pain relief administered in more complex situations such as war or disaster settings.

Many of the patients transported by ambulance services or retrieval teams will have pain that requires treatment prior to and during transport. However, there are some specific features of the prehospital environment that will impact on the way that the pain can and should be managed. The environment is often uncontrolled, there may well be a shortage of assistance, light, shelter and suitable equipment, and the patient is often in the acute or evolving stage of their condition, which may change rapidly.

Provision of prehospital analgesia is important, given that pain in the prehospital setting is common. Pain severity is rated as intense to severe in up to 64% of ambulance patients (Galinski 2010 **Level IV**). In these patients, the factors associated with severe pain were cardiac pain and trauma, yet the proportion of patients given analgesics (opioid or inhalational) prior to transfer to an ED varies significantly. Factors associated with under treatment of pain in a setting of physician-managed prehospital care were: treatment by a female physician (OR 2.0; 95%CI 1.0 to 4.0), severe pain at initiation of treatment (OR 8.8; 95%CI 5.1 to 15.2) and relative inexperience of the physician (<5 y experience) (Albrecht 2013 **Level IV**).

The presence of cognitive impairment in patients managed by ambulance staff is associated with markedly less analgesic administration despite having significant injuries (McDermott 2014 **Level IV**). "Unnecessary pain" was the second most common type of injury in 56 of 272 claims against ambulance trusts in the UK between 1995 and 2005 (Dobbie 2008 **Level IV**).

One survey of 1,073 adult patients with suspected extremity fractures showed that just 18 (1.7%) were given any analgesia and only 2 received morphine (White 2000 **Level IV**). A later survey showed that only 12.5% of patients with isolated extremity injuries received any prehospital parenteral pain relief (Abbuhl 2003 **Level IV**). Another study reported prehospital opioid administration in 18.3% of patients with lower extremity fractures; however older patients and those with hip fractures were less likely to be given analgesia prior to arrival in the ED (McEachin 2002 **Level IV**). In contrast, another group reported that 51% of elderly patients with a fractured neck of femur were given prehospital analgesia; methoxyflurane in 47% of cases, N_2O in 10% and morphine in 6% (Vassiliadis 2002 **Level IV**).

A large audit of ambulance patients who received analgesia (n=97,705, NSW Ambulance service) found that 87% of all patients received single analgesic therapy (Bendall 2011b **Level IV**). Overall, inhaled methoxyflurane was the most commonly used analgesic (given to 60% of patients) followed by morphine IV (26% of patients) and fentanyl IN (19%).

Prehospital use of opioids may be increasing. In a 2005 survey, 29% of patients with isolated extremity injuries had been given morphine (Michael 2007 **Level IV**) and 13% of females and 17% of males in pain had been given morphine (Lord 2009 **Level IV**). Adequate use of morphine during the early treatment of acute pain after military trauma may significantly reduce the risk of developing post-traumatic stress disorder (OR 0.47; 95%CI 0.34 to 0.66) (Holbrook 2010 **Level III-2**). With use of systemic opioids, 60–70% of prehospital care patients have pain scores above 30/100 at 10 min, falling to 30% at 30–40 min (Park 2010 **Level I,** 21 RCTs, n=6,212). Only two patients required naloxone and none needed ventilatory support.

Paediatric patients may also not receive prehospital pain relief. One study of children with fractures or soft tissue injuries reported that 37% received prehospital analgesic medicines (Rogovik 2007 **Level IV**). Another, which included patients with a diagnosis of limb fracture or burns, reported that analgesia was given to 51% of children between the ages of 5 and 15 y but not to any child aged <5 y; a greater proportion of this younger group (70 vs 54%) were given opioid analgesia once in the ED (Watkins 2006 **Level IV**). A large study of ambulance patients found that when a single agent was used, females were less likely to receive opioid analgesia than males (RR 0.83; 95%CI 0.82 to 0.84) (Bendall 2011b **Level III-2**). Opioid use increased with increasing age; those aged >60 were the most likely to receive opioids. Children were less likely to receive opioids compared to methoxyflurane (RR 0.65; 95%CI 0.63 to 0.67) and it was more commonly IN fentanyl when given.

Despite such studies showing that pain relief prior to arrival in an ED needs to be improved and although pain relief has been acknowledged as a key area for investigation, evidence regarding management of acute pain in patients in the prehospital setting remains limited with few RCTs available. Although many analgesic techniques that work in hospital environments have been transcribed to the prehospital environment, these do not always comply with the ideal of simplicity, safety and effectiveness when used in the field. Another factor in the apparent underuse of prehospital analgesia may be the attitude toward analgesia by the prehospital caregivers. In a small survey of experienced paramedics (n=15), the following themes arose as reasons why analgesia was withheld: reluctance to administer opioid unless there were significant signs (for example an obvious fracture), concerns regarding malingering behaviour, uncertainty regarding the endpoint ("pain free" or "take the edge off"), concern regarding analgesia masking diagnostic symptoms and a reluctance to use larger initial opioid doses (>5 mg morphine) (Walsh 2013 **Level IV**).

8.10.1 Assessment of pain in the prehospital environment

As in other settings, pain intensity is best assessed using patient self-report measures such as VAS (Galinski 2005 **Level II**, n=54, JS 4; Kober 2002 **Level II**, n=60, JS 5), VNRS (McLean 2004 **Level IV**; Woollard 2004 **Level II**, n=175, JS 3; Rickard 2007 **Level II,** n=258, JS 3; Bounes 2008 **Level II**, n=106, JS 5), VDS (McLean 2004 **Level IV**; Vergnion 2001 **Level II**, n=105, JS 5) or faces pain scale (Rogovik 2007 **Level IV**) (see Chapter 2). A ruler incorporating both visual analogue and faces pain scales has also been used to measure pain in patients prior to arrival at hospital (Lord 2003 **Level IV**). A cohort study of ambulance patients having had acute trauma showed that patients had poor recall of initial pain scores at 1–2 d after injury (Easton 2012 **Level III-3**).

In some instances it may not be possible to obtain reliable self-reports of pain (eg patients with impaired consciousness or cognitive impairment, young children [see Section 9.3], elderly patients [see Section 10.2.2], or where there are failures of communication due to language difficulties, inability to understand the measures, unwillingness to cooperate or severe anxiety). In these circumstances other methods of pain assessment based on observation of patient behaviours should be used.

8.10.2 Systemic analgesics

The ideal prehospital analgesic agent should be simple to use, safe (both in terms of side effects and adverse effects on the patient's condition), effective, not lead to delays in transport and have a rapid onset and short duration of action, so that it can be repeated as often as necessary and titrated to effect for each patient (Alonso-Serra 2003 **NR**). Consideration should be given to both choice of analgesic medicine and route of administration.

8.10.2.1 Opioids and tramadol

The administration of systemic opioids as an effective prehospital analgesic is widespread in ambulance services staffed by paramedics and retrieval services. Their application is influenced by the knowledge and judgment required to use them and the differing legislation for the drugs of dependence between countries. In this setting, use of IV or IN routes will enable a more rapid and predictable onset of action than other routes of administration. Opioids should not be administered IM/SC in the prehospital environment, because of

unpredictable pharmacokinetics in the poorly perfused patient. Following resuscitation, morphine may undergo reabsorption from earlier IM administration, which may lead to a potential risk of delayed adverse effects.

Both morphine and fentanyl are commonly used for prehospital analgesia. Morphine (Bruns 1992 **Level IV**; Fullerton-Gleason 2002 **Level IV**), fentanyl (Kanowitz 2006 **Level IV**) and tramadol (Ward 1997 **Level IV**) have been shown to provide effective and safe pain relief in patients being transported by road. Fentanyl was also safe and effective when given to patients during helicopter transfers (Thomas 2005 **Level IV**; Krauss 2011 **Level IV**).

Morphine doses of 0.1 mg/kg IV followed by 0.05 mg/kg every 5 min as needed provided more rapid pain relief and patient satisfaction than doses that were 50% lower (Bounes 2008 **Level II**, n=106, JS 5).

In a comparison of IV fentanyl and morphine bolus doses given every 5 min as needed for prehospital analgesia, no difference was found in pain relief or incidence of adverse effects (Galinski 2005 **Level II**, n=54, JS 4). Similarly, there was no difference in pain relief or adverse effects reported in a comparison of IV tramadol and morphine (Vergnion 2001 **Level II**, n=105, JS 5).

When used to treat acute cardiac chest pain during prehospital transfer, IV alfentanil provided more rapid relief than IV morphine (Silfvast 2001 **Level II**, n=40, JS 4; Rickard 2007 **Level II**, n=258, JS 3).

A comparison of 5 mg and 10 mg nalbuphine doses given IV and repeated at 3-min intervals to a total of 20 mg showed that use of the larger dose led to better pain relief but higher patient-reported drowsiness; over half the patients in both groups still had significant pain on arrival at the hospital (Woollard 2004 **Level II**, n=175, JS 3).

IN fentanyl is often used in the prehospital setting for treating acute pain in both children and adults (19% of patients) (Bendall 2011a **Level III-2**). This route requires a high-concentration preparation of fentanyl (typically 300 mcg/mL) and atomisation as with the MAD® device, which is attached to a syringe. In Australia, this route is sanctioned under an exemption from the TGA. Fentanyl has a relatively high lipid-solubility that enables rapid absorption from the nasal mucosa. Compared with IV fentanyl, the IN route shows similar pharmacokinetics (Foster 2008 **PK**). Bioavailability is 89% with an interpatient variability of 30%. Absorption and onset of analgesia are slightly delayed compared with IV fentanyl (T_{max} 13 vs 6 min) (see Section 5.5.2).

The analgesic efficacy of IN fentanyl compared with alternatives (IV morphine, methoxyflurane) for the treatment of pain in the prehospital setting is unclear. There is only low-quality evidence to support the use of IN fentanyl (Hansen 2013 **Level III-3 SR**, 4 studies, n unspecified). The single RCT in the review found no significant difference in pain score reduction between IN fentanyl and IV morphine (Rickard 2007 **Level II**, n=258, JS 3). This could have been due to the study being underpowered and IV morphine being given for rescue analgesia in the IN fentanyl group.

Oral transmucosal fentanyl (Actiq®) in battlefield casualties showed suitable effectiveness and safety with ease of administration (Wedmore 2012 **Level IV**).

8.10.2.2 Inhalational agents

Inhalational analgesics can provide early pain relief in the prehospital environment. However, variations in the availability of different agents have a marked impact on regional practices. In one series, patients with extremity fractures were more likely to receive N_2O than morphine (White 2000 **Level IV**), whereas in another series N_2O was not used at all (Rogovik 2007 **Level IV**).

N_2O is included in prehospital management protocols for manipulation, splinting and transfer of patients with lower-limb fracture (Lee 2005b **Level IV**) and as a second-line in burns patients if opioids are not available (Allison 2004b **Level IV**). Although N_2O has been reported to provide pain relief in >80% of patients requiring prehospital analgesia (Thomas 2008 **Level IV**), this practice was not based on RCTs (Faddy 2005 **NR**) and there are few studies comparing efficacy with other agents. In one paediatric series, a higher proportion of children receiving N_2O rather than opioids had pain on arrival in the ED but interruption of delivery during transfer

from the ambulance may have contributed (Watkins 2006 **Level IV**). Based on data from hospital studies, N_2O has been suggested as a safe analgesic in prehospital settings, although specific contraindications (such as pneumothorax and decreased consciousness) may be particularly relevant in this patient group (Faddy 2005 **NR**) (see Section 4.5.1 for further details). Administration of 50% N_2O compared with medical air to trauma patients in the prehospital setting showed effective analgesia; 67% of the N_2O group had pain score ≤3/10 at 15 min compared with only 27% in the air group (Ducasse 2013 **Level II,** n=60, JS 4).

Provision of N_2O in ambulances is hampered by difficulties providing scavenger systems that minimise occupational exposure and the bulk/logistical issues associated with managing cylinders of oxygen and N_2O (Entonox® cylinders are a mixture of 50% N_2O and 50% oxygen) that separate at low temperatures. The demand valves are costly and require maintenance, and the inability to activate the valve and effectively use Entonox® equipment has been rated as a major factor limiting use in children <5 y (Watkins 2006 **NR**).

Methoxyflurane is not available in most countries but in Australia it has replaced N_2O in prehospital settings for three decades. Methoxyflurane is delivered by a Penthrox® inhaler which contains 3 mL of methoxyflurane and lasts for 25–30 min (Medical Developments International 2001). It is not licensed in the UK, European Union or the USA. It is more costly per dose than opioid analgesics (>$20/dose). Methoxyflurane is contraindicated in patients with renal impairment, which is difficult to reliably assess in the acute prehospital environment. Caution against its use has been expressed by one UK medical college until further studies have been undertaken (Fairhurst 2011 **GL**).

Methoxyflurane reduced pain scores (mean 2.47/10 ± 0.24) in adults, the majority of whom had musculoskeletal pain. The incidence of nausea was 8%, and 11% had increased drowsiness (Buntine 2007 **Level IV**). Methoxyflurane produced greater initial reduction in pain scores than IN fentanyl (2.0 vs 1.6/10) but IN fentanyl produced greater pain reduction by the time of arrival at hospital (3.2 vs 2.5/10) (Johnston 2011 **Level III-3**). Methoxyflurane reduced NRS pain score by ≥30% for 78% of children (aged 5–15 y), while among those who received IV morphine and IN fentanyl this was achieved for 88 and 90% respectively (Bendall 2011a **Level III-2**). In a smaller series, methoxyflurane also reduced pain scores in children and adverse effects were reported (Babl 2006 **Level IV**). The overall incidence of drowsiness was 27% but the risk of deep sedation was significantly higher in younger children (see Section 9.7).

There have been no reports of toxicity with analgesic use if doses are limited to 3 mL repeated once per event with a maximum of 15 mL per wk or a maximum of 0.5% for 1 h (Grindlay 2009 **NR**) (see also Section 4.5.2). A large population database study (n=17,629) found no long-term (up to 14 y) adverse effects in patients who had been given methoxyflurane by an ambulance service (Jacobs 2010 **Level IV**).

8.10.2.3 Ketamine

Ketamine has been administered for prehospital procedural analgesia and sedation in both adults (Porter 2004 **Level IV**; Bredmose 2009b **Level IV**) and children (Bredmose 2009a **Level IV**) for many years. A case-series of patients treated by paramedics trained in the use of ketamine combined with midazolam found it was highly efficacious (reduction of mean pain score from 8/10 to 3/10) and safe (adverse effects 2.8%, no change in vital signs) (Haske 2014 **Level IV**). IV ketamine provided similar analgesia to IM morphine for trauma patients in rural areas (Tran 2014 **Level II**, n=308, JS 2). The ketamine group had a higher rate of agitation and hallucinations (11 vs 1.5%) but a lower rate of vomiting (5 vs 19%). After trauma, patients who responded poorly to a first dose of 5 mg morphine IV had better analgesia with subsequent IV ketamine than morphine bolus doses but with more minor adverse effects (Jennings 2012 **Level II**, n=135, JS 3).

8.10.2.4 NSAIDs and paracetamol

The use of parenterally administered NSAIDs has been suggested for prehospital analgesia (Alonso-Serra 2003 **NR;** McManus 2005 **NR**) but the slower onset of effect as well as the risk of adverse effects (eg bleeding, renal impairment; see Section 4.3), especially in patients who have lost blood and may be hypovolaemic, means they are not commonly used. Similarly

injectable paracetamol is not commonly used. Oral paracetamol or other analgesics have a limited role in the prehospital management of moderate to severe pain.

8.10.3 Anxiolytics

Anxiolytics, for example low doses of midazolam, are sometimes used to alleviate some of the acute anxiety or agitation that may complicate effective control of pain in stressful prehospital conditions (McManus 2005 **NR**). However, there are no studies looking at efficacy and safety. It should be remembered that the combination with opioids will increase the risk of respiratory depression and that anxiety and agitation may be indicators of other more serious underlying conditions such as a head injury or hypoxia (McManus 2005 **NR**). Low-dose midazolam (1 mg typically) in combination with ketamine administered by ambulance officers did not produce any drug-related adverse effects (Haske 2014 **Level IV**).

8.10.4 Regional analgesia

Use of regional analgesia in the prehospital setting (excluding war or disaster situations) is uncommon. Initiation of a fascia iliaca block for analgesia in patients with isolated femoral shaft fractures provided effective pain relief prior to arrival at an ED (Lopez 2003 **Level IV**). Prehospital FNBs performed by physicians for femoral fractures were highly effective for pain relief with a success rate of 91% (Gros 2012 **Level IV**)

8.10.5 Nonpharmacological management of pain

Although analgesic agents are often used to treat pain in the prehospital setting, the importance of nonpharmacological treatments should not be forgotten. The role of psychological intervention with reassurance and distraction in the management of acute pain in an anxious patient is often undervalued.

Physical interventions specific for traumatic injuries include ice, elevation and splinting. Local active warming resulted in significant analgesia for females in pelvic pain during prehospital transport (Bertalanffy 2006 **Level II**, n=100, JS 3).

TENS applied over the painful flank during prehospital transport reduced pain scores, anxiety and nausea in patients with renal colic (Mora 2006 **Level II**, n=100, JS 4).

Acupressure performed by paramedics using “true points” led to better pain relief and less anxiety than acupressure using “sham points” (Lang 2007 **Level II**, n=32, JS 5) or sham or no acupressure (Kober 2002 **Level II**, n=60, JS 5).

8.10.6 Analgesia in specific conditions

8.10.6.1 Acute cardiac pain

The mainstay of analgesia in acute coronary syndrome is the restoration of adequate myocardial oxygenation, including the use of supplemental oxygen (Pollack 2008 **GL**; Cannon 2008 **GL**) and nitroglycerine (Henrikson 2003 **Level IV**). Whether supplemental oxygen is beneficial or harmful (especially if used in a nontargeted way) when used in acute coronary syndrome remains unclear (Cabello 2013 **Level I** [Cochrane], 4 studies, n=430); current guidelines by NICE (NICE 2010 **GL**) and the Australian and New Zealand Cardiac Society (Chew 2011b **GL**) state that the use of supplemental oxygen is not recommended unless hypoxia (SaO_2<94%) is present. Opioid analgesia may also be required; see Section 8.6.3.

8.10.6.2 Abdominal pain

As noted in Section 8.6, administration of opioids does not interfere with the diagnostic process in acute abdominal pain.

8.10.6.3 Patients with head injury

Caution is often expressed about the use of opioids for pain relief in patients with a head injury (Thomas 2008 **NR**). This is largely because of the potential adverse effects of opioids and their ability to interfere with recovery and neurological assessment, as well as the concern that OIVI will lead to hypercarbia and increased intracranial pressure (Nemergut 2007 **NR**).

While there is little specific information regarding the use of opioids in patients with a head injury in the prehospital setting, they have been safely used in patients after craniotomy (see Section 8.1.8).

The use of opioids in patients with a head injury in the prehospital environment will need to be based on an individual risk-benefit assessment for each patient.

Key messages

1. Intravenous morphine, fentanyl and tramadol are equally effective in the prehospital setting (**N**) (**Level II**).
2. Nitrous oxide is an effective analgesic agent in prehospital situations (**S**) (**Level II**).
3. Methoxyflurane, in low concentrations, is an effective analgesic with rapid onset in the prehospital and hospital setting with good safety data (**S**) (**Level II**).
4. Ketamine is a safe and effective analgesic in the prehospital setting (**S**) (**Level II**).
5. Effective early treatment of trauma pain may reduce the incidence of post-traumatic stress disorder (**N**) (**Level III-3**).
6. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**U**) (**Level IV**).
7. Oral transmucosal fentanyl may be an effective and easy to administer alternative to intravenous morphine for trauma pain in the prehospital setting (**N**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Nonpharmacological measures are effective in providing pain relief and should always be considered and used if practical (**U**).

8.11 Discharge medication for acute pain management

The number of patients discharged from hospital with opioid medication is rising (Macintyre 2014 **NR**), partially because the range of patients and procedures considered suitable for short-stay or early discharge are increasing (see Section 8.1.7).

Ideally, multimodal analgesia approaches should be the cornerstone of the discharge analgesic regimen, however some patients will require opioid medications at discharge to manage moderate to severe postoperative pain and optimise recovery and rehabilitation (Association of Anaesthetists of Great Britain and Ireland 2011 **GL**; Steyaert 2013 **NR**).

Before prescribing opioids as a discharge medication, consideration needs to be given to possible opioid adverse effects; these include the potential risks of long-term opioid use, drug diversion, misuse/abuse and death from accidental overdose (Macintyre 2014 **NR**).

8.11.1 Adverse effects

8.11.1.1 Opioid-induced ventilatory impairment

There is little published data on risk factors for OIVI that would be specific to adult patients discharged from hospital taking opioids at home (Macintyre 2014 **NR**). However, additional nonprescribed opioids, alcohol and other nonopioid sedating medications (eg benzodiazepines and antidepressants) are known to contribute to opioid-related deaths when taken with prescribed opioids (Webster 2011b **Level IV**; Gomes 2011 **Level III-2**; Rintoul 2011 **Level IV**). As these are more accessible at home and their use is unsupervised, the risk of OIVI may be significantly increased at home compared to in hospital.

The time periods of greatest risk of OIVI occurrence being the day of and the night following surgery has implication for discharge of short-stay surgery patients (Lee 2013a **Level IV**); in children following tonsillectomy with or without adenoidectomy most clinically significant OIVI cases occurred within 2 d of the procedure (FDA 2012 **Level IV**).

Other risk factors for inpatient OIVI include sleep disordered breathing, fatigue, obesity and COPD (Macintyre 2011 **NR**, Lee 2013a **Level IV**) and, for chronic opioid users, a history of alcohol dependence (Gomes 2011 **Level III-2**) and increasing daily opioid dose (Gomes 2011 **Level III-2**; Bohnert 2011 **Level III-2**). These have presumed but unproven significance in patients discharged home postoperatively with opioids.

8.11.1.2 Patient falls

Those using opioids chronically for noncancer pain may be at greater risk of falling and requiring hospital admission than those not on opioid medication; the overall risk is greatest in wk 1 following initial prescription and decreases over time (Rolita 2013 **Level III-2**). Patients newly treated with opioids for any reason may similarly be at increased risk of falling; in an analysis of fall-injured patients (n=167,257) 4.5% had a first opioid prescription within 28 d prior to their fall (Soderberg 2013 **Level III-2**). Fall risk was greatest in younger patients (18–29 y) and decreased with increasing time from initial prescription. The mechanism by which prescribed opioids may trigger injurious falls is unclear; it may be directly due to adverse opioid effects (sedation, dizziness or cognitive impairment), underlying patient risk factors or comorbidities that make the prescription of opioids more likely, or increase of risky activities which the opioid analgesic effect allows (Soderberg 2013 **Level III-2**).

8.11.1.3 Impaired driving

The prevalence of testing positive for opioid drugs in drivers who die in motor vehicle accidents in the USA seems to be increasing. In 1999–2002, 2.2% of men and 4.3% of women drivers who died in road traffic accidents in the USA tested positive for opioids (Brady 2014 **Level IV**). In 2007–2010 prevalence had increased to 4.0 and 7.6% respectively. This increase has occurred over the same period of time as the increase in opioid use (both acute and chronic) in the USA community.

Opioids are known to cause sedation, to diminish reaction times, reflexes and coordination and to decrease the ability to concentrate (Wilhelmi 2012 **Level IV**, SR of 58 studies, n unspecified). They may thus interfere with the ability to perform a complicated task such as driving. These effects are both subjectively and objectively evident when opioid naïve patients take medicinal opioids in commonly prescribed amounts, although some studies have found less significant objective than subjective impairment (Wilhelmi 2012 **Level IV**, SR of 58 studies, n unspecified).

The overall degree of driving impairment by prescription opioids was similar to that of a blood alcohol reading of 0.05–0.08 g/dL (EMCDDA 2012 **Level III-2**) or to cause a 2.2-fold increase over baseline in crash risk (when considered as one of a group of psychoactive drugs including benzodiazepines and antidepressants) (Li 2013 **Level III-2**). The driving risk is greatly magnified when opioids (illicit or prescribed) are combined with alcohol (EMCDDA 2012 **Level III-2**; Brady 2014 **Level IV**). No attempt was made in these analyses to distinguish between acute and chronic opioid use.

In chronic pain patients, it has been traditionally considered that the driving performance of patients on long-term stable opioids may not be negatively affected by their medication and they may not have an increased crash risk as tolerance develops (Wilhelmi 2012 **Level IV**, SR of 58 studies, n unspecified; Dassanayake 2011 **Level III-2**, SR of 10 studies [opioids], n unspecified). However, driving risk may be increased in the first few weeks following the initiation of a prescription opioid (Dassanayake 2011 **Level III-2**, SR of 10 studies [opioids], n unspecified) and may be dose dependent (Gomes 2011 **Level III-2**; EMCDDA 2012 **Level III-2**). Similarly, when patients on long-term opioids have their dose increased, their psychomotor impairment returns (Wilhelmi 2012 **Level VI**, SR of 32 studies, n unspecified). These findings may have implications for the discharge management of acute postoperative pain.

8.11.1.4 Risk of inducing long-term opioid use

Short-term opioid therapy may, in some patients, lead to longer-term opioid use (Steyaert 2013 **NR**). Up to 8% of patients continue to use opioid medication for months or even years following its postoperative initiation (Singh 2010 **Level IV**; Singh 2012 **Level III-3**; Singh 2014

Level III-3; Alam 2012a **Level III-2**; Carroll 2012 **Level III-2**; Clarke 2014 **Level III-2**). Factors other than the surgical procedure itself, including pre-existing anxiety and depression, have been shown to correlate with increased postoperative pain (Ip 2009 **Level IV**, SR of 48 studies, n=23,037). This may lead to increased acute postoperative analgesic consumption (Clarke 2014 **Level III-2**) and finally ongoing opioid use (Macintyre 2014; Carroll 2012 **Level III-2**; Singh 2010; Singh 2012; Singh 2014 **Level III-2**; Alam 2012a **Level III-2**).

Of 39,000 opioid naïve patients having major elective surgery, 3.1% showed prolonged opioid use after discharge (Clarke 2014 **Level III-2**). Risk factors for prolonged opioid use included: the type of surgical procedure, younger age (<85 compared with >86), lower household income, specific comorbidities (diabetes, heart failure, pulmonary disease) and preoperative use of specific drugs (benzodiazepines, SSRIs and ACE inhibitors). Preoperative prescription opioid use and depressive symptoms more accurately predicted opioid use 6 mth postoperatively than did the duration or severity of postoperative pain (Carroll 2012 **Level III-2**).

Prolonged opioid use following lower limb arthroplasty has been reported; 2.3% of patients at 2 y following total hip replacement (Singh 2010 **Level IV**) and 5.4% at 2 y and 5.9% at 5 y following total knee replacement (Singh 2014 **Level III-2**) were still using opioid medication that had been initiated postoperatively. Female sex, younger age (<60 y) and anxiety were predictive factors for opioid use after total knee joint replacement (Singh 2012 **Level III-2**).

Early discharge after day-stay surgery with a prescription of opioids or NSAIDs carries an increased risk of subsequent long-term use of these analgesics. In a population of 391,139 opioid-naïve patients >65 y having short-stay surgery, patients receiving an opioid prescription within the 7 d after surgery were more likely to become long-term opioid users within 1 y in comparison to those without a prescription (OR 1.44; 95%CI 1.39 to 1.50) (Alam 2012a **Level IV**). Discharge NSAID prescriptions were also more likely to be associated with persistent NSAID use (OR 3.74; 95%CI 3.27 to 4.28).

8.11.1.5 Risk of diversion and abuse

The past decade has seen a growing awareness of prescription opioid abuse in the general population and among injecting drug users (Fischer 2010 **NR**; Degenhardt 2013 **Level IV**). This has been described by some as a major public health problem and associated with prescription opioid-related overdoses and deaths (Rintoul 2011 **Level IV**; CDC 2012**Level IV**). Unused opioids prescribed for postoperative pain are potentially a large reservoir for opioid abuse, misuse and diversion. In the USA, one third of college students prescribed an analgesic for acute pain report diverting opioids to others (Arria 2011 **Level IV**).

Following urological surgery, 67% of those who filled their prescriptions for opioids had leftovers, which 91% planned to keep (Bates 2011 **Level IV**). After dermatological surgery, 35% of those prescribed an opioid did not use it at all and 55% of these planned to keep the leftover tablets (Harris 2013 **Level IV**). Following upper limb surgery, 31% of 245 patients used fewer than half of the opioid tablets prescribed with over 4,000 tablets in total unused (Rodgers 2012 **Level IV**).

This rate of "over-prescription" may be explained by difficulties in estimating the postoperative opioid analgesic requirements of patients following day surgery or short inpatient stay. However, even when opioid requirements have been established, excessive prescription commonly occurs; 19% of postoperative patients prescribed oxycodone for discharge from a large Australian teaching hospital had not needed any opioid in the 24 h prior to discharge (Platis 2011 **Level IV**).

Patients who retain unused tablets are willing to share them. After receiving opioid prescriptions for an acute episode, 64% of patients kept unused opioids and 34% shared them with others (Lewis 2014 **Level IV**). Sharing opioid medication may expose the user to an increased risk of adverse reaction or drug interaction as there is often no assessment made of the underlying cause of the opioid requirement and no advice given by a doctor or pharmacist (Ellis 2009 **NR;** Ward 2011 **Level IV**).

Hoarded medication may also be a source of opioids for nonmedical use (Macintyre 2014 **NR**). The most common source of prescription opioids for nonmedical use in both the USA

(Jones 2014 **Level IV**) and Australia (Belcher 2014 **Level IV**) is a friend or relative, with no charge incurred. How much of this hoarded opioid pool is derived from opioid prescription for acute pain is difficult to estimate but a recent analysis of deaths related to opioid toxicity in Canada found that the source of opioid in 6.6% of cases was acute pain prescription (Madadi 2013 **Level IV**).

A small pilot study has shown that patients discharged from EDs with opioid medication do not safely store and dispose of these medicines (Tanabe 2012 **Level IV**).

Patients should be advised of these risks and also of the safe way to dispose of unused opioid medicines, which, in Australia, is to return them to a pharmacy (Macintyre 2014 **NR**). A clear plan for analgesia reduction after discharge and robust systems for communication with usual treating practitioners in the community is essential and will assist in avoiding unintended dose escalation (Huxtable 2011 **NR;** Quinlan 2012 **NR;** Schug 2012 **NR**).

Pain specialists and clinics have a role in assisting with transition of these patients to the community postoperatively and future developments may include transitional pain services for those discharged home with high dose opioids (De Pinto 2012 **NR**).

8.11.2 Selection of opioid for discharge medication

There is no available evidence to suggest that any one oral opioid or formulation (immediate or slow-release) is best for the management of pain on discharge following surgery (Macintyre 2014 **NR**), however IR formulations are recommended (Thorson D 2014 **GL**). There is equally no evidence that any opioid has greater abuse potential, although much has been written about the "like-ability" of the available prescription opioids (Cicero 2013 **Level IV**; Butler 2010 **Level IV**).

In the USA, hydrocodone, codeine and oxycodone have been the most commonly abused prescription opioids (Johnston 2013 **Level IV**), while in Australia these are methadone, morphine and oxycodone (Stafford 2013 **Level IV**). Overdose patterns involving prescription opioids also vary by country and possibly prescribing pattern (Hakkinen 2012 **Level IV**). The most common prescription opioids involved in overdose are oxycodone, morphine and codeine in Canada (Madadi 2013 **Level IV**), methadone, oxycodone and morphine in Australia (NCIS 2014 **Level IV**) and codeine, buprenorphine and tramadol in Finland (Hakkinen 2012 **Level IV**).

Abuse deterrent opioid formulations have and are being developed; these are primarily aimed at reducing the risk of nonoral intake (parenteral, snorting, etc) and are based on using physical barriers, the inclusion of an opioid antagonist or an aversive agent, or prodrug formulations (Raffa 2012 **NR**).

8.11.3 Identification of patients at risk

Many screening tools have been proposed to predict the risk of opioid misuse before opioid prescription in chronic pain patients (Passik 2008 **NR;** Chou 2009 **Level IV**, SR of 16 studies, n unspecified) and are often recommended and utilised in the chronic pain setting (Webster 2011a **NR**).

A significant proportion of patients who ultimately seek medical help for opioid addiction were first prescribed opioids for the management of acute pain. Of these, many had a previous history of alcohol, other drug abuse or other "red flags" in their history at first presentation (Webster 2011a **NR**). Thus the use of screening tools may be advisable prior to postoperative discharge opioid prescription, although any tool used routinely would have to conform to the time restraints of acute pain medicine (Macintyre 2014 **NR**).

Even if a formal risk tool is used it has been recommended that prescribing physicians use a "universal precautions" approach to opioid prescribing, as most risk assessment tools rely to some degree on self-assessment and none are fail safe (Gourlay 2005 **NR;** Macintyre 2014 **NR**). Universal precautions have been described as a "systematic set of procedures and tools that aid the physician in gathering relevant information, help the physician interpret the information collected and provide a pathway for responsible decisions" (Webster 2010 **NR**). These include risk assessment (as above), appropriate opioid dose, limited prescribing and duration of therapy (which should be communicated clearly to the patient), monitoring of

effect and compliance (close follow-up of at risk patients after discharge) and having a plan should opioid abuse, misuse or diversion be suspected (Passik 2009 **NR;** Webster 2010 **NR;** Thorson D 2014 **GL**).

Key messages

1. Short-term opioid therapy may lead to long-term opioid use (**N**) (**Level III-2**).
2. Recent introduction of opioid therapy may increase the risk of falls (**N**) (**Level III-2**).
3. Recent introduction of opioid therapy or recent dose escalation may impair driving (**N**) (**Level III-2**).
4. Many patients who retain unused opioid tablets are willing to share them with others (**N**) (**Level III-2**).
5. The most common source of prescription opioids for nonmedical use is a friend or relative (**N**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Unused opioids prescribed for postoperative pain are potentially a large reservoir for opioid abuse, misuse and diversion (**N**).

☑ Screening tools used to assess the risk of opioid misuse prior to opioid prescription in chronic pain patients may be used before prescribing discharge opioids (**N**).

☑ A "universal precautions" approach for opioid prescribing should be used in the setting of prescribing discharge medications (**N**).

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9. THE PAEDIATRIC PATIENT

9.1 Developmental neurobiology of pain

The majority of information on this topic to date is experimental (mostly rodent) data, which presents translational challenges to the interpretation of developmental changes in the neurodevelopmental pathways of the human embryo-fetus-infant. In embryonic life, nociceptive pathways develop under the influence of several trophic signalling pathways eg nerve growth factor and tyrosine kinase receptors (NGF-TrK) and (generally non-noxious) afferent input (Li 2011a **BS**; Lewin 2014 **NR BS**). Growth factor signalling systems are extremely important in the developing cytoarchitecture of nociceptor pathways and remain well conserved across species (Wheeler 2014 **BS**). Interspecies differences appear to stem from divergent roles played by (downstream) transcription factors (Guo 2011 **BS**).

By 7 wk gestation, human primary afferent nerve fibres that innervate skin and projection neurones from the dorsal horn of the spinal cord reach the thalamus. Activity-dependent maturation is a cornerstone of development and, in early gestation, intrinsically active neurons (endogenous pacemaker cells) contribute significantly to this (Li 2011b **BS**). Ascending pathways are present and functional by 25 wk gestation. Central neural projections and synaptic connections continue to mature and, from 26 wk gestation, peripheral noxious stimuli can elicit responses in the increasingly layered thalamic and cortical neurons (Kostovic 2010 **NR BS**). Postnatal tuning of the nociceptive pathways requires continued somatosensory (again non-noxious) input at a spinal level. The development of inhibitory pathways within nociceptor systems appears somewhat later and involves a developmentally regulated alteration in the synaptic effects of glycine and GABA (Rajalu 2009 **BS**; Hathway 2012 **BS**). Little is known about the trophic factors and essential synaptic inputs that guide the development of these pathways. Modulation of activity within these pathways by tissue injury and inflammation appears to be mediated through glutaminergic signalling in an age-dependent fashion (Baccei 2010 **BS**).

Anatomical and electrophysiological evidence confirms that biological systems necessary for nociception are intact and functional from 26 wk gestation. This is clearly confirmed during fetoscopy and medical interventions *in utero*. Despite this, inferences regarding fetal pain are limited. Our understanding of the conscious, cognitive, affective and evaluative experience of pain during fetal and late gestational life remains conjectural (Derbyshire 2006 **NR**). In contrast to the protected environment *in utero* (in which the fetus is buffered from environmental stimuli and continuously exposed to the anaesthetic effects of progestogens), postnatal life brings intense afferent stimulation and wakefulness (Lagercrantz 2009 **Level IV**). With this, comes the possibility of psychological processes involving content derived from the environment (objects, people and symbols) (Derbyshire 2006 **NR**). Following birth, the neural pathways required for nociception are functional and cortical responses to noxious stimuli such as skin lancing can be demonstrated in even the most premature neonate (Slater 2006 **Level IV**). However, as significant functional and structural changes occur in nociceptive pathways during the postnatal period (Hirschfeld 2012 **Level IV**), the pattern of activity evoked by tissue trauma also changes (Fitzgerald 2009 **Level IV**). The expression of a number of molecules and channels involved in nociception are developmentally regulated, there are changes in the distribution and density of many important receptors and the levels and effects of several neurotransmitters alter significantly during early life (Fitzgerald 2005 **NR**). Important signalling systems in early development include the ephrin-receptor tyrosine kinase system which influences cell movements (Wilkinson 2001 **NR**).

Rodent studies confirm that C-fibre polymodal nociceptors are mature in their pattern of firing at stages equivalent to term gestation in humans. They are capable of being activated in the periphery by exogenous stimuli, although their central synaptic connections in the dorsal horn are initially immature. However, “wind-up” can be produced by relatively low-intensity A-fibre (rather than C-fibre) stimulation, as A-beta fibres initially extend up into laminae I and II and only withdraw once C fibres have matured. This overlap means there is less discrimination between noxious and non-noxious stimuli and, as the receptive fields of dorsal horn neurones

are large, peripheral stimuli can excite a greater number of central neurones. In addition, descending inhibitory pathways and inhibitory networks in the dorsal horn are not fully mature in early development. Therefore, rather than neonates being less sensitive to painful stimuli as once thought, the relative excess of excitatory mechanisms and delayed maturation of inhibitory mechanisms produce more generalised and exaggerated reflex responses to lower intensity stimuli during early development (Fitzgerald 2005 **NR**). Although the underlying mechanisms may differ, nociceptive pathways can be sensitised by painful stimuli in early life, as demonstrated by a reduction in reflex thresholds in neonates following repeated heel lance (Fitzgerald 1988 **Level IV**) and infants following abdominal surgery (Andrews 2002 **Level IV**).

Factors affecting the pharmacokinetic profile of analgesic drugs (body water and fat composition, plasma protein binding, hepatic metabolism and renal function) change rapidly during the first weeks of life (Funk 2012 **NR**). Postnatal changes in the pharmacokinetic profile of a number of analgesic drugs (eg morphine and paracetamol [acetaminophen]) resulted in significant age-related changes in dose requirements during infancy and childhood (Bouwmeester 2004 **NR**; Palmer 2008 **PK**; Prins 2008 **PK**; Allegaert 2014 **NR**). In addition, changes in nociceptive processing may have significant effects on the pharmacodynamic response to analgesics in early life (Walker 2008 **NR**). Therefore, developmental age and not just weight should be considered when calculating analgesic dosing (Allegaert 2014 **NR**) (see also Section 9.4 for pharmacokinetics of analgesic drugs). Laboratory studies have demonstrated postnatal changes in the mechanism of action, analgesic efficacy and adverse-effect profile of analgesics that can inform subsequent clinical trials (Nandi 2005 **NR**; Walker 2008 **NR**; Fitzgerald 2009 **NR**). In addition, prolonged reductions in synaptic activity by general anaesthetics and analgesics can produce unexpected neurotoxic effects, such as apoptosis, in the developing nervous system, although the clinical significance of these findings requires further research (Mellon 2007 **NR**).

Key messages

1. Following birth, even the most premature neonate responds to nociceptive stimuli (**S**) (**Level IV**).
2. In early development, more generalised reflex nociceptive responses occur in response to lower intensity stimuli (**S**) (**Level IV**).

9.2 Consequences of early pain and injury

9.2.1 Early neurodevelopmental consequences

Significant reorganisation of synaptic connections occurs in the postnatal period. Activity within sensory pathways is required for normal development but abnormal or excessive activity related to pain and injury during the neonatal period may alter normal development and produce persistent changes in sensitivity that outlast the injury (Fitzgerald 2009 **NR**; Walker 2009 **Level III-2**; Walker 2013 **NR**).

However, the effect of pain in the neonatal period on neurodevelopment and the child or adult's later pain experience is difficult to quantify. In researching this there are many factors that may confound the determination of the contribution of early pain to altered neurodevelopment and the extent to which this can be modulated by interventions. The likely patient confounders include sex, birth weight, gestational age at birth and at the time of insult, intercurrent illness type and severity (including hypotension), and the extent of tissue damage (Brummelte 2012 **Level IV**). While the treatment confounders that may influence neurodevelopment include type, dose and duration of analgesia (including opioids and benzodiazepines), other drugs administered such as dexamethasone (for chronic lung disease) and anaesthetic agents (Davidson 2013 **NR**), as well as the neonatal unit's practices (which vary) and the quality of neonatal intensive care (see below: Montirosso 2012 **Level IV**), which may also be confounding factors. An additional confounder is the limited ability to quantify the neonate's pain experience in the intensive care setting; some studies have used the number of skin-breaking procedures (including blood tests, heel lances, vascular access and surgery)

received by the neonate as a surrogate measure to then investigate impact on adverse outcomes.

In clinical studies of ex-preterm neonates, neuroimaging studies done at term age equivalent showed greater pain exposure was associated with structural changes. White matter and subcortical grey matter maturation was reduced in infants born at 24–32 wk (related to the number of heel lances and single but not multiple surgical interventions), as assessed by diffusion tension and magnetic resonance spectroscopy (Brummelte 2012 **Level IV**). In a group of similarly premature infants, both neonatal pain and greater early illness severity (measured by the Score for Acute Neonatal Physiology–II) were associated with delayed microstructural development of the corticospinal tract (Zwicker 2013 **Level IV**).

Among extremely preterm infants (born at <30 wk gestation), those exposed to surgery (and anaesthesia) had greater white matter injury and smaller total brain volumes, particularly smaller deep nuclear grey matter volume (Filan 2012 **Level III-3**). In those born at <29 wk gestation, clinical outcomes associated with greater pain exposure were delayed growth with lower body weight at 32 wk (Vinall 2012 **Level IV**) and poorer cognitive and motor function at 8 and 18 mth (Grunau 2009 **Level III-2**). No difference was seen in mental development scores at 2 y in very ex-premature patients who had surgery vs no surgery, following adjustment for confounders (Filan 2012 **Level III-3**).

9.2.2 Longer term consequences of early pain and injury

Longer-term consequences of early pain and injury have been well described, particularly in rodent models and ex-neonatal intensive care unit (NICU) populations. In laboratory studies, the degree of long-term change varies with the type and severity of injury (Fitzgerald 2009 **NR**). Inflammation, full thickness skin wounds and skin incision produce prolonged alterations in sensitivity and the response to future injury, in the absence of any visible persistent peripheral injury. By contrast, allodynia following nerve injury is less apparent in early life (Howard 2005 **BS**; Moss 2007 **BS**). These findings are of considerable importance, as pain and injury in neonates may have effects on nociceptive processing that differ in mechanism and duration from those experienced by older children and adults.

Neonatal pain results in an increased response to future painful stimuli months to years after the initial insult. Surgery (neonatal circumcision) without anaesthesia or analgesia is associated with an increased behavioural response during immunisation at 4–6 mth when compared to uncircumcised infants (Taddio 1995 **Level III-2**). Increased perioperative analgesia requirements and pain scores occurred when subsequent surgery was performed months later in the same dermatome, compared to children who had no previous surgery (Peters 2005 **Level IV**).

Ex-preterm preschool children show alterations in pain-related behaviour such as increased somatisation (Grunau 1994 **Level IV**) and ex-NICU school-aged children had higher levels of pain-related catastrophisation (Hohmeister 2009 **Level III-2**). In ex-NICU preterm children and adolescents, thermal pain thresholds were reduced at age 9–14 y (Hermann 2006 **Level III-2**), and at 11 y in ex-extreme preterm children born at <26 wk gestation (along with reduced thermal and mechanical sensitivity around their neonatal thoracotomy scars) (Walker 2009 **Level III-2**). Increased gain in pain pathway signalling was seen at 11–16 y on fMRI study in response to painful heat stimulus (Hohmeister 2010 **Level III-2**) and responses were enhanced to noxious stimuli (dolorimetry and number of tender points) compared with term peers at age 12–18 y, more so in girls (Buskila 2003 **Level III-2**). The clinical significance of these findings is uncertain.

A prospective cohort study of children born in 1958 investigated the association of chronic widespread pain in adulthood with "early trauma" (Jones 2009 **Level III-2**, n=7,571). It found no association between surgery in childhood before the age of 7 y (RR 1.0; 95%CI 0.9 to 1.1) but positive association for hospitalisation following a road traffic accident (RR 1.5; 95%CI 1.1 to 3.0). A later survey of this British cohort showed no increased risk of chronic widespread pain at 45 y in ex-premature adults (RR 1.26; 95%CI 0.95 to 1.67) (Littlejohn 2012 **Level III-2**, n=8,572).

9.2.3 Modification by analgesic intervention

Importantly analgesia at the time of the initial painful stimulus may modulate long-term adverse effects. The behavioural response to immunisation of male infants was reduced in those who had neonatal circumcision with local anaesthetic applied prior to surgery, compared to the neonates who had no local anaesthetic (Taddio 1995 **Level III-2**). Infants undergoing surgery in the neonatal period who received morphine did not show any increase in response to later immunisation compared to infants without significant previous pain experience (Peters 2003 **Level III-2**). The quality of pain management in the NICU setting may also be important. Very preterm infants cared for in NICUs with high-quality infant pain management (ie use of pharmacological and nonpharmacological treatments for procedural pain, use of pain assessment tools and guidelines for preventing and treating pain) had better neurobehavioural outcomes compared with low-quality scoring NICUs (Montirosso 2012 **Level IV**).

Further research is required to determine the most developmentally appropriate and effective analgesia regimens for modulating the effects of early pain and injury.

Key messages

1. Pain and injury in early life cause structural changes in cortical and subcortical pathways and are associated with alteration in somatosensory thresholds in later life (**S**) (**Level III-2**).
2. Analgesia may modulate the long-term effects of pain and injury in early life but more information is required to determine the optimal dosing and type of agents to avoid negative impact of the pharmacological intervention itself (**N**) (**Level III-2**).
3. Improving quality of infant pain management delivery in neonatal intensive care (including pharmacological and nonpharmacological interventions) may result in improved neurodevelopmental outcomes (**N**) (**Level III-2**).

9.3 Paediatric pain assessment

Pain assessment is a prerequisite to optimal pain management in children and should involve a clinical interview with the child and/or their parent/carer, physical assessment and use of an age- and context-appropriate pain intensity measurement tool (Howard 2008a **NR**). However, pain in hospitalised children is often assessed infrequently (Taylor 2008 **Level IV**; Twycross 2007 **Level IV**; Johnston 2007 **Level III-1**). Improvements in pain management and in patient, parent and staff satisfaction have been associated with regular assessment and measurement of pain (Treadwell 2002 **Level IV**; Deindl 2013 **Level IV**). Adoption of written guidelines or pain management algorithms improved both assessment and management of pain in neonates and children (Gharavi 2007 **Level IV**; Falanga 2006 **Level IV**). As in adults, other domains of pain (eg location, quality) and the multidimensional nature of the pain experience (eg concomitant emotional distress, coping style of the child, previous pain experience) and parental expectations (Liossi 2007 **Level IV**) should be incorporated into overall assessment. Clinical trials have focussed on assessment of pain intensity and rescue analgesic use. Further evaluation and validation of tools for measurement of global satisfaction, adverse effects, assessment of the emotional and financial impact and physical recovery following paediatric acute pain are required (Berde 2012 **NR**; McGrath 2008 **GL**).

Verbal self-report is considered to be the best measure of pain in adults. Use of a child's self-report is desirable but it is not always possible as their understanding of pain and ability to describe it changes with age. Therefore, the measurement tools employed must be appropriate to the developmental stage. Examples of acute pain measurement tools are listed in Tables 9.1 to 9.4. The tools can be unidimensional, using only behavioural indicators (on single or multiple domains), or multidimensional combining behavioural, physiological or contextual factors. Beyond the use of these tools, the pain assessment process can be considered a complex social transaction with multiple factors contributing to the child's pain experience, its expression, subsequent interpretation and response (Voepel-Lewis 2012 **NR**).

9.3.1 Pain assessment in neonates

Over 40 scales have been developed for neonates and infants, encompassing a number of surrogate measures (eg physical signs such as increased heart rate) or behavioural responses (eg facial characteristics and cry). Choice of the most appropriate tool depends on contextual factors (the age of the infant, health status), the stimulus (eg procedural or postoperative pain and whether repeated acute, also termed "persistent", pain) and the purpose of the measurement (eg clinical care or research). Table 9.1 lists several uni and multidimensional scales used in neonates. A detailed review is published (Lee 2014 **NR**), with recent research focused on objective measurement devices (van Dijk 2012 **NR**; Holsti 2011 **NR**).

9.3.1.1 Physiological measures

Changes in physiological parameters associated with procedural interventions are assumed to indicate the presence of pain, including increases in heart rate, respiratory rate, blood pressure, intracranial pressure, cerebral blood flow and palmar sweating; and decreases in oxygen saturation, transcutaneous CO_2 tension and vagal tone (Cong 2013 **NR**). As these changes are reduced by analgesia they are useful surrogate outcome measures of pain but, as their sensitivity and specificity are also influenced by concurrent clinical conditions (eg heart rate increases due to sepsis) and other factors (eg distress, environment, movement), they should be used in conjunction with other behavioural measures (Cong 2013 **NR**).

Researchers have pursued the use of physiological parameters as objective measures of pain particularly for premature neonates (van Dijk 2012 **NR**; Holsti 2011 **NR**).

Heart rate variability analyses the R-R interval as a noninvasive marker of autonomic sinoatrial node input. It decreases during procedures (Padhye 2009 **Level IV**) and with postoperative pain (Faye 2010 **Level IV**). This is in contrast to changes seen in adults with experimentally induced pain where an increase in heart rate variability generally occurs (Koenig 2013 **Level IV SR** [PRISMA], 20 studies, n unspecified).

Skin conductance measures palmar/plantar stress-induced sweating electrically. It is affected by movement artefact, gestational age, skin temperature and, counterintuitively, can be increased following oral glucose (Munsters 2012 **Level IV**). Skin conductance measurement may be a useful adjunct in ventilated, sedated, near-term neonates (Karpe 2013 **Level IV**).

Near infrared spectroscopy (NIRS) measures regional cerebral blood flow changes in the somatosensory cortex, contralateral to the side receiving a painful stimulus. NIRS failed to correlate with FLACC scores (Ranger 2013 **Level IV**), although it did previously correlate with Premature Infant Pain Profile (PIPP) scores (r=0.57), particularly the facial expressions component (r=0.74) (Slater 2008 **Level IV**). Confounders include gestational age, activation of nearby motor cortex and sleep-wake cycle. Of note, one third of infants showed NIRS responses without facial changes during some procedures (Slater 2008 **Level IV**).

Scalp electroencephalogram (EEG) is used to map maturation of tactile and nociceptive responses in the developing brain — from 28 wk gestation nonspecific neural bursts transition to specific somatosensory tactile and nociceptive potentials at 35–37 wk (Fabrizi 2011 **Level IV**). The same authors assessed oral sucrose as reducing PIPP score but not altering cortical nociceptive activity to heel lance (Slater 2010 **Level II**, n=59, JS 5), controversially concluding that sucrose may not be an effective analgesic.

Markers of stress have been measured in blood and urine postoperatively (Franck 2011 **Level IV**) and saliva peri-heel stick (Shibata 2013 **Level IV**) but are not candidates to assist acute pain management. An integrated system (NIRS, EEG, ECG, electromyelograph [EMG], combined with physiological and behavioural indices) has shown reliable and reproducible measurements of noxious stimulation (Worley 2012 **Level IV**). This expensive system may feasibly assist bedside tool validation.

9.3.1.2 Behavioural measures

Noxious stimuli produce a series of behavioural responses in neonates and infants that can be used as surrogate measures of pain (Chorney 2014 **NR**) including crying, changes in facial

activity, movement of torso and limbs, consolability and sleep state. Crying can be described in terms of its presence or absence, duration, amplitude or pitch. Up to 20% of preterm and some acutely ill infants do not cry or cry inaudibly during heel stick (Johnston 1999 **Level IV**).

Facial expression in response to pain is widely studied and forms part of a number of pain scales, for premature neonates up to school-aged children (Schiavenato 2012 **Level IV**) (see Tables 9.1 to 9.3). Video recordings permit recognition of the commonalities in facial pain expression and intervals can be applied for objective development of faces pain scales' graphic depictions (Schiavenato 2012 **Level IV**). In neonatal intensive care, facial actions were more reliable than physiological measures for evaluating pain responses (Stevens 2007a **Level IV**) but may be dampened in preterm neonates (Holsti 2007 **Level IV**; Slater 2008 **Level IV**).

Contextual influences

The specificity and sensitivity of the behavioural responses can be influenced by a number of contextual factors (Sellam 2011 **Level IV SR**, 23 studies, n=1,649). Pain can be affected by behavioural state (awake, asleep, activity prior to a stimulus), other states of distress (eg hunger and fatigue), age (postmenstrual and postnatal) and neuromuscular developmental status. Previous pain exposure and handling (Holsti 2006 **Level IV**) alters both behavioural and physiological responses eg infants experiencing higher numbers of procedures have reduced facial expression in response to pain, reduced brain maturation (Brummelte 2012 **Level IV**; Ranger 2013 **Level IV)** and long-term alteration of pain pathway processing on MRI (Hohmeister 2010 **Level III-3**). Female neonates, both premature and at term, show more facial actions than males. In most studies, severity of illness or neurological impairment is not associated with altered pain responses. Health providers' knowledge and attitude affect scoring and provision of pain relief (Akuma 2012 **Level IV**).

The reliability and validity of behavioural measures is best established for procedural interventions such as heel stick and many assessment tools have not been rigorously evaluated. The PIPP (Stevens 2010 **Level IV SR**, 62 studies, n=3,158) and COMFORT scales are the best validated and most widely used (McGrath 2008 **NR**).

The following are recommended (Howard 2008a **NR**; Cong 2013 **NR**; Lee 2014 **NR**) (see Tables 9.1 and 9.2, which also contain all relevant references):

- acute procedural pain — PIPP; Crying, Requires oxygen, Increased vital signs, Expression, Sleeplessness (CRIES); Neonatal Facial Coding Scale (NFCS); Neonatal Pain, Agitation and Sedation Scale (N-PASS);
- postoperative pain — PIPP; CRIES; N-PASS;
- intensive care — COMFORT; COMFORTneo; COMFORT B (for prolonged pain, a term applied for intensive care patients having repeated acute pain exposures); Échelle Douleur Inconfort Nouveau-Né (EDIN) (Debillon 2001 **Level IV**); Faceless Acute Neonatal Pain Scale (FANS) (when facial expression is concealed eg with nasal continuous positive airway pressure) (Milesi 2010 **Level IV**).

9.3.2 Observational and behavioural measures in infants and children

Many scales incorporate both physiological and behavioural parameters to determine an overall pain score and may result in more comprehensive measurement (Franck 2000 **NR**; Lee 2014 **NR**; Chorney 2014 **NR**). Some examples are included in Table 9.2 but a wider range of measures, their strengths and limitations and issues of testing reliability and validity have been reviewed (Johnston 2003 **NR**; von Baeyer 2007 **Level IV SR**, 129 studies, n unspecified; McGrath 2008 **NR**; van Dijk 2012 **NR**; Lee 2014 **NR**; Chorney 2014 **NR**). In infants and young children, behavioural items that predicted analgesic demand in the postoperative period were crying, facial expression, posture of the trunk and legs and motor restlessness but physiological variables were unreliable (Buttner 2000 **Level III-2**).

There is still no single gold standard for pain assessment as requirements vary with the age and developmental stage of the child, the type of pain (eg procedural vs postoperative), and the context (eg clinical utility vs research reliability). Based on current data the following

observational/behavioural measurement tools were recommended for pain measurement in infants ≥1 y (McGrath 2008 **NR**), children and adolescents (von Baeyer 2007 **Level IV SR**, 129 studies, n unspecified; Chorney 2014 **NR**) (see also Table 9.2):

- acute procedural pain — FLACC and Children's Hospital of Eastern Ontario Pain Scale (CHEOPS);
- postoperative pain — FLACC;
- postoperative pain managed by parents at home — Parents Postoperative Pain Measure (PPPM); and
- intensive care — COMFORT & COMFORT B scales.

9.3.3 Self-report in children and adolescents

Self-report of pain is preferred when feasible, and is usually possible by 4 y of age, dependent upon the child's cognitive and emotional maturity. Scales for self-report need to consider the child's age and ability to differentiate intensity levels and separate the emotional from the physical components of pain (von Baeyer 2014 **NR**) (see Table 9.3). It is important that a measurement tool be used regularly and uniformly within each centre as staff familiarity and ease of use are major factors in the successful implementation of a pain management strategy (von Baeyer 2006 **NR**). At 4–5 y of age, children can differentiate "more", "less" or "the same" and can use a Faces Pain Scale (FPS) (Figure 9.1) if it is explained appropriately and is relatively simple with a limited number of options. At this age, children have some capacity to appraise current pain and match it to previous experience but they are more likely to choose the extremes of the scale (von Baeyer 2009a **NR**; Hicks 2001 **Level IV**). In scales anchored with smiling or tearful faces, pain may be confused with other emotional states such as happiness, sadness or anxiety (Tomlinson 2010 **Level IV SR**, 127 studies, n=17,372). Reducing the number of faces from six to three (low, medium, high hurt) improved the performance of the scale in children aged 3–4 y (von Baeyer 2013 **Level IV**).

Between ages 7 and 10 y, children develop skills with measurement, classification and seriation (ie putting things in ascending or descending order). The upper end of the scale is less static than in adults as it will change with the individual child's ability to objectify, label and remember previous pain experiences (Gaffney 2003 **NR**; von Baeyer 2014 **NR**). It is not until 10–12 y of age that children can clearly discriminate the sensory intensity and the affective emotional components of pain and report them independently (McGrath 1996 **Level III-2**). Verbally competent children aged 12 y and above can understand and use the MPQ (Gaffney 2003 **NR**).

Of over thirty self-report scales, only six have well-established evidence of reliability and validity for acute pain assessment in children (>3 y) and adolescents — Pieces of Hurt tool (scored 0–4); FPS (scored 0–6); Faces Pain Scale-Revised (FPS-R) (0–10); Oucher pain scale (0–10); and Wong-Baker Faces Pain Rating Scale (WBFPRS) (0–10) and VAS (0–100 mm) (Stinson 2006 **Level III-1 SR**, 9 studies, n=1,415; McGrath 2008 **NR**; von Baeyer 2014 **NR**). One scale cannot be recommended over another as debate continues as to any agreement between these scales (Cook 2013 **NR**; Sanchez-Rodriguez 2012 **NR**).

There are fourteen Faces pain scales of which four have undergone extensive psychometric testing: FPS, FPS-R, Oucher & WBFPRS (Tomlinson 2010 **Level IV SR**, 127 studies, n=13,388). When given the choice, children preferred faces scales in general and the WBFRS was preferred among these but its use of smiling and crying anchor faces may lead to confounding with affect. FPS-R was recommended for research purposes. An electronic version of the FPS-R has been validated and was preferred by children (Wood 2011 **Level III-1**). FPS-R has also been validated in the ED setting (Tsze 2013 **Level IV**) and may perform better in this setting than WBFPRS (Garra 2013 **Level IV**). The French Evaluation ENfant DOuLeur (EVENDOL) tool for children aged 0–7 y was developed to address the need in EDs for a single pain tool that spanned the ages; it has been translated to English (Fournier-Charriere 2012 **Level IV**).

Although chronological age may not always be an accurate indicator of developmental stage, the following general age ranges are suggested (von Baeyer 2014 **NR**):

- 3–4 y — Pieces of Hurt (Poker Chip) tool;
- 4–12 y —FPS-R; and
- >8 y — 0–100 VAS.

Suggested VAS cut-offs for children and adolescents are 35 mm for mild pain and 60 mm for severe pain (Hirschfeld 2013 **Level IV**). Pain intensity measurements within 12 mm on the paper VAS may be considered the same (Bailey 2012 **Level IV**).

The NRS used for adults has been used in the paediatric setting but criticised for its limited psychometric evaluation (McGrath 2008 **NR**). Recently this has been addressed through correlation with VAS and FPS-R in children >7 y (von Baeyer 2009b **NR**; Miro 2009 **Level IV**; Page 2012 **Level IV SR**, 129 studies, n unspecified). The NRS has shown good correlation in the recovery room between children aged 4–16 y, nurse and parent (Brahmbhatt 2012 **Level IV**).

The validity of the current gold standard of asking and documenting of pain scores is being questioned, due to the inherent subjective nature of self-report (von Baeyer 2014 **NR**; Berde 2012 **NR**). As is occurring in paediatric chronic pain assessment (Varni 2010 **Level IV**), acute paediatric pain measurement may warrant inclusion of measures of self and observed functional impairment (eg post laparatomy the child is remaining in bed vs able to sit out in chair vs attend ward play room or in-hospital school) combined with rescue analgesic use. This is particularly relevant when self-reported pain scores are either high or low and conflict with the clinical context and the paediatric clinicians' observations (von Baeyer 2014 **NR**).

9.3.4 Children with cognitive impairment or intellectual disability

Most children with intellectual disability (ID) probably experience pain in a similar way to their peers but there are some examples of disorder-specific alterations in pain perception eg the higher pain and temperature threshold seen in patients with Prader-Willi-Syndrome (de Knegt 2011 **NR**). In addition, children with ID and/or communication difficulties may experience more pain episodes than other children because of their associated complex medical disorders, physical comorbidities and increased need for procedures (Breau 2009 **NR**).

Assessment of pain is difficult in this cohort and can contribute to inadequate analgesia. Neonates at risk for neurological impairment required more procedural interventions in intensive care but received less analgesia (Stevens 2003 **Level III-2**) and may be perceived as being less responsive to painful stimuli (Breau 2006 **Level III-2**; Stevens 2007b **Level IV**). Older children with cognitive impairment received less analgesia during surgery but comparable amounts and types of analgesics as cognitively intact children postoperatively (Koh 2004 **Level III-2**; Long 2009 **Level III-3**; Valkenburg 2012 **Level III-3**) contrasting with the findings in an earlier series (Malviya 2001 **Level III-3**).

Self-report tools may not be reliable in those with mild to moderate ID (Benini 2004 **Level IV**). Specific tools have been developed for cognitively impaired children (Valkenburg 2010 **NR**) (see Table 9.4). Behaviours reported by caregivers to be associated with potentially painful stimuli, and that discriminate these from distressful or calm events, have been compiled in the revised Non-Communicating Children's Pain Checklist (NCCPC-R) for home (Breau 2002a **Level IV**) and postoperative use (NCCPC-PV) (Breau 2002b **Level IV**). Cut-off scores for NCCPC-PV were developed against VAS scores, with good interobserver reliability between primary care giver and the researcher, who had not met the child. It has been translated and validated in French, Swedish and German. The NCCPC scales have formed the basis of new recently validated adult tools — Chronic Pain Scale for Non-verbal Adults with Intellectual Disabilities (CPS-NAID) (24 items for persistent pain) and Non-Communicating Adult Pain Checklist (NCAPC) (18 items for acute/procedural pain) (Breau 2009 **NR**). The Paediatric Pain Profile (PPP) rates 20 behaviours to assess pain in children with severe neurological disability (Hunt 2004 **Level IV**). This scale has demonstrated potential for children with recurrent acute (persistent) pain at home. Salivary cortisol was not useful as a marker for pain assessment in this group (Hunt 2007 **Level IV**). A revised FLACC scale, incorporating specific descriptors and parent-

identified behaviours for individual children, has also been developed for cognitively impaired children (Malviya 2006a **Level IV**) and remains the easiest and most flexible tool to use in the acute hospital setting (Crosta 2014 **NR**). An Individualised Numeric Rating Scale (INRS) has been validated for pain assessment in individuals with ID, where carer proposed pain indicators are ranked on a 0–10 NRS scale. The bedside nurse INRS scoring correlated with the caregiver's assessment (Solodiuk 2010 **Level IV**).

Key messages

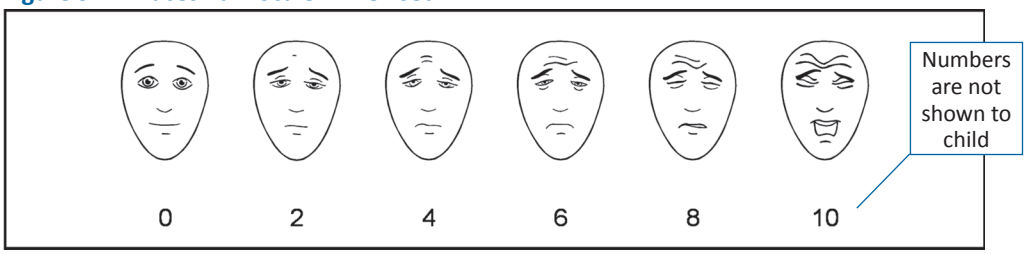
1. Pain measurement tools are available for children of all ages (**S**) (**Level IV** SR).
2. Paediatric pain measurement tools must be matched to the age and development of the child (**S**) (**Level IV** SR).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Pain assessment and measurement are important components of paediatric pain management (**U**).

☑ Pain measurement tools must be appropriate for the clinical context and be explained and used consistently (**Q**).

Figure 9.1 Faces Pain Scale — Revised



Note: The full-size version of the FPS-R, together with instructions for administration (available in many languages), are freely available for noncommercial clinical and research use from www.iasp-pain.org/FPSR.

Source: FPS-R; (Hicks 2001); adapted from (Bieri 1990).

Table 9.1 Acute pain intensity measurement tools — neonates

Scale	Indicators	Score	Utility
Unidimensional			
NFCS (Grunau 1987; Johnston 1993)	Brow bulge Deep nasolabial fold Eyes squeezed shut Open mouth Taut tongue Horizontal mouth stretch Vertical mouth stretch Pursing of lips Chin quiver Tongue protrusion	Presence or absence of action during discrete time intervals scored	Preterm to 4 mth Procedural pain

Scale	Indicators	Score	Utility
Multidimensional			
PIPP (Stevens 1996) PIPP-Revised (PIPP-R) (Stevens 2014)	Postmenstrual age Behavioural state Heart rate Oxygen saturation Brow bulge Eye squeeze Nasolabial furrow	Each scored on 4-point scale (0,1,2,3) 6 or less = minimal pain; >12 = moderate to severe pain In the revised form postmenstrual age and behavioural state points are only applied if other variables indicate pain.	Procedural pain preterm and term neonates Postoperative pain in term neonates
Neonatal Infant Pain Scale (NIPS) (Lawrence 1993)	Facial expression Cry Breathing patterns Arms Legs State of arousal	Each scored on 2 (0,1) or 3-point (0,1,2) scale; total score: 0–7	Preterm and term neonates; Procedural pain
CRIES (Krechel 1995)	Crying Requires oxygen for SaO_2 >95% Increased vital signs (heart rate/blood pressure) Expression Sleeplessness	Each scored on 3-point scale (0,1,2); total score: 0–15	32–60 wk Postoperative pain
N-PASS (Hummel 2008)	Crying/irritability Behavioural state Facial expression Extremities tone Vital signs (heart rate/blood pressure/SaO_2)	Each scored on 5-point scale (2,-1,0,1,2); Total score: -10 to +10 with minus scores reflecting responses if sedated Extra point added for prematurity <30 wk Score >3 indication for treatment	23–40 wk Postoperative pain Procedural pain Persistent pain Sedation level
EDIN (Debillon 2001)	Facial activity Body movement Quality of sleep Quality of contact with nurses Consolability	Each scored on 4-point scale (0,1,2,3); total score: 0–15 Treated if >7	25–36 wk Persistent pain

Scale	Indicators	Score	Utility
COMFORTneo Modified from COMFORT B (van Dijk 2009)	Alertness Calmness/agitation Respiratory response (ventilated) or crying (spontaneous ventilation) Body movement Facial tension Muscle tone	Each scored on 5-point scale (1–6); total score: 6–30 Score >14 indicating moderate-severe pain/ distress	24–42 wk Prolonged pain Sedation
FANS (Milesi 2010)	Acute discomfort Limb movements Vocal expression Heart rate variation	Each scored differently; total score: 0–10 Nonintubated but face not visible	30–35 wk Procedural Pain

Note: *Further details available in* Howard 2008a; Bandstra 2008; Cong 2013; Lee 2014.

Table 9.2 Composite scales for infants and children

Scale	Indicators	Score	Utility
CHEOPS (Chorney 2014)	Cry Facial expression Verbal expression Torso position Touch Leg position	Each scored as 0, 1, 2 or 3; total score 4–18	1–7 y Postoperative pain Procedural pain
FLACC (Merkel 1997)	Face Legs Activity Cry Consolability	Each scored on 3point scale (0,1,2); total score 0–10	Young children Postoperative pain
COMFORT scale (Ambuel 1992) COMFORT B scale (behavioural elements) (van Dijk 2000)	Alertness Calmness/agitation Respiratory response Physical movement Muscle tone Facial expression Mean arterial pressure Heart rate	Total score 8–40	Newborn to adolescent Distress in paediatric intensive care unit; Postoperative pain 0–3 y (van Dijk 2000) Downs Syndrome 0–3 y (Valkenburg 2011) Burns 0– 5 y (de Jong 2010) Post cardiac surgery in term infants (Franck 2011)

Further details available in Howard 2008a and Chorney 2014

Table 9.3 Self-report tools for children

Scale	Components	Anchors	Utility
Poker Chip Tool (Hester 1979)	4 chips = pieces of "hurt"	± white "no pain" chip; 1 chip = "a little hurt"; 4 chips = "most hurt you could ever have"	4–8 y
FPS-R (Hicks 2001)	6 graphically depicted faces	Neutral anchors	>4 y
WBFPRS (Wong 1988)	6 cartoon faces	Faces graded from smiling to tears	3–8 y Postoperative and procedural pain
Coloured Analogue Scale McGrath 1996	Modification of 10 cm horizontal VAS; scored 0–10 in 0.25 increments	Gradations in colour (white to dark red) and area (progressively wider tetragon); labels "no pain" to "most pain"	5 y and above

Note: Further details available in Howard 2008a and von Baeyer 2014

Table 9.4 Sample of observational pain assessment scales for intellectually disabled children

Scale	Components	Score	Utility
NCCPC-PV (Breau 2002b) NCCPC-R for home setting (Breau 2002a)	Facial Vocal Social Activity Body and limbs Physiological (Eating/sleeping in NCCPC-R)	27 items over 6 domains, rated 0–3 based on frequency of behaviour over a 10-min observation period; total score 0–81 score 6–10 mild pain >11/81 mod pain (≥3 on VAS) (NCCPC-R 30 items scored over a 2-h period: >7/90 indicates pain)	Nonverbal/ID 3–18 y Postoperative pain Familiarity with child not necessary Other languages
PPP (Hunt 2004)	20 typical pain behaviours selected based on interview and questionnaire	20 items scored 0–3 based on frequency of behaviour; total score 0–60 14/60 moderate pain	1–18 y Pain
Revised FLACC (Malviya 2006a)	Face Legs Activity Cry Consolability	5 items each scored on 3point scale (0,1,2); total score 0–10 4/10 Moderate Pain	4–19 y ID Postoperative pain
INRS (Solodiuk 2010)	Individual Pain indicators proposed by caregivers	0–10 NRS scale with pain indicators superimposed	6–18 y Nonverbal ID Postoperative

Note: Further details available in Valkenburg 2010 and Chorney 2014

9.4 Analgesic agents

The following section describes the evidence supporting the use of various medications as analgesics in children. Most medications listed (beyond paracetamol, ibuprofen and morphine) are not licensed for paediatric use. Consequently they are often used off-label for acute (and also chronic) pain management, or are used below licensed age cut-offs (such as 6 or 12 mth or 12, 16 and 18 y) or by nonlicensed routes, with both being "accepted practice" (which may vary locally and regionally), as well as via novel routes. The use is commonly in doses extrapolated from adult dosing and is frequently unsupported by paediatric pharmacokinetic data in particular but also by pharmacodynamic study. Considerations pertinent to paediatrics are that countries differ in their licensing for single agents including nonuniformity of age cut-offs and in the formulation types and strengths available. Further to this, when a suspension is not available, adult tablets and capsules require cutting/crushing/dispersing and often disguising (eg in food to improve palatability), which has implications for compliance and dose administration error.

9.4.1 Paracetamol

Paracetamol is effective for mild pain in children (Anderson 2008 **NR**) but the dose required for analgesia is greater than for an antipyretic effect (Anderson 2004 **NR**). The mechanism of action of paracetamol has been reviewed (Graham 2013 **NR**) (see Section 4.2.1).

9.4.1.1 Efficacy

Paracetamol has similar efficacy to nsNSAIDs depending on the surgery type assessed. It is a useful adjunctive treatment as part of multimodal analgesia for more severe pain. A systematic review of paracetamol has defined the NNT for different doses in adults, with no evidence of dose-dependent effect (see Section 4.2.2); this has not been defined for children. Paracetamol is established as opioid sparing in adults (see Section 4.2.2). In children, opioid-sparing efficacy is variably demonstrated and dependent upon the route of administration, the duration of therapy and follow-up, and dose size used. Of 13 RCTs in a systematic review of paediatric use, 7 RCTs are positive (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624). Within this review, comparisons of paracetamol and nsNSAIDs, and combination therapy also have varying results. Interpretation of these results is complicated by study heterogeneity and inclusion of surgical procedures with low postoperative analgesic requirements.

Additional studies have reported various outcomes for paracetamol for different paediatric surgeries.

Following scoliosis surgery, paracetamol 90 mg/kg/d IV for 24 h reduced pain scores but not opioid use compared to placebo (Hiller 2012 **Level II**, n=36, JS 5). Post ophthalmic surgery, 20 and 40 mg/kg rectally reduced early pain scores (Gandhi 2012 **Level II,** n=135, JS 5). Post cleft palate repair, paracetamol 12.5 mg/kg IV and 15 mg/kg orally, given every 6 h for 24 h, reduced postoperative morphine requirements vs placebo (Nour 2014 **Level II**, n=48, JS 5). Post paediatric dental restorations, patients who received paracetamol 15 mg/kg IV compared to pethidine 1 mg/kg had modestly higher pain scores but with less sedation and were discharged 10 min earlier from recovery (Alhashemi 2007 **Level II**, n=40, JS 5). In neonates and infants undergoing cardiac surgery, IV paracetamol reduced cumulative morphine dose in the first 48 h postoperatively but did not reduce pain scores or opioid-related adverse effects (Ceelie 2013 **Level II,** n=71, JS 5).

Post paediatric (adeno)tonsillectomy:

- 40 mg/kg orally vs rectally reduced opioid requirements (Anderson 1996 **Level II**, n=100, JS 5);
- 40 mg/kg rectally compared to 15 mg/kg IV resulted in a longer time to first rescue analgesic request (median 10 vs 7 h) (Capici 2008 **Level II**, n=46, JS 5);
- 15 mg/kg rectally vs 10 mg/kg IV had slightly lower pain scores at 4 and 6 h, with more patients pain free (44 vs 10%) and a longer time to analgesic rescue (5 vs 3.8 h) (Haddadi 2014 **Level III-1**);

- 15 mg/kg orally, as a single preoperative dose, resulted in lower early pain scores compared to ibuprofen 10 mg/kg and placebo (Mahgoobifard 2014 **Level II**, n=60, JS 5);
- 12 mg/kg orally and 6 mg/kg ibuprofen, alone and in combination, were similarly effective over 48 h with similar area under the curve for pain scores at rest and on swallowing (Merry 2013 **Level II**, n=152, JS 5);
- 15 mg/kg IV was similarly effective compared with meperidine 1 mg/kg IM with similar pain scores, slightly less sedation and discharge from recovery 10 min earlier. However, 17% vs 0% of patients required morphine rescue (Alhashemi 2006 **Level II**, n=80, JS 4); and
- 15 mg/kg IV provided similar analgesic effects to IV tramadol 1 mg/kg in the early postoperative period (Uysal 2011 **Level II**, n=64, JS 5).
- Oral paracetamol 15 mg/kg combined with diclofenac 1 mg/kg provides equivalent analgesia to paracetamol 30 mg/kg orally (Hannam 2014 **Level I**, pooled data from 3 RCTs, n=466).

9.4.1.2 Pharmacokinetics and pharmacodynamics

Paracetamol's bioavailability is dependent on the route of administration. Oral bioavailability is high (hepatic extraction 0.11–0.37) and peak plasma concentrations are reached in 30 min (Anderson 2014a **NR**); the equilibration halftime ($t_{1/2keo}$) between plasma and effect compartment is 53 min (Anderson 2001 **PK**). Rectal administration is associated with slower and less predictable absorption and loading doses of 30–40 mg/kg paracetamol may be required to achieve therapeutic plasma concentrations associated with analgesia (eg 10 mg/L which correlates with VAS reduction of 2.6/10) (Howell 2003 **Level II,** n=24, JS 2; Anderson 1996 **Level II**, n=100, JS 5). An IV formulation of paracetamol achieves more predictable concentrations, because pharmacokinetic variability attributable to absorption is avoided but also has more rapid offset than a rectal formulation because of slow delayed absorption (Capici 2008 **Level II**, n=50, JS 5).

Clearance is reduced in neonates and increases with age to reach adult rates during infancy (using allometric scaling expressed as L/h/kg). The volume of distribution (Vd: L/kg) is increased in neonates and rapidly reduces in the first year of life (Mohammed 2012 **PK**; Allegaert 2011a **PK**; Allegaert 2013 **NR**; Wang 2014 **PK**). Dose regimens that target a steady state plasma concentration of 10–20 mg/L have been determined. There is some evidence for analgesic efficacy at this concentration in children and neonates (Anderson 2001 **Level III-1 PK**; Allegaert 2013 **NR**). A pharmacokinetic model based on data from 220 subjects (neonatal up to adult) proposes dosing to achieve a concentration of 9 **mg**/L, chosen as this concentration is predicted with the clinically used schedule of 15 mg/kg every 6 h (for patients weighing 10–50 **kg)** (Wang 2014 **PK**). For paracetamol dosing see Table 9.5 where expert opinion is combined with supportive pharmacokinetic data, where available.

Table 9.5 Suggested paracetamol dosing for infants and children

Postmenstrual age or weight	Oral/rectal dose	IV dose	Maximum daily dose	Reference
Infants 28–29 wk	Nil data	10 mg/kg every 12 h proposed	20 mg/kg/d proposed	Caution against use (van den Anker 2011) Note: Limited data in extreme premature (Allegaert 2011a **PK**; Allegaert 2013 **NR**; Veyckemans 2014)
Infants 30–31 wk	Nil data	10 mg/kg every 8–12 h	25–30 mg/kg/d	
(Weight 0.5–2 kg)		12 mg/kg load with 6–7 mg/kg every 6 h		Wang 2014 **PK**

Postmenstrual age or weight	Oral/rectal dose	IV dose	Maximum daily dose	Reference
Infants 32–44 wk (Weight 3–5 kg)	15 mg/kg every 8 h	10 mg/kg every 6 h (with load 0–20 mg/kg)	40 IV–45 oral mg/kg/d	Palmer 2008 **Level III-3 PK**; Allegaert 2011a **PK**; Allegaert 2013 **NR**; Wang 2014 **PK**; Veyckemans 2014
Infants >45 wk		15 mg/kg every 6 h	60 mg/kg/d	Veyckemans 2014; Palmer 2007 **Level IV**; Howard 2008b **NR**; Wang 2014 **PK**
Older children 6 mth–12 y	15–20 mg/kg every 4–6 h	15 mg/kg every 6 h	60 IV–90 oral mg/kg/d suitable for acute administration for 2–3 d	Anderson 2002 **PK**; Wang 2014 **PK**

9.4.1.3 Adverse effects and safety

Overall safety

Paracetamol use at therapeutic doses can generally be considered safe. A review assessing a range of adverse effects (including abdominal, hepatic, skin, respiratory and neurological effects) suggests paracetamol and ibuprofen have similar safety and tolerability profiles vs placebo if prescribed and administered at recommended doses in children (Southey 2009 **Level IV SR**, 24 RCTs, n=119,166 and 12 studies, n=221,459). Data regarding safety of IV paracetamol in neonates is scant and cautious dosing and monitoring of hepatic function is recommended (Anderson 2009 **NR**). There is minimal safety data available for neonates aged <32 wk (Allegaert 2011a **PK**). Some authors caution against any use in this age group (van den Anker 2011 **NR**).

Hepatotoxity

Paracetamol is metabolised in the liver, predominantly via glucuronidation and sulphation. Increased production of a reactive oxidative product, N-acetyl-p-benzoquinone imine (NAPQI), occurs if the usual metabolic enzyme systems become saturated (eg acute overdose) or if glutathione is depleted (eg with prolonged fasting). An increased contribution of sulphation to metabolism and reduced production of oxidative metabolites may reduce the risk of toxicity in neonates, particularly in the presence of unconjugated hyperbilirubinaemia (Palmer 2008 **Level IV**) but as overall clearance is reduced a lower dose is appropriate. Hepatotoxicity has been reported in three infants (3–7 wk) having received oral dosing of 60 mg/kg/d for 3 and 6 d and 100 mg/kg/d for 2 d (Bucaretchi 2014 **Level IV**).

Risk factors for paracetamol hepatotoxicity may include fasting, vomiting, dehydration, systemic sepsis, pre-existing liver disease and prior paracetamol intake, however the situation remains unclear (Kaplowitz 2004 **NR**) (see also 4.2.3). In an adolescent overdose series (n=25), early predictors of severity of paracetamol hepatotoxicity included the initial INR elevation, presence of hyperbilirubinaemia and hypophosphataemia, the number of prehospital vomiting episodes (≥3) and time to Nacetylcysteine (NAC) administration (Hedeland 2014 **Level IV**). In contrast to adults, no relationship was found for the severity of hepatoxicity and the amount ingested (either as overall dose [mean 16.4 g, range 6.5–60 g] or when weight adjusted). All patients received NAC and recovered; none required transplant.

A review of therapeutic dosing of paracetamol beyond 24 h in children assessed hepatic adverse effects (Lavonas 2010 **Level IV SR**, 62 studies, n=32,414). It reports no cases of liver disease, need for antidote or transplantation or death (95%CI 0.000 to 0.009) and only 10 children experienced major or minor hepatic adverse effects (0.031%; 95%CI 0.015 to 0.057). This review identified 22 case reports of hepatotoxicity associated with therapeutic doses of paracetamol; in 9 cases, Naranjo scoring suggested probable causation.

Asthma

The scientific literature currently debates whether paracetamol can precipitate asthma (by increased *de novo* myeloperoxidase production) or causes a shorter less severe asthmatic episode in aspirin-sensitive people with asthma (Graham 2013 **NR**). The epidemiological literature reports an association between childhood asthma and paracetamol exposure (pooled OR 1.60; 95%CI 1.48 to 1.74) with one study reporting an association with high doses (Etminan 2009 **Level III-3 SR,** 19 studies [15 paediatric, n≈361,018], n=425,140). Two systematic reviews, with no overlap of included studies, report an association between paracetamol use in pregnancy and subsequent childhood wheezing (OR 1.5; 95%CI 1.1 to 2.1) (Etminan 2009 **Level III-3 SR**, 5 studies [wheezing], n unspecified) and asthma (OR 1.28; 95%CI 1.13 to 1.39) (Etminan 2009 **Level III-3 SR**, 4 studies [asthma], n unspecified) (OR 1.21; 95%CI 1.02 to 1.44) (Eyers 2011 **Level III-2 SR**, 6 studies, n=28,038). Caution should be used with interpretation of retrospective analyses because of the possible effect of unknown or unmeasured confounding factors, particularly where the indication for paracetamol is fever due to viral upper respiratory tract illness, which in itself precipitates asthma.

Attention deficit hyperactivity disorder

There are also claimed associations between the use of paracetamol in pregnancy and subsequent child hyperkinetic disorder (HR 1.37; 95%CI 1.19 to 1.59), use of ADHD medications (HR 1.29; 95%CI 1.15 to 1.44) and ADHD-like behaviours at age 7 y (RR 1.13; 95%CI 1.01 to 1.27) (Liew 2014 **Level III-2**). The relevance of these reports to limited acute use is unclear.

Key messages

1. Paracetamol is effective for moderately severe pain and decreases opioid requirements after major surgery in children (**S**) (**Level I**) (PRISMA).
2. Paracetamol has a similar safety and tolerability profile compared with ibuprofen and placebo if prescribed and administered at recommended doses in children (**N**) (**Level IV SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Safe dosing of paracetamol requires consideration of the age and body weight of the child and the duration of therapy (**U**).

☑ Retrospective epidemiological studies linking paracetamol use to later development of childhood disorders such as asthma are inherently confounded (**N**).

9.4.2 Nonselective NSAIDs

For mild to moderate pain, nsNSAIDs are effective analgesic agents. The product information states that safety in children <2 y is unestablished, while the lower age limit for licensing varies by country and by NSAID agent. Despite this, nsNSAIDs have been studied and used in all age groups including infants, as reported by surveyed anaesthetists (n=314) (Eustace 2007 **Level IV**). Use of nsNSAIDs for analgesia is generally not approved for infants aged <3 mth (with an off-label indication for neonatal use in patent ductus arteriosus [PDA] closure providing limited safety data). The choice between ibuprofen, diclofenac, ketorolac, naproxen, ketoprofen and others mainly depends on available formulations and convenience of administration.

9.4.2.1 Pharmacokinetics and pharmacodynamics

Data on pharmacokinetics for the commonly used NSAIDs are available for children but pharmacodynamic studies are few. The clearance of diclofenac (Litalien 2001 **NR**), ketorolac (Lynn 2007 **PK**) and ibuprofen (Kyllonen 2005 **PK**) is immature in neonates and matures within the first year of life. Equilibration half times of drug concentration with clinical effect ($t_{1/2\ keo}$) are 14 min for diclofenac (Hannam 2014 **Level II** n=151, JS 3), 24 min for ketorolac (Mandema 1996 **PK**) and 28 min for ibuprofen (vs 53 min for paracetamol) (Li 2012a **PK**). Studies of analgesic

effects to date have frequently been flawed by failing to account for the variations in time to onset when assessing outcomes.

Rectal bioavailability of diclofenac is high in children (van der Marel 2004 **PK**). A population pharmacokinetic study estimated diclofenac clearance as 16.5 L/h/70 kg and bioavailability as 35% for dispersible tablet or suspension and 63% for suppository (Standing 2011 **PK**). Dosing for children aged 1–12 y was predicted as 0.3 mg/kg IV, 0.5 mg/kg rectally and 1 mg/kg orally. A pharmacokinetic-pharmacodynamic study revealed the maximum effect of both paracetamol and diclofenac (VAS reduction 4.9/10; 95%CI 4.7 to 5.2) (Hannam 2014 **Level II**, n=151, JS 3) as similar to that described for ibuprofen in adults (Li 2012a **PK**). Combination therapy of diclofenac 1 mg/kg orally with paracetamol 15 mg/kg is predicted to achieve equivalent analgesia to paracetamol 30 mg/kg. Synergistic interaction is complex as the drugs have different onset and half-lives. Studies must take this into account to determine the optimum combination-dosing schedule to improve or extend duration of analgesia.

Plasma and CSF concentrations after oral naproxen have been studied in children (mean age 5–6 y, range 0.25–12 y), establishing that clearance and Vd <5 y of age are similar to values for adults and children >5 y (Valitalo 2012 **PK**). High-unbound naproxen concentrations in CSF suggest an active uptake mechanism. Ketoprofen pharmacokinetics are summarised in a narrative review (Kokki 2010 **NR**). Pharmacokinetics in children (aged 0.25–13 y) after oral and IV flurbiprofen have been reported with increased concentrations in CSF compared to plasma (Kumpulainen 2010 **PK**).

In adolescents, the pharmacokinetics of IN ketorolac 15–30 mg (via metred aerosol device) has good bioavailability (81%) and similar T_{max} and clearance to adults, reaching a predicted analgesic concentration of 0.37 mg/L at 30 min (Drover 2012 **PK**).

For ibuprofen, analgesic plasma concentrations of 10–25 mg/L have been suggested post paediatric inguinal hernia repair (Kokki 2007 **NR**). Target analgesic concentrations for other NSAIDs (ideally surgery-specific), developmental changes in pharmacodynamics, and the impact of different stereoisomer forms and the influences of various covariates (including weight, postmenstrual and postnatal age, renal function, obesity, enzyme maturation and influence of race/pharmacogenomics and comedications) on the differential pharmacokinetic, efficacy and adverse-effect profile require further evaluation (Anderson 2011 **NR**; Admiraal 2014 **NR**).

9.4.2.2 Efficacy

Clinical studies of nsNSAIDs and paracetamol suggest similar (Tay 2002 **Level II**, n=63, JS 2; Hiller 2006 **Level II**, n=120, JS 5; Riad 2007 **Level II,** n=108, JS 3; Shepherd 2009 **Level II,** n=72, JS 3) or superior efficacy of nsNSAIDs (Wong 2013b **Level I** [PRISMA], 4 RCTs [nsNSAID vs paracetamol], n=330). Benefit is dependent on dose and route (absorption pharmacokinetics eg rectal vs IV routes), timing (preop/intra/postoperative), intermittent vs regular and duration of administration, and type of surgery (eg cleft palate, hernia repair vs laparotomy).

Two systematic reviews on use of NSAIDs in paediatrics are published, reporting results differently. The first includes two RCTs using coxibs and finds NSAIDs, alone or as a component of multimodal analgesia, decrease opioid consumption in PACU ($p<0.00001$) and at 24 h ($p<0.00001$) (Michelet 2012 **Level I** [QUOROM], 27 RCTs, n=985). NSAIDs also reduce pain intensity in PACU but not in the first postoperative 24 h. The second meta-analysis overlaps by 24 RCTs, including 1 of the RCTs using coxibs but also incorporates outcomes for paracetamol (13 RCTs). NSAIDs (and/or paracetamol) reduce opioid consumption in 38 of 48 treatment arms (21 of 31 RCTs), with a higher proportion positive in NSAID-only trials and with this being more apparent in moderate to major surgery. Where systemic opioids were available via PCA or nurse-controlled analgesia (NCA) (ie after major surgery), mean opioid consumption was reduced by 32% (95%CI 17 to 47) (7 RCTs) when studied for >24 h and not reduced when studied for ≤6 h (24%; 95%CI -1.7 to 50) (3 RCTs) (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624). Where systemic opioids were available by intermittent bolus (21 RCTs, usually short or day-stay surgery) opioid consumption was decreased by 24% (95%CI 6.3 to 43). Pain scores, reported

in various ways, were reduced in 16 of 29 RCTs. The impact on adverse effects is difficult to interpret due to study heterogeneity and small study size.

In a review of diclofenac studies only (74 studies overlapping by 1 and 2 RCTs respectively with the above meta-analyses), diclofenac reduces the need for postoperative rescue analgesia compared to placebo (5 RCTs) and paracetamol (2 RCTs) (NNT 3.6; 95%CI 2.5 to 6.3) (Standing 2009 **Level I** [Cochrane], 7 RCTs [analgesic rescue], n=404).

Additional trials have found NSAIDs effective with reduced pain scores and rescue morphine use post inguinal hernia repair (Riad 2007 **Level II**, n=108, JS 5), reduced need for early rescue analgesia post tonsillectomy (Pickering 2002 **Level II,** n=103, JS 5), reduced pain scores post multiple dental extractions (Gazal 2007 **Level II,** n=201, JS 5) and reduced pain scores and need for rescue opioid for up to 48 h post cleft palate repair (more so when combined with paracetamol) (Mireskandari 2011 **Level II,** n=120, JS 5). A ketorolac infusion was more effective than fentanyl infusion following ureteric-bladder surgery with less bladder spasm (4 vs 30%) and less rescue analgesic administration over 48 h (21 vs 65%) (Jo 2011 **Level II**, n=52, JS 5). SL ketorolac has been shown to be equianalgesic to SL tramadol for moderate and severe pain secondary to fracture or dislocation (Neri 2013 **Level II,** n=131, JS 5). Intraoperative ibuprofen IV resulted in a small reduction in early postoperative fentanyl rescue administration after adenotonsillectomy surgery (Moss 2014 **Level II,** n=161, JS 4). A combination of individually titrated intraoperative opioids and regularly administered perioperative nonopioid analgesics (NSAID and/or paracetamol) is recommended for pain management following paediatric tonsillectomy (Hamunen 2005 **Level I,** 36 RCTs, n=2,309). The combination of paracetamol (48 mg/kg/d) and ibuprofen (24 mg/kg/d) was not superior to either agent alone following tonsillectomy (Merry 2013 **Level II**, n=152, JS =5). Ketoprofen has been studied using IV, oral and rectal route (Kokki 2010 **NR**). It is not currently used in children in Australia and New Zealand, where it is available as CR and topical forms only.

NSAIDS and reduction of postoperative nausea and vomiting

Diclofenac use in acute pain is associated with reduced nausea and vomiting (or both) compared to placebo, paracetamol and opioids (OR 0.58; 95%CI 0.47 to 0.73) (NNT 7.7; 95%CI 5.3 to 14.3) (Standing 2009 **Level I,** 13 RCTs, n=775). NSAIDs do not affect vomiting in PACU but reduce vomiting over 24 h (OR 0.75; 95%CI 0.57 to 0.99) (Michelet 2012 **SR Level I** [QUOROM], 17 RCTs, n=1,302 [events analysed]). Less vomiting occurs following tonsillectomy when nsNSAIDs are part of the analgesic regimen (RR 0.72; 95%CI 0.61 to 0.85) (Lewis 2013 **Level I** [Cochrane], 13 RCTs, n=1,021). The suggested mechanism is through improved pain relief, rather than reduced opioid rescue requirement. A fourth meta-analysis, of heterogeneous surgery types, found only a trend between opioid-sparing effect and PONV reduction; 47% (95%CI 22 to 72) for those reporting PONV reduction vs 26% (95%CI 20 to 31) for those reporting equivalent PONV rates (Wong 2013b **Level I** [PRISMA], 31 RCTs, n=2,624).

9.4.2.3 Adverse effects

Overall safety

In large series of children with febrile illnesses (n=55,785), the risk of serious adverse effects following short-term use of ibuprofen was low, and similar to that following the use of paracetamol (Lesko 1995 **Level II**, n=84,192, JS 4) including in the subgroup of children aged <2 y (Lesko 1999 **Level II**, n=27,065, JS 4). Diclofenac use for postoperative pain is also safe, with an overall serious adverse effect rate (including bleeding) of 8 in 10,000 (95%CI 2 to 24) (Standing 2009 **Level IV SR** [Cochrane], 18 RCTs and 54 studies [diclofenac], n=3,611) (see also Section 4.2.3).

Anaphylaxis and allergy

Anaphylaxis rates to NSAIDs are very low (0/100,000 hospitalisations; 95%CI 0 to 5.4) (Lesko 1995 **Level II**, n=84,192, JS 4). Allergic reactions are infrequently reported with diclofenac: one fatal (n=3,611) from study data and nine nonfatal from case reports (Standing 2009 **Level IV**). Due to established cross-sensitivity, nsNSAIDs should be avoided in children with a reaction to aspirin or other nsNSAIDs (Quiralte 2007 **Level IV**).

Reye's syndrome

Aspirin should be avoided in children with a febrile illness, as it has been associated with Reye's syndrome (encephalopathy and liver dysfunction) (Schror 2007 **NR**). The Australian TGA (TGA 2004), the FDA (FDA 2003) and the Medicines and Healthcare Products Regulatory Agency (MHRA 2003) all recommend against aspirin under the ages of 12, 12 and 16 y respectively.

Aspirin or NSAID-exacerbated respiratory disease

A subset of children with moderate to severe asthma and nasal disease/polyps are susceptible to NSAID-exacerbated respiratory disease (Palmer 2005 **CR**). In children with mild asthma, nsNAIDS may be safe as single-dose diclofenac had no significant effect on respiratory function tests (spirometry) in children with asthma (Short 2000 **Level III-3**) and short-term use of ibuprofen (compared to paracetamol) reduced the risk of outpatient visits for asthma (RR 0.56; 95%CI 0.34 to 0.95) (Lesko 2002 **Level II**, n=1,879, JS 4).

Platelets and bleeding

The issue of nsNSAIDs and postoperative bleeding risk remains controversial. In a small trial, ketorolac did not increase the risk of bleeding complications after congenital cardiac surgery (Gupta 2004 **Level III-1**). Diclofenac use for various surgery types was not associated with increased bleeding risk requiring reoperation (OR 1.25; 95%CI 0.31 to 5) (Standing 2009 **Level I** [Cochrane], 7 RCTs, n=463).

Bleeding after tonsillectomy is of clinical significance but occurs infrequently; studies have been small to date and results remain contradictory. Bleeding risk has been the subject of several meta-analyses with six to seven trial overlap. Ketorolac use is associated with increased post tonsillectomy bleeding in adults (RR 5.64; 95%CI 2.08 to 15.27) (n=246) but not children (RR 1.39; 95%CI 0.84 to 2.30) (n=1,111) (Chan 2014 **SR Level III-2** [PRISMA], 10 studies [7 paediatric], n=1,357). An earlier review of only paediatric trials (with seven ketorolac trials overlap) demonstrates no increased bleeding after tonsillectomy requiring either nonsurgical (OR 0.99: 95%CI 0.41 to 2.4) or surgical intervention (OR 1.69; 95%CI 0.71 to 4.01) (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101). A larger tonsillectomy review also found no increased bleeding risk (surgical or nonsurgical) for all NSAIDs in adults and children (OR 1.3; 95%CI 0.9 to 1.88) or children only (OR 1.06; 95%CI 0.65 to 1.71) or for specific NSAIDs (Riggin 2013 **Level I**, 36 RCTs, n=3,193 [1,747 children]). Importantly, to definitively answer the question of whether NSAIDs increase bleeding post tonsillectomy, a study size of 2,400 is required (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101).

Of additional note, the majority of studies included in these meta-analyses have used a single dose of NSAIDs compared to placebo. Multiple postoperative dosing for some days is routine clinical practice and has not yet been studied with regard to the issue of bleeding, and surgical techniques are evolving.

Adverse gastrointestinal effects

Epigastric discomfort, gastric or duodenal inflammation, oesophageal and peptic ulceration has occurred in association with nsNSAID use for fever and pain in children (Autret-Leca 2007 **Level IV**). Following ibuprofen use for fever management, the incidence of hospital admission for gastrointestinal bleeding was low at 7.2 per 100,000 (95%CI 2 to 18) and similar to those treated with paracetamol (Lesko 1995 **Level II**, n=84,192, JS 4).

Although NSAIDs are not used for analgesia in young infants, limited data on adverse gastrointestinal effects is available following oral, IV, bolus and infusion for PDA closure. Ibuprofen is as effective as indomethacin (indometacin) for PDA closure (oral or IV; 20 RCTs, n=1,019) with reduced risk of necrotising enterocolitis (15 RCTs, n=865) (Ohlsson 2013 **Level I** [Cochrane], 27 RCTs, n unspecified).

Renal and vascular effects

Renal blood flow, glomerular filtration and renal drug clearance are affected by nsNSAIDs (Allegaert 2005a **PK**). Acute kidney injury and renal failure (due to acute tubular necrosis or interstitial nephritis) in association with nsNSAID use is rare. It has occurred in all age groups (Misurac 2013 **Level IV**; Musu 2011 **NR**) from newborns (after maternal use), neonates (Andreoli

2004 **NR**), infants to older children (Taber 2006 **NR**). A review has shown the risk in children is lower than in adults but paediatric fatality has occurred (Musu 2011 **NR**). No risk factors for different NSAIDs have been established for children. No renal impairment was observed in the large fever trial (n=84,192), including the subgroup of patients admitted to hospital (95%CI 0 to 5.4/100,000) (Lesko 1995 **Level II**, n=795, JS 4).

Retrospective analysis of the FDA's spontaneous reporting system suggests increased risk of acute kidney injury with ibuprofen alone that is higher when paracetamol is coprescribed (Yue 2014 **Level IV**). But no data on illness type, severity, comorbidity or suspected causation (determined by expert panel review) is provided.

Neonatal bolus and short-term use for PDA closure can produce pulmonary hypertension and alterations in cerebral (Naulaers 2005 **NR**), gastrointestinal and renal blood flow (Allegaert 2005c **PK**; Aranda 2006 **NR**) and oliguria (Musu 2011 **NR**). Ibuprofen for PDA closure is associated with reduced risk of transient renal insufficiency vs indomethacin (Ohlsson 2013 **Level I** [Cochrane], 20 RCTs [renal insufficiency], n=1,019). Relative effects of indomethacin and ibuprofen on the risk of intraventricular haemorrhage continue to be debated (Ment 2004 **Level III-2**; Musu 2011 **NR**).

Bone healing

NSAID use in orthopaedic surgery remains controversial (see also Section 4.3.1.2). NSAIDs do improve analgesia, increase mobility and reduce opioid consumption following orthopaedic (including spinal) surgery. The paediatric data is limited. Three small retrospective reports of paediatric spinal fusion patients did not find adverse effects from <14 d of ketorolac use (total n=415) (Horn 2010 **Level III-3**; Sucato 2005 **Level III-3**; Vitale 2003 **Level III-3**). Specifically the incidence of pseudarthrosis and revision surgery was not increased. Two retrospective series of fracture and osteotomy surgery (with one surgeon) report no delayed or nonunion with perioperative ketorolac (0.5 mg/kg every 6 h) (n=468 ketorolac treated vs n=80 not) (Kay 2010 **Level III-3**; Kay 2011 **Level III-3**). The balance of low-level evidence suggests that a short-duration NSAID regimen is safe for post fracture or osteotomy pain control and for postoperative use in spinal fusion surgery.

Local necrosis following intramuscular injection

Serious local necrosis following IM injection of diclofenac is reported in six patients (Standing 2009 **Level IV**).

Key messages

1. Nonselective NSAIDs do not increase the risk of either surgical or nonsurgical intervention for bleeding after tonsillectomy in paediatric patients (**S**) (**Level I** [Cochrane Review]).
2. Nonselective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major paediatric surgery (**S**) (**Level I** [PRISMA]) and postoperative nausea and vomiting (**N**) (**Level I** [QUOROM]).
3. Serious adverse effects after nonselective NSAIDs are rare in children over 6 months of age (**S**) (**Level II**)
4. Short term use of ketorolac does not increase rates of nonunion or reoperation in children undergoing posterior spinal fusion, osteotomy or fracture surgery (**N**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Aspirin should be avoided in children (**U**).

☑ Combined population pharmacokinetic-pharmacodynamic modelling is required to inform targeted dosing recommendations of analgesics in children (**N**).

9.4.3 Coxibs

Paediatric trial data is very limited and thus the understanding of the degree of COX-2 selectivity, the pharmacokinetic-pharmacodynamic relationship and adverse effects of these agents in children remains poor.

9.4.3.1 Pharmacokinetics

The pharmacokinetics of a celecoxib suspension, capsule sprinkles and the commercial capsule have been compared (Krishnaswami 2012 **PK**). The different formulations achieve similar area under the curve post ingestion. Clearance is reduced in younger patients; by 40% in infants weighing 10 kg and by 24% in children weighing 25 kg. For pain relief in juvenile idiopathic arthritis (JIA), a suggested dosing regimen is 2–4 mg/kg bd.

A dose of up to 1 mg/kg (maximum 40 mg) parecoxib IV is suggested to maintain the concentration of valdecoxib (the active metabolite) above the *in vitro* 50% inhibitory concentration for cyclooxygenase for >12 h (Hullett 2012 **PK**). A dose reduction or increased dosing interval is suggested for children aged <2 y.

9.4.3.2 Efficacy

Rofecoxib (prior to its withdrawal from the market) has been the most evaluated in small-scale paediatric efficacy studies in the perioperative (tonsillectomy) setting. These studies highlight the need to do dose-efficacy studies in paediatrics as low dose (0.625 mg/kg) was inferior to ibuprofen (in combination with paracetamol) (Pickering 2002 **Level II**, n=98, JS 5), 1 mg/kg was superior to placebo (Sheeran 2004 **Level II** n=45, JS 4; Joshi 2003 **Level II** n=66, JS 4), and multi-day postoperative dosing provided superior analgesia to paracetamol (Vallee 2007 **Level III-3**) and paracetamol/hydrocodone combination (Bean-Lijewski 2007 **Level II** n=60 [n=40 analysed], JS 5).

Celecoxib use has previously been reported in children with chronically painful medical conditions. Celecoxib (3–6 mg/kg twice/d) was as effective as naproxen (7.5 mg/kg twice/d) in children with JIA (Foeldvari 2009 **Level II**, n=242, JS 5). Celecoxib use was reported in a series of JIA patients (n=68; 68 person-years) compared with nsNSAID treatment (mostly naproxen, meloxicam, and nabumetone) (268 person-years) (Sobel 2014 **Level III-2**) and in a small series of haemophiliac patients (Rattray 2006 **Level IV**).

Parecoxib 20–40 mg IV (alone and combined with topical local anaesthetic) was superior to fentanyl 2 mcg/kg IV for pain after repair of corneal perforation, with reduced rescue analgesic requirements and PONV (Subramaniam 2007 **Level II,** n=90, JS 2).

9.4.3.3 Adverse effects

Overall safety

Data from 3–12 mth use in JIA patients is reassuring but limited (overall n=220) (Krishnaswami 2012 **PK**; Sobel 2014 **Level III-2**) (See Section 4.3.2 for discussion of safety and adverse effects in adults).

Safety in overdose

Paediatric overdose of celecoxib was reported in 177 children aged 0–5 y (Forrester 2009 **Level IV**). For 92 patients, the dose was known and was large; mean 506 mg (range 10–2,300 mg) equating to mean ingested amounts of 22–39 mg/kg (for the half with their weight documented) across the age groups. This resulted in no adverse effects in 96%, and minor effect (rash, abdominal pain, vomiting, agitation or drowsiness) in only 4%.

NSAID-exacerbated respiratory disease, bronchospasm, allergy and anaphylaxis

Based upon adult data (see Section 4.3.2), coxibs are generally considered safe for use in paediatric patients with asthma and aspirin- or NSAID-exacerbated respiratory disease. In 223 patients (aged 5–78 y) with various levels of allergic reaction to nsNSAIDs or paracetamol (cutaneous/angioedema/urticaria/rash [61%], naso-ocular/cutaneous/asthma [15%], respiratory alone [9%] and anaphylaxis [16%]) having placebo-controlled multidrug oral challenges (n=697), celecoxib precipitated no events (n=223) and meloxicam one event (Quiralte

2007 **Level IV**). Other smaller series have reported cross-sensitivity for coxibs in patients with cutaneous or naso-ocular reactions. In 28 nsNSAID-sensitive patients (aged 10–61 y), use of rofecoxib and valdecoxib produced urticaria or angioedema in 3 (10%) (Sanchez-Borges 2005b **Level IV**). Of 58 similarly aged patients, 5 (9%) had reactions to celecoxib and 3 (5%) had reactions to etoricoxib (Sanchez-Borges 2005a **Level IV**). As a small percentage of patients have reactions suggesting cross-sensitivity, oral challenge under medical supervision is advisable.

Bleeding

In adolescent haemophiliac patients, etoricoxib and rofecoxib treated patients had similar numbers of presentations for bleeding vs placebo (Tsoukas 2006 **Level II**, n=102, JS 5). Bleeding following paediatric tonsillectomy has been assessed (Lewis 2013 **Level I** [Cochrane], 15 RCTS, n=1,101) (see Section 9.6.4.1). This meta-analysis includes only one small coxib trial, with no differences in bleeding rates of rofecoxib vs ibuprofen vs placebo (added to paracetamol) (Pickering 2002 **Level II,** n=98, JS 5).

Gastrointestinal

In children with JIA treated chronically (where 68–71% were receiving disease-modifying agents, with the number on corticosteroids unspecified), rates of abdominal pain were similar between those treated with nsNSAIDs (15/100 patient years; 95%CI 10 to 19) (225 patient years) and celecoxib (18/100 patient years; 95%CI 8 to 28) (68 patient years) and not statistically different from patients in "off-NSAID" periods (8/100 patient years, 95%CI 2 to 15) (75 patient years) (Sobel 2014 **Level III-2**). One patient experienced gastrointestinal ulceration in an off-NSAID period. Nausea and vomiting rates were similar in the three groups.

Renal

Two unspecified renal disorders occurred in chronically celecoxib-treated children with JIA during 68 patient years of therapy (Sobel 2014 **Level III-2**). Celecoxib's safety profile for acute kidney injury in adults is specified in Section 4.2.3.

Key message

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ The safety profile of coxibs in the setting of allergy or contraindication to nonselective NSAID in adults and children is encouraging (**N**).

9.4.4 Opioids and tramadol

There are significant developmental changes in the pharmacokinetic handling and pharmacodynamic response to opioids (Allegaert 2014 **NR**; Holford 2012 **PK**; Anderson 2014b **NR**). Doses must therefore be adjusted according to age, bodyweight, coexistent liver or renal impairment, and individual response. Routine and regular assessment of pain severity, the analgesic response, and the incidence of adverse effects (particularly nausea, vomiting, sedation and OIVI) is essential, with titration of opioid treatment according to individual needs. As with adult patients, appropriate dose regimens, guidelines for monitoring, documentation, management of adverse effects, and education of staff and carers are required (Wrona 2007 **Level IV**; Ellis 2011 **Level IV**) (see Section 4.1.1.4).

9.4.4.1 Pharmacogenomics

Understanding of the influence of pharmacogenomics upon opioid metabolism and effects is emerging. Examples of relevant polymorphisms include: the liver enzyme cytochrome P450 CYP2D6 (Friedrichsdorf 2013 **Level IV**; Kelly 2012 **Level IV;** Yee 2013 **Level IV**; Soderberg Lofdal 2013 **NR**); liver cell transporter proteins (OCT1) (Fukuda 2013 **Level IV**), ATP-binding cassette (ABC) subfamily member B1 (or MDR1) (Sadhasivam 2015 **NR**) and ABCC3 (Venkatasubramanian 2014 **Level IV**); and opioid receptor subtypes (Anderson 2014b **NR**), including OPRM1 (Chidambaran 2015 **Level IV**) and COMT, a regulating enzyme involved in pain pathways (Sadhasivam 2014 **Level IV**). Further considerations are the differential risk with genetic differences and varying

prevalence of racial/ethnic phenotypes (Anderson 2014b **NR**) and consequent variability in sensitivity to adverse effects (Fukuda 2013 **Level IV**; Jimenez 2012 **Level III-3**) (see also Sections 1.7.2 and 1.7.3).

9.4.4.2 Medication prescribing errors

Medication errors continue to be problematic, particularly in children. Ten-fold dose errors in prescribing made up a small proportion of hospital prescribing errors (3.8%) but were associated with significant morbidity when involving opioids (Doherty 2012 **Level IV**). In a single paediatric centre (with ≈1,320 medication error reports per year over 5 y), the most frequently implicated drug class was opioids (8.5%) (Doherty 2012 **Level IV**) and drug was morphine (3.2%) (Mc Donnell 2011 **Level IV**). This is concerning due to the frequency of prescription within hospitals and the community and the adverse effect profile of opioids.

9.4.4.3 Morphine

Morphine has a long history of use in paediatric acute pain management as either the gold standard comparator or rescue agent in analgesic trials.

Pharmacokinetics and pharmacodynamics

Morphine clearance is influenced by postmenstrual/postnatal age and weight (Holford 2012 **PK**; Krekels 2011 **PK**). Morphine clearance is reduced and half-life prolonged in neonates and infants, achieving adult values from age 2 y. Mechanical ventilation reduces hepatic blood flow (up to 45%) and is associated with reduced clearance. Within age groups, individual variability in kinetics results in two- to three-fold differences in plasma concentration with the same rate of infusion (Lynn 1998). In neonates, infants and children to 3 y, age is the most important factor affecting morphine requirements and plasma morphine concentrations (Bouwmeester 2003b **Level II**, n=68, JS 2), and in older children average patient-controlled morphine requirements also change with age (Hansen 1996 **Level IV**).

The risk of respiratory depression is reduced when infusions are targeted to plasma morphine concentrations <20 mcg/L. However, no minimum effective concentration for analgesia has been determined (Anderson 2014b **NR**). No clear relationship between plasma concentration and analgesia has been identified due to variability in individual requirements, clinical state of the child, type of surgery, assessment measure used, and small sample size in many studies.

Efficacy

Morphine (administered via IV, epidural, IM and IT routes) has analgesic efficacy in comparison with inactive controls but with significantly increased vomiting and sedation (Duedahl 2007 **Level I**, 36 RCTs, n=1,908). The majority of studies analysed compared single perioperative doses and only one study evaluated a postoperative infusion of morphine. A further trial in bilateral myringotomy demonstrated equivalence of IN fentanyl, IV and IM morphine (Hippard 2012 **Level II**, n=171, JS 5).-

9.4.4.4 Fentanyl

Fentanyl use in paediatric acute pain management is increasing. It is a highly lipophilic and potent mu-opioid agonist.

Pharmacokinetics

Fentanyl's rapid redistribution contributed to its relatively rapid offset of action following single IV bolus doses (Tibboel 2005 **NR**). Fentanyl is metabolised by CYP3A4 to inactive metabolites and clearance is only 70–80% of adult levels in neonates but rapidly matures. After transbuccal administration, when children retained the dose in the cheek, the bioavailability was 50% compared to another study where swallowing likely contributed to the lower bioavailablity of 36% (Lotsch 2013 **NR**). IN pharmacokinetics have been assessed demonstrating high bioavailability (and rapid onset of effect) in adults but not in children to date. Small volumes are necessary to reduce delivery to the posterior pharynx (where it is swallowed).

TD fentanyl has high bioavailability. In children compared with adults, the time to reach steady-state serum drug concentrations following TD application is longer, and the elimination half-life is shorter as clearance is enhanced (Zernikow 2007 **NR**).

Efficacy

Fentanyl has been administered for perioperative pain management in neonates and children (APAGBI 2012 **GL**) and also in the intensive care setting (Anand 2013 **Level III-2**) by multiple routes, including IV bolus (Elshammaa 2011 **Level II**, n=60, JS 4; He 2013 **Level I,** 3 RCTs, n=283), infusion (Jo 2011 **Level II**, n=52, JS 5), PCA (Antila 2006 **Level II** n=45, JS 4) (see Section 9.6.), IT injection (Batra 2008 **Level II**, n=56, JS 5; Duman 2010 **Level II**, n=50, JS 5) and as an additive to peripheral nerve and epidural infusions and PCEA (Saudan 2008 **Level III-3**) (see Section 9.6).

Due to its rapid onset and short duration of action, fentanyl can be used alone or in combination with sedatives to control procedural pain (see Section 9.7.2 and APAGBI 2012 **GL**; Tibboel 2005 **NR**).

Due to its high lipophilicity, fentanyl can also be administered via transmucosal (transbuccal and IN) and TD routes. Transmucosal fentanyl is attractive when IV access is challenging or unavailable. Transbuccal fentanyl has been used as described in Section 9.7.2 for children having burns dressing changes and lumbar punctures. In the prehospital setting for orthopaedic trauma, 10–20 mcg/kg transbuccally (Davis 2011 **Level IV SR**, 2 studies [paediatric], n=117) and 1–4 mcg/kg IN have been used effectively (Karlsen 2014 **Level IV**; O'Donnell 2013 **Level III-3**). It has also been used to manage pain from abdominal, back and other conditions (Bendall 2011 **Level III-2**). In paediatric EDs, IN fentanyl 1.5–2 mcg/kg was used for pain from injured extremities, burns, the abdomen and other sources (Hansen 2012 **Level IV SR**, 8 studies [paediatric], n=575). A systematic review overlaps by five studies and describes further efficacy of similar dosing in three ED studies (one of fractures, one mixed pain types and one in burns [see Section 9.4.4]) and four perioperative myringotomy studies (Mudd 2011 **Level IV SR**, 12 studies, n=1,743). Further studies in myringotomy surgery have also been published (Hippard 2012 **Level II,** n=171, JS 5**;** Dewhirst 2014 **Level II**, n=100, JS 5; Karlsen 2014 **Level IV**). There have been no randomised trials of efficacy of the TD route.

Adverse effects

Opioid-related adverse effects, such as nausea, vomiting and respiratory complications, occur at similar rates to other opioids or may be increased.

Both fentanyl and morphine can produce tolerance and withdrawal symptoms in patients discharged from paediatric intensive care units (PICUs) following cessation (Anand 2013 **Level III-2**; Anand 2010 **NR**; Birchley 2009 **NR**). Fentanyl administered as a prolonged IV infusion in the NICU and PICU has been associated with more rapid dose escalation and greater likelihood of doubling the daily dose than when the primary opioid is morphine (Anand 2013 **Level III-2**). This was also true for the subgroup admitted immediately postoperatively.

Accidental toddler death (remnant of patch found in mouth) (Paparella 2013 **CR**) and deliberate misuse of TD fentanyl patches in an adolescent suicide attempt have been reported (five 100 mcg/h patches applied) (Lyttle 2012 **CR**). Partial occlusion of fentanyl patches does not reduce the dose received (Nelson 2009 **NR**); some authors still inappropriately suggest this practice (Mitchell 2010 **NR**).

9.4.4.5 Codeine

Codeine has been used for decades in paediatric acute pain. Recent publications of deaths and increased understanding of relevant pharmacogenomics (see below) are influencing prescribing of this opioid prodrug.

Pharmacokinetics

Oral codeine has a similar time to peak effect but decreased total absorption compared with rectal and IM delivery (McEwan 2000 **PK**). Administration IV should be avoided as severe hypotension may result (Shanahan 1983 **Level IV**).

Pharmacogenomics and adverse effects

Relevant to codeine as a prodrug, the CYP2D6 enzyme has numerous polymorphisms (Zhou 2009a **NR**; Zhou 2009b **NR**) resulting in four phenotypes, which demonstrate a spectrum of activity with overlap (Vuilleumier 2012 **NR**) (see also Sections 1.7.3 and 4.1.1.2).

The phenotypes are variably represented in populations depending on ethnicity. The most common (>70% of Caucasians to 92% of Asians) "normal" phenotype, termed extensive metabolisers, has 100–200% CYP2D6 activity and thus analgesic effect with codeine. Intermediate and poor metabolisers have reduced (intermediate: 50% CYP2D6 activity) to no effect (poor: 0% CYP2D6 activity) from codeine (46% of children undergoing tonsillectomy in a UK population) (Williams 2002 **Level II PK**, n=96, JS 4) and 49% (intermediate 44% and poor 5.3%) of children with sickle-cell disease (Yee 2013 **Level IV**); while ultra metabolisers (>200% activity) attain high peak morphine levels and are at risk of sedation and respiratory depression (Kelly 2012 **Level IV;** Yee 2013 **Level IV;** Racoosin 2013 **Level IV**; Niesters 2013 **Level IV**). Several paediatric deaths associated with codeine administration have been reported, some with confirmed ultra and extensive metaboliser phenotype. Subgroups at particular risk included breastfeeding neonates (whose ultra/extensive mothers were taking codeine in the puerperium) (Madadi 2007 **CR**) and toddlers (Kelly 2012 **Level IV,** Racoosin 2013 **Level IV**) and obese older children (Friedrichsdorf 2013 **Level IV**) following adenotonsillectomy.

In response to the reported deaths, the FDA has relabelled codeine with black-box warnings applied to maternal postpartum use and children (<18 y) undergoing adenotonsillectomy with instruction "to prescribe an alternative analgesic for postoperative pain control" (FDA 2012, FDA 2013). The European Medicines Agency has responded similarly (EMA 2013), as has the WHO in removing codeine from its tiered analgesic ladder for treatment of (persistent) pain in children (WHO 2012 **GL**). Several paediatric hospitals have removed codeine from their drug formularies (Tremlett 2013 **NR**).

Efficacy

In the majority of studies with a codeine treatment arm (see below), CYP2D6 activity is not accounted for and is a significant confounder contributing to conflicting reports of efficacy for postoperative pain. Perceived advantages of codeine include less respiratory depression in neonates and reduced nausea and vomiting compared with morphine (in one of four time points) (Williams 2002 **Level II**, n=96, JS 4). These conclusions are probably compromised by low levels of active metabolites and resultant reduced efficacy (Williams 2001 **NR**). Comparison of codeine and morphine for tonsillectomy has shown either no difference (Semple 1999 **Level II**, n=40, JS 4) vs an increased requirement for rescue analgesia following codeine (Williams 2002 **Level II**, n=96, JS 4). Codeine was less effective than ibuprofen for acute musculoskeletal pain in children (Clark 2007 **Level II**, n=336, JS 5). Addition of codeine to paracetamol has been reported to improve analgesia (Pappas 2003 **Level II**, n=120, JS 5) or have no effect (Moir 2000 **Level II**, n=79, JS 5) and was as effective as ibuprofen for fracture pain but ibuprofen-treated patients had fewer adverse effects and better functional outcomes (Drendel 2009 **Level II,** n=336, JS 5). Codeine is still prescribed due to the influence of efficacy data when combined with nonopioids in adults, familiarity and lower pharmaceutical scheduling with over-the-counter availability (Tremlett 2013 **NR**). Following paediatric neurosurgery, some centres still use codeine routinely for postoperative pain management (Bronco 2014 **Level IV**), others less so (Teo 2011 **Level IV**).

9.4.4.6 Oxycodone

Oxycodone is increasingly used in paediatric acute pain management.

Pharmacokinetics and pharmacogenomics

In children aged >6 mth, the pharmacokinetic profile of oxycodone is similar to adults and dosing can be based on weight (El-Tahtawy 2006 **PK**). Similar absorption is seen following buccal and SL administration (Kokki 2006 **PK**) but there is less interindividual variability following IV administration (Kokki 2004 **PK**). In neonates and infants, the half-life is prolonged and increased variability in kinetics is seen even following IV administration (Pokela 2005 **PK**). The parent compound contributes the majority of drug effect but the impact of polymorphisms

and cotherapies that influence CYP2D6 and CYP3A4 enzymes and thus metabolite (eg oxymorphone, noroxymorphone and noroxycodone) concentration is being debated in adults (Kokki 2012a **NR**) (see Section 1.7.3).

Efficacy

Oxycodone's efficacy has been shown in various paediatric settings; oral use of 0.1–0.2 mg/kg in the ED for children with orthopaedic injuries (Charney 2008 **Level II**, n=107, JS 5; Koller 2007 **Level II,** n=66, JS 5), use of an oral CR preparation as a step-down following PCA in adolescents after spinal fusion (Czarnecki 2004 **Level IV**), IV bolus dose administration for postoperative rescue analgesia (Kokki 2006 **Level IV**) and IV PCA in adolescents and adults (Silvasti 1999 **Level II**, n=52, JS 4). There has been no study reporting paediatric use of the CR oxycodone/naloxone combination to date.

9.4.4.7 Other opioids

A large number of opioid preparations have been used in children but availability varies by country and many have not been investigated in controlled trials. For additional details see (APAGBI 2012 **GL**).

Hydromorphone

Hydromorphone has no advantage over other opioids in terms of analgesic efficacy or adverse-effect profile, administered by IV, oral, caudal or epidural route (Quigley 2002 **Level I** [Cochrane], 4 RCTs [paediatric], n=122). Hydromorphone IV has been used in the PICU setting usually as second- or third-line opioid therapy for analgesia and sedation for malignancy and following trauma with a median dose 10 mcg/kg/h (Reiter 2012 **Level IV**). See Section 9.7 for neuraxial use.

Hydrocodone

Hydrocodone is not available for analgesic use in Australia or New Zealand. In other countries, it is generally used in combination with paracetamol (Sutters 2010 **Level II**, n=123, JS 3).

Hydrocodone is metabolised by CYP2D6 to hydromorphone and CYP3A4 to norhydrocodone. Inhibition of these enzymes by coadministered antibiotics and anticonvulsants resulted in a child's death where hydrocodone was being used for antitussive effect (Madadi 2010 **CR**).

Methadone

Methadone is generally used in children for cancer pain, in PICU settings to assist opioid weaning (Bowens 2011 **Level II**, n=78, JS 4) and in NAS. One centre reported its use as a third-line intervention for acute neuropathic pain in paediatric patients post limb salvage surgery (Anghelescu 2011a **Level IV**).

Buprenorphine

Buprenorphine use via various routes (IV, SL, caudal usually 2.5–5 mcg/kg and TD) has been reported in a few small paediatric studies (Michel 2011 **Level IV SR**, 8 studies and 3 RCTs, n unspecified). Following a single IV dose, allometric scaling suggested clearance is higher in children, with possible paradoxical prolongation of effect. Buprenorphine 50 mcg SL rescue use has been reported for acute pseudo-obstruction pain crises in three children who had chronic abdominal pain managed with TD buprenorphine (Prapaitrakool 2012 **Level IV**).

Sufentanil

Sufentanil IN 0.5 mcg/kg combined with ketamine IN spray via an actuating device was effective for various procedures (n=50) with respective bioavailabilities of 25 and 36% (Nielsen 2014 **Level IV**). Epidural sufentanil use alone and with local anaesthetic is described in Section 9.6.2.

Diamorphine (diacetylmorphine, heroin)

This opioid is not available for analgesic use in Australia and New Zealand. In the UK, it is used IN in paediatric EDs (by 118 of 205 surveyed paediatric EDs) (Hadley 2010 **Level IV**), for trauma pain management such as post fracture (Kendall 2001 **Level II**, n=404, JS 3; Kendall 2015 **Level IV**;

Kidd 2009 **Level III-2**; Regan 2013 **Level III-3**) and for sickle cell crises (Telfer 2009 **Level IV**) (see Section 8.6.4.1). The bioavailability following IN drop installation is 33%, with T_{max} at 10 min (Kidd 2009 **Level III-2**).

9.4.4.8 Tramadol

Evidence for the use of tramadol in paediatric acute pain is currently limited by studies of small sample size and difficulty determining comparative analgesic doses.

Pharmacokinetics and pharmacogenomics

Oral administration is subject to extensive first-pass hepatic metabolism. Rectal bioavailability is good with low interindividual variability (Zwaveling 2004 **PK**). Maximum plasma concentrations post IV, oral, and rectal dosing are achieved between 0.3–2.4 h post administration (Bozkurt 2005 **Level III-3 SR**, 20 studies, n unspecified). Analgesic efficacy is associated with a plasma concentration of tramadol of 100 ng/mL in adults and children and Odesmethyltramadol (M1) of 15 ng/mL (Garrido 2006 **PK**).

The primary active metabolite at the mu receptor, M1, is formed by the enzyme CYP2D6 (see also Sections 1.7.3 and 4.1.1.2). Pharmacogenomics has relevance with interindividual variability in functional allele expression (resulting in poor, normal, extensive or ultra metabolisers) (see also Section 9.4.4.5). The clinical significance of this has become apparent recently for codeine but the impact in terms of tramadol/M1's analgesic efficacy and adverse-effect profile is as yet unknown. The age-related changes in maturation of CYP2D6 are also a relevant consideration (Allegaert 2005b **PK**; Allegaert 2008 **PK**). Using amalgamated pooled tramadol disposition data, the time–concentration profile of tramadol and its M1 metabolite depends on maturational trends in drug metabolism (CYP2D6 ontogeny and polymorphisms) and renal elimination (Allegaert 2011b **NR**). Tramadol clearance is linked to weight in older children (Bressolle 2009 **PK**) and to weight and postmenstrual age in infants; increasing rapidly from 25 wk postmenstrual age to 50% of the adult value by 44 wk postmenstrual age and to 90% by 1 y of age (Allegaert 2011b **NR**).

Dose and efficacy

Systemic administration

In children IV dosing is the same as in adults (1–2 mg/kg every 6 h), with an initial 2 mg/kg IV loading dose being recommended, followed by infusion rates of 0.25–0.41 mg/kg/h (6–10 mg/kg/24 h) (Bressolle 2009 **PK**; Allegaert 2011b **NR**). Lower infusion rates have been reported (Moyao-Garcia 2009 **Level II**, n=24, JS 5; Alencar 2012 **Level II**, n=160, JS 5).

A review indicated efficacy following oral, rectal, and IV administration (Bozkurt 2005 **Level III-3 SR**, 20 studies, n unspecified). Tramadol has been administered via PCA to children (see Section 9.5.2). SL use in paediatric fracture pain was effective (Neri 2013 **Level II**, n=131, JS 5) but pharmacokinetic data to support this route is not available.

For tonsillectomy, tramadol 2.5 mg/kg oral was more effective than low-dose rectal paracetamol (Pendeville 2000 **Level II**, n=50, JS 5), 1 mg/kg IV had similar efficacy to IV paracetamol 15 mg/kg (Uysal 2011 **Level II,** n=64, JS 5) and 1–2 mg/kg had similar efficacy to 0.1 mg/kg morphine (Engelhardt 2003 **Level II**, n=60, JS 5; Ozalevli 2005 **Level III-1**). Conversely 1 mg/kg IV was less effective than pethidine 1 mg/kg (Ozer 2003 **Level II**, n=50, JS 3), oral dextromethorphan 1 mg/kg (Ali 2008 **Level II**, n=90, JS 1), ketoprofen (IV load 2 mg/kg and 6 h infusion of same dose) (Antila 2006 **Level II**, n=45, JS 4) and ropivacaine infiltration, while being similarly effective to placebo (Cocelli 2012 **Level II**, n=90, JS 3). Tramadol 2 mg/kg was similarly effective to pethidine 1 mg/kg for abdominal surgery (Ekemen 2008 **Level II**, n=110, JS 3). Addition of IV tramadol 2 mg/kg every 6 h vs placebo to IV paracetamol and morphine infusion in ventilated neonates did not offer clinical benefit in pain scores, morphine requirements or time to extubation (Olischar 2014 **Level II**, n=71, JS 5). Tramadol infusion (0.1–0.2 mg/kg/h) was similar to fentanyl infusion (1–2 mcg/kg/h) in ventilated neonates following major (abdominal) and minor surgery in terms of pain scores over 72 h, time to extubation and time to full enteral feeding (Alencar 2012 **Level II**, n=160, JS 5). Tramadol infusion 0.12 mg/

kg/h for 72 h was trialled against nalbuphine infusion in children having various surgery types (Moyao-Garcia 2009 **Level II**, n=24, JS 5).

Neuraxial administration

After neuraxial administration, efficacy has generally not been compared to systemic administration; the safety of this route remains uncertain (Walker 2012b **NR**; Engelman 2012 **Level I** [PRISMA], 9 RCTs [tramadol], n=258). Tramadol 1–2 mg/kg added to caudal local anaesthetic prolongs the time to first rescue analgesic (4.5 h; 95%CI 2.8 to 6.1) at the expense of increased vomiting (OR 2.5; 95%CI 1.3 to 4.6) with no IV comparator.

Caudal tramadol 2 mg/kg added to bupivacaine and levobupivacaine was similarly effective for inguinoscrotal surgery (Sezen 2014 **Level II**, n=68, JS 5). Tramadol 2 mg/kg added to epidural ropivacaine 0.2% was superior to ropivacaine alone, with lower pain scores, reduced rescue requirement and longer time to first analgesic request (14.5 vs 5 h) post abdominal surgery (Inanoglu 2010 **Level II**, n=44, JS 5). As a sole agent for urological surgery and without a systemic comparator or epidural local anaesthetic comparator, epidural tramadol 2 mg/kg compared to morphine 0.1 mg/kg had similar pain scores and time to first rescue analgesic but with reduced adverse effects (Demiraran 2005 **Level II**, n=80, JS 3) (see also Section 9.6.2).

Infiltration and topical administration

Whether tramadol has clinically useful local anaesthetic effects has been debated. Peritonsillar infiltration of tramadol 2 mg/kg has been studied in several small RCTs and was effective for control of early (0–8 h) postoperative pain following adenotonsillectomy. Its benefits were similar to lignocaine (Heiba 2012 **Level II**, n=60, JS 4), similar (Ugur 2013 **Level II**, n=75, JS 5) and superior to ketamine infiltration (Ayatollahi 2012 **Level II**, n=126, JS 4), superior to placebo (Atef 2008 **Level II**, n=40, JS 5) and, when combined with ketamine IV, superior to either agent alone and placebo (Honarmand 2013 **Level II**, n=75, JS 5). Only one small systemic comparator trial is available, which found infiltration of tramadol 2 mg/kg to be superior to IM administration and placebo (Ugur 2008 **Level II**, n=45, JS 5).

Post hernia repair, 2 mg/kg SC infiltration resulted in higher initial pain scores but similar time to first rescue analgesic request compared to bupivacaine infiltration with both having a longer effect than tramadol IM (6.7 vs 6 vs 4.5 h) (Demiraran 2006 **Level II**, n=75, JS 5). Preincisional infiltration of tramadol 2 mg/kg was as effective as bupivacaine 0.25% with regard to pain scores and average time to first analgesic use in young children undergoing inguinal herniorrhaphy (Numanoglu 2014 **Level II,** n=52, JS 4). For awake circumcision, ring block combined with pudendal nerve block with tramadol 5%/adrenaline was effective and superior to prilocaine/adrenaline with reduced rescue requirements (Kargi 2010 **Level II,** n=40, JS 4) but was ineffective compared to lignocaine/adrenaline (Polat 2013 **Level II**, n=47, JS 4).

A small tonsillectomy study showed no benefit on d 1 following single topical application of tramadol 5% but pain scores were reduced on d 7 (Akbay 2010 **Level II**, n=40, JS 5). Tonsillar application of tramadol 40 mg/ketamine 20 mg was superior to placebo, with similar pain scores and rescue analgesic requirements on d 1 (Tekelioglu 2013 **Level II**, n=60, JS 5).

Adverse effects

Tramadol has similar or reduced rates of nausea and vomiting (10–40%), sedation and fatigue to those found with opioid use but lower rates of constipation and pruritus (Bozkurt 2005 **NR**).

OIVI is reported in adults, generally following supratherapeutic or overdose (Hassanian-Moghaddam 2013 **Level IV**) (see Section 4.1.1) and in children, following accidental ingestion (n=3) (Hassanian-Moghaddam 2014 **Level IV**). After tonsillectomy in children with OSA, fewer desaturation events were reported with tramadol 2 mg/kg than with morphine 0.1 mg/kg, significant only between 1 and 2 h postoperatively (Hullett 2006 **Level II**, n=66, JS 4). Of twenty ex-premature infants given tramadol 2 mg/kg (with local anaesthetic drops) for outpatient eye examination, three experienced prolonged sedation, returned and were admitted. One experienced frequent apnoea required continuous positive airway pressure (CPAP) and transfusion, one required supplemental oxygen and one was observed only (Bilgili 2012

Level IV). In the event of excess sedation, naloxone is a consideration as a reversal agent (Grosek 2009 **CR**).

Lowering of the seizure threshold and seizures are reported in adults (see Section 4.1) and children with therapeutic, supratherapeutic (Li 2012b **Level IV**) and overdose (Mazor 2008 **Level IV**).

There is no data in the acute paediatric pain setting but drug interactions are also a consideration, as are serotonin syndrome (Marechal 2011 **CR**) and withdrawal after chronic (maternal) exposure (Hartenstein 2010 **CR**; Willaschek 2009 **CR**). Following a large tramadol overdose with plasma level >1 mg/mL, a seizure and cardiogenic shock have been reported in a child; cardiac function normalised within 48 h (Perdreau 2015 **CR**).

Further data is required to determine the role, optimum dose and safety of tramadol in children and the monitoring level required. This is particularly important now that codeine use is being limited in adenotonsillectomy patients (Constant 2014 **NR**) (see Section 9.5.4), especially as tramadol's effect is partly dependent on the same CYP2D6 pathway (Marzuillo 2014 **NR**).

A concentrated drop formulation (100 mg/mL) is available in many countries, licensed for adult palliative care. Dosing error confusing the number of drops with the number of mL is a concern in paediatrics (10 drops = 25 mg = 0.25 mL). Two children were dosed at home with oral tramadol drops post adenotonsillectomy with adverse outcome. One aged 5 y with ultrarapid genotype experienced significant respiratory depression (Orliaguet 2015 **CR**). The single urine sample of M1 reported for this case was not accompanied by plasma concentrations of tramadol or M1. Thus the accuracy of the stated single analgesic dose administered cannot be determined and raises the issue of dosing confusion with the concentrated formulation. The second child aged 2 y died due to tramadol toxicity with tramadol oral drops treatment. The TGA subsequently does not support the use of this formulation in children aged <12 y (TGA 2015).

Key messages

Opioids

1. The efficacy of oral codeine in children is unpredictable due to genetic differences in the ability to generate the active metabolite morphine (**S**) (**Level II**), as are adverse effects and serious toxicity (**S**) (**Level IV**).
2. Young and obese children with history of obstructive sleep apnoea syndrome are at higher risk of developing serious opioid-induced ventilatory impairment and death (**N**) (**Level IV**).
3. Safe dosing of opioids requires consideration of the child's age, body weight, comorbidities and ethnicity (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Careful titration of opioids is advised according to the individual child's response (analgesia and adverse effects) (**N**).

☑ Because of its unpredictable effect, codeine should not be used in children, especially after adenoidectomy or tonsillectomy, due to an increased risk of opioid-induced ventilatory impairment and death (**N**).

☑ The practice of applying an occlusive dressing to the skin surface of a transdermal opioid delivery system to limit drug delivery is not supported (**N**).

Tramadol

1. Tramadol has similar efficacy to opioids in children of all ages administered by various routes for multiple surgery types (**N**) (**Level II).**

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Tramadol shares some adverse effects with the opioid class in children, with similar or reduced rates of nausea and vomiting, sedation and fatigue but less constipation and pruritus (**N**).
- ☑ Tramadol may cause less ventilatory impairment in adults and children. However, as its active opioid metabolite (M1) is produced by CYP2D6, it may share in part the concerns raised for codeine (and hydrocodone) in patients who are ultrametabolisers, particularly when at risk of opioid-induced ventilatory impairment (**N**).
- ☑ Tramadol concentrated drops formulation use is potentially harmful in children with possible dosing confusion (drops with millilitres) and resultant overdose (**N**).

9.4.5 Ketamine

Ketamine has been used in anaesthetic, sedative and analgesic (subanaesthetic) doses perioperatively for intra and postoperative analgesia. It has been administered at varying doses, via various routes, with different timing and duration, for multiple paediatric surgery types, in small studies rendering interpretation challenging. This section covers perioperative use in paediatrics (see also Section 9.7 for use in paediatric procedural sedation, Section 9.6.3 for paediatric peritonsillar infiltration and regional adjunct use, Section 9.8 for use in cancer pain and Section 4.6 for adult data).

9.4.5.1 Pharmacodynamics and pharmacokinetics in children

Pharmacodynamic effects have been investigated in children mainly following procedural sedation use and ketamine and norketamine pharmacokinetics have been investigated in this patient group (Herd 2007a **PK**; Herd 2007b **PK**). Pharmacokinetic modelling reveals ketamine infusions of 0.2 mg/kg/h for 24 h will achieve a median steady-state concentration of 0.15 mg/L, which is maintained for 0.5 h post cessation, with norketamine plasma concentrations contributing for a further 1 h; the half-life for equilibration ($t_{1/2}$keo) is short at 11 s. Ketamine undergoes extensive hepatic metabolism. The active metabolite norketamine is thought to be more potent, contributing to 30% of the parent compound's analgesic effect (Herd 2007b **PK**), although in an adult volunteer study an antalgesic effect is also proposed (Olofsen 2012 **EH**). Norketamine plasma concentration peaks 1 h post bolus ketamine administration (Herd 2007b **PK**).

The isomeric formulation S(+)-ketamine has twice the analgesic potency, is shorter acting with slightly less adverse cognitive effects in adults (Mion 2013 **NR**) but is not available in Australia and New Zealand. Following major urological procedures, children treated with intraoperative low-dose S-ketamine (bolus 0.2 mg/kg then infusion 0.3 mg/kg/h) vs placebo had a longer time to first analgesic request but had similar pain scores and 72 h morphine consumption (administered by NCA) (Becke 2005 **Level II**, n=30, JS 5).

9.4.5.2 Efficacy

Perioperative use

The efficacy of perioperative use of ketamine has been assessed in children, mostly having tonsillectomy, urological and hernia surgery in two systematic reviews (Dahmani 2011 **Level I** [QUORUM], 35 RCTs, n=1,925; Cho 2014 **Level I** [PRISMA], 24 RCTs, n=1,257). In the earlier systematic review, the routes and surgery types are heterogeneous. Ketamine administered IV was assessed in 18 RCTs (n=985); most commonly by bolus (median 0.5, range 0.1 to 6.0 mg/kg) in 13 tonsillectomy and 2 circumcision RCTs, or then followed by intraoperative infusion in a scoliosis RCT, and as a postoperative infusion in 2 RCTs following urological or lower limb surgery and post appendectomy (see below). Initial PACU pain scores (SMD -0.45/10; 95%CI 0.73 to -0.16) and analgesic requirement (OR 0.46; 95%CI 0.3 to 0.77) are reduced (10 RCTs, n=627) compared to placebo but later (6–24 h) pain scores and analgesic requirement are not.

The second review of trials only in tonsillectomy overlapped by eight RCTs (four IV and four peritonsillar and topical ketamine use). It assessed pre-emptive administration including 16 further RCTs (Cho 2014 **Level I** [PRISMA], 24 RCTs, n=1,257). It confirmed the earlier findings of reduced early (but not later) pain scores with ketamine vs placebo at 0 h (SMD -1.7/10; 95%CI 3.17 to -0.24) (6 RCTs, n=290) and 4 h (SMD -0.8/10; 95%CI -1.2 to -0.4) (14 RCTs, n=718), with reduced need for (LogOR -1.2) and amount of analgesia required (SMD -1.3) and longer time to first rescue analgesic (SMD 0.96 h) (p≤0.001). Pain scores were similar for ketamine when compared to opioid at five time points ranging from 0–24 h (9 RCTs, n=428).

Two tonsillectomy studies not included in these meta-analyses had similar conclusions. Ketamine 0.5 mg/kg administered IV and SC at surgery cessation was superior to placebo (Javid 2012 **Level II**, n=75, JS 5) and topical application of ketamine, morphine and lignocaine (without systemic comparator) similarly reduced PACU pain scores and rescue analgesic requirement in PACU, with all three superior to placebo (Hosseini Jahromi 2012 **Level III-1**).

Postoperative infusion

Children who received low-dose bolus 0.15 mg/kg and then infusion of 0.084 mg/kg/h for 24 h (in addition to multimodal therapy with caudal local anaesthetic, paracetamol, nsNSAID and nalbuphine infusion) had similarly low pain scores and minimal rescue nalbuphine requirements compared to placebo-treated children following mixed lower abdominal or orthopaedic surgery (Bazin 2010 **Level II**, n=37, JS 4). Bolus dose 0.5 mg/kg alone or followed by 0.084 mg/kg/h for 48 h post appendectomy had similar morphine requirements vs placebo (Dix 2003 **Level II**, n=75, JS 4). A higher dose (0.15 mg/kg/h), when added to fentanyl PCA, was effective in Nuss procedure with opioid consumption reduced by 15–23%, less postoperative vomiting and improved pain scores (0.5/10 at 24 and 48 h) (Cha 2012 **Level II**, n=60, JS 2). Loading dose 0.5 mg/kg, intraoperative 0.25 mg/kg/h infusion and postoperative 0.1 mg/kg/h infusion for 72 h following scoliosis surgery had similar morphine consumption over 96 h vs placebo (Pestieau 2014 **Level II**, n=54, JS 5). Low-dose bolus and higher infusions (median 0.2 mg/kg/h) combined with systemic opioid analgesia has been used after scoliosis surgery (Palmer 2010 **NR**).

Acute pain and relevant pharmacokinetics

Ketamine has also been used prehospital and in the ED for analgesia, commonly for severe pain (>6/10) following limb injury/fracture, burns, falls or road traffic accidents. Doses of 0.25–1 mg/kg have been used in children via IV, IM and IN routes (Bredmose 2009a **Level IV**; Bredmose 2009b **Level IV**; Reid 2011 **CR**; Yeaman 2013 **Level IV**), as well as higher doses IM (Svenson 2007 **Level IV**).

Beneficial use of low-dose 0.1–0.2mg/kg/h infusion in sickle cell crises is described in children in addition to (n=4) and to replace (n=1) opioid IV PCA (Zempsky 2010 **Level IV**).

When IV ketamine is used for procedural sedation, there is a steep concentration-response relationship (almost all or no response) with an EC50 for arousal of 0.56 mg/L (Herd 2008 **Level IV**).

Oral ketamine has a high first-pass effect. This property results in high early norketamine concentrations compared to IV administration. The peak ratio of norketamine/ketamine at 1 h is 2.8 after oral administration allowing an analgesic contribution from the metabolite at this time. This property has proved useful when racemic ketamine is given 1 h before burns dressings (Brunette 2011 **Level IV**).

For procedural analgesia, the bioavailability of IN racemic ketamine (0.5 mg/kg combined with sufentanil 0.5 mcg/kg) was 36%, with a T_{max} of 8.9 min in awake children (half the value reported in anaesthetised children) (Nielsen 2014 **Level IV**). The IN spray was acceptable to the majority of patients. S-ketamine 2 mg/kg has also been administered IN in anaesthetised children and its pharmacokinetics assessed but data quantifying effect are not available (Weber 2004 **PK**).

Modification of remifentanil-induced hyperalgesia

Two adolescent scoliosis trials have assessed intraoperative ketamine for reducing hyperalgesia associated with remifentanil. The four-fold difference in ketamine dose administered (0.06 vs 0.24 mg/kg/h) and small sample size mean a conclusion regarding ketamine's utility in this setting cannot be drawn (Dahmani 2011 **Level I** [QUOROM], 1 RCT [scoliosis], n=34; Pestieau 2014 **Level II**, n=54, JS 5).

9.4.5.3 Adverse effects

Ketamine IV (median 0.5 mg/kg) is not associated with PONV (during the first 24 h) (OR 1.35; 95%CI 0.99 to 2.09) or psychomimetic manifestations such as hallucinations, dysphoria-euphoria and sedation (OR 1.52; 95%CI 0.72 to 3.24). The odds ratios were similar for these outcomes in the caudal ketamine RCTs (Dahmani 2011 **Level I** [QUOROM], 35 RCTs, n=1,925).

Following major Nuss procedure and scoliosis surgery, no patients experienced hallucinations, dreaming or agitation in either ketamine or placebo-treated groups (Cha 2012 **Level II**, n=60, JS 2; Pestieau 2014 **Level II**, n=54, JS 5). Emergence reactions are described following anaesthetic dosing for procedural use along with other rare reports of laryngospasm, vomiting and itch in a large case series (n=8,282) (Green 2009b **Level IV**; Green 2009c **Level IV**) but not following analgesic doses or infusions.

Neurotoxicity

The possible neurodegenerative effect of ketamine (and other analgesic/anaesthetic agents) on the developing brain is under discussion (Davidson 2013 **NR**; Walker 2012b **NR**). Racemic ketamine (with its preservative benzethonium chloride) and S-ketamine have been associated with neuronal apoptosis and sensorineural consequence in animal models following high-dose and/or long-term IV and IT administration (Green 2009a **NR**; Walker 2010 **BS**; Walker 2012b **NR**; Davidson 2013 **NR**). The translatability to humans is questioned and the impact of lower subanaesthetic doses (bolus and perioperative infusion) is uncertain.

Key messages

1. Low-dose ketamine bolus IV perioperatively is similarly effective to opioids and superior to placebo in reducing early pain scores and analgesic requirements in children (**N**) (**Level I** [PRISMA]).
2. Low-dose ketamine bolus IV perioperatively does not increase the postoperative incidence of nausea and vomiting, sedation, agitation, dreams or hallucinations in children (**N**) (**Level I** [QUOROM]).
3. Peritonsillar infiltration and topical application of ketamine for paediatric tonsillectomy reduces early pain scores and analgesic requirements versus placebo (**N**) (**Level I** [PRISMA]).
4. When added to multimodal analgesia, low-dose intra and postoperative ketamine infusion for minor or moderately invasive paediatric surgery is not opioid sparing with similarly low pain scores vs placebo (**N**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ High-dose long-term ketamine is neurotoxic in animal models. The neurodevelopmental impact in children of subanaesthetic/analgesic doses of ketamine administered by bolus or postoperative infusion is unclear (**N**).
- ☑ The benefit of perioperative ketamine in preventing remifentanil-induced hyperalgesia has not been adequately assessed in paediatric surgery (**N**).

9.4.6 Alpha-2-delta ligands (gabapentin/pregabalin)

In paediatric scoliosis patients, 5 d of perioperative gabapentin reduced total morphine consumption in PACU, postoperative d 1 and 2 by 16–23% and pain scores in PACU and the

first postoperative morning only, with no differences in other outcomes vs placebo (Rusy 2010 **Level II**, n=59, JS3). See Section 4.8 for a summary of use of gabapentinoids in adults.

9.4.7 Alpha-2 adrenergic agonists

The alpha-2 agonists clonidine and dexmedetomidine are attractive for use in paediatrics with their analgesic, sympatholytic (anxiolytic, haemodynamic modulation), antinausea/antiemetic and behavioural modification/sedative effects. Administered as bolus and/or infusion via various routes, both agents have been used in various paediatric settings, including preoperatively as premedication, intraoperatively for controlled hypotension and to modify anaesthetic/perioperative opioid requirements, postoperative nausea and vomiting, shivering and emergence agitation, and as local anaesthetic adjuvants (see Section 9.6). They are also used in PICUs and NICUs, particularly in ventilated patients (Playfor 2006 **GL**; Gupta 2012 **Level III-2**; Nemergut 2013 **NR**), for sedation and analgesia, to modify distress hypertensive response and escalating opioid requirements, and to prevent and treat opioid withdrawal symptoms (Honey 2009 **Level IV SR**, 9 studies, n=44; Oschman 2011 **NR**) and facilitate opioid weaning. For similar indications, they are used in paediatric ward settings and also for procedural sedation and analgesia in the outpatient, emergency and radiology settings (McMorrow 2012 **NR**).

9.4.7.1 Clonidine

Clonidine has been used for the above indications for decades (Eisenach 1996 **NR**; Nishina 2002 **NR**; Basker 2009 **NR**).

Preoperative clonidine 2–4 mcg/kg administration (oral in 10 RCTs, rectal in 1 RCT) reduces postoperative pain scores, analgesic requirement and PONV when compared with midazolam and placebo but not fentanyl (Lambert 2014 **Level I** [Cochrane], 11 RCTs [comparators: 6 midazolam, 4 placebo and 1 fentanyl], n=748). An earlier review (overlapping by 4 RCTs) draws similar conclusions (Dahmani 2010 **Level I,** 10 RCTs, n unspecified). It additionally reports superiority of clonidine over midazolam for sedation at induction (OR 0.49; 95%CI 0.27 to 0.89) (2 RCTs) and reduced incidence of emergence agitation (OR 0.25, 95%CI 0.11 to 0.58) (3 RCTs) and superiority over diazepam for PONV (OR 0.34, 95%CI 0.13-0.94) (2 RCTs).

Intraoperative IV administration of clonidine reduces postoperative emergence agitation compared with placebo (OR 0.5; 95%CI 0.26 to 0.95) (Pickard 2014 **Level I,** 2 RCTs [clonidine], n=170).

Typical bolus clonidine doses are 1–2 mcg/kg: IV, regionally and for infiltration (see Section 9.6).

Clonidine has been infused in cardiac surgery and intensive care at widely ranging rates: 0.18 to 1–3 mcg/kg/h (Basker 2009 **NR**).

Aerosolised IN clonidine 3–8 mcg/kg is unreliable in terms of sedative efficacy and time to onset of effect (Larsson 2012 **Level II**, n=60, JS 5). This route has not been used for analgesic indications.

Pharmacokinetics

Bioavailability of clonidine after oral and rectal administration is high (100%) but after nasal drop administration is erratic in supine anaesthetised children (Almenrader 2009 **PK**).

9.4.7.2 Dexmedetomidine

Dexmedetomidine is more alpha-2 selective than clonidine. Its use is increasing in various paediatric settings (Phan 2008 **NR**; Tobias 2007 **NR**).

Following paediatric ear, tonsillectomy, laparoscopic appendectomy and genital surgery, intraoperative dexmedetomidine 0.15–2 mcg/kg IV/IN compared to placebo reduced postoperative pain (RR 0.51; 95%CI 0.32 to 0.81) (2 RCTs, n=138) and need for postoperative opioid rescue (RR 0.4; 95%CI 0.26 to 0.62) (4 RCTs, n=249) but not overall morphine requirement (MD -0.12 mg/kg; 95%CI -0.25 to 0.01) (2 RCTs, n=98) (Schnabel 2013 **Level I** [PRISMA], 11 RCTs [10 IV, 1 IN], n=874). Compared with intraoperative opioids, dexmedetomidine

0.75–4mcg/kg reduced postoperative pain (RR 0.49; 95%CI 0.25 to 0.94) (3 RCTs, n=234) but not the need for postoperative opioids (RR 0.77; 95%CI 0.6 to 1.1) (4 RCTs, n=394).

Intraoperative IV administration of dexmedetomidine reduces postoperative emergence agitation compared with placebo (OR 0.22; 95%CI 0.14 to 0.33) (Pickard 2014 **Level I**, 8 RCTs [dexmedetomidine], n=499), propofol (Ali 2013 **Level II**, n=120, JS 5) and ketamine (Chen 2013 **Level II**, n=68, JS 5).

Dexmedetomidine IN has been compared with fentanyl IN, with and without midazolam premedication, for myringotomy in children aged 1–8 y, with similar postoperative pain scores (Dewhirst 2014 **Level II**, n=100, JS 5).

Following scoliosis surgery, postoperative infusion (0.4 mcg/kg/h for 24 h) added to morphine IV PCA had no effect on morphine consumption or adverse effects (Sadhasivam 2009 **Level III-2**). In ventilated scoliosis patients, dexmedetomidine (0.4 mcg/kg/h) compared to midazolam (0.1 mg/kg/h) reduced pain scores and modestly reduced low 24 h fentanyl consumption (124 mcg +/-28 vs 165.8 +/-33) (Aydogan 2013 **Level II,** n=32, JS 4). Dexmedetomidine 0.05–0.2 mcg/kg/h was coadministered for 5 d to a child aged 2 y with chemotherapy-induced enterocolitis improving pain control and allowing hydromorphone infusion reduction (Winton 2011 **CR**).

Pharmacokinetics

The pharmacokinetics of dexmedetomidine 1 mcg/kg IV have been studied in a small series of children (Vilo 2008 **PK**). The volume of distribution is larger in children aged <2 y.

9.4.7.3 Adverse effects

Hypotension and bradycardia are desirable effects with use of these agents for "controlled hypotension". Alpha-2 adrenergic agents have provided cardiac stability in the setting of paediatric cardiac surgery and intensive care patients (Basker 2009 **NR;** Gupta 2012 **Level III-2**; Phan 2008 **NR**; Tobias 2007 **NR**). The haemodynamic effects can be undesirable but have been variably reported (Phan 2008 **NR**; Basker 2009 **NR**) and are more apparent with high bolus doses of dexmedetomidine. RCTs (using 2–5 mcg/kg clonidine) reported no significant differences in hypotension/bradycardia incidence but interpretation was complicated by the use of atropine pretreatment and there were no comments made on the use of corrective interventions (Lambert 2014 **Level I** [Cochrane], 4 RCTs, n=279). Hypotension and bradycardia, defined as a 20% drop from baseline, occurred in 10 of 60 clonidine-treated vs 0 of 30 placebo-treated (Mikawa 1996 **Level II**, n=90, JS 4). Hypotension defined as <70 mmHg and bradycardia defined as <60 beats/min occurred in 4 of 30 clonidine-treated and 0 of 15 midazolam-treated (Cao 2009 **Level II**, n=45, JS 3).

The sedative effect may be undesirable. A few small studies assess the outcome of time spent in PACU or delay in discharge following perioperative administration. For clonidine, delayed discharge (WMD 10.8 min; 95%CI 4.2 to 17.5) and increased sedation frequency post discharge were reported vs placebo (Malviya 2006b **Level II,** n=120, JS 5). In contrast, slightly earlier discharge is reported compared to placebo (1 RCT, n=46) and no difference reported in comparison with midazolam (2 RCTs, n=194) (Lambert 2014 **Level I** [Cochrane], 11 RCTs, n=748). Following IV dexmedetomidine, there is minimal clinical impact (of ≈3 min) on time spent in PACU (4 RCTs, n=275) and time to discharge (2 RCTs, n=92) (Pickard 2014 **Level I**, 12 RCTs, n=771).

Reviews assessing impact on these outcomes after caudal clonidine administration are conflicting; individual dexmedetomidine trials have reported some impact on emergence, higher sedation scores, longer duration of postoperative sedation and no impact on time to postoperative extubation (see Section 9.6.2).

In contrast to most anaesthetic agents used, neuraxial clonidine has not been implicated in any reports or studies of neural toxicity/apoptosis and neither has epidural or intraperitoneal dexmedetomidine in animal models (Walker 2012b **NR**; Davidson 2013 **NR**).

Key messages

1. Preoperative oral clonidine reduces postoperative pain scores and analgesic requirement in children compared to placebo or midazolam but not fentanyl **(N) (Level I** [Cochrane Review]).
2. Preoperative oral clonidine reduces postoperative nausea and vomiting in children compared to placebo or midazolam **(N)** (**Level I** [Cochrane Review]).
3. Intraoperative dexmedetomidine reduces postoperative pain scores and need for opioid rescue in children compared to placebo via intravenous (**N**) (**Level I** [PRISMA]) and intranasal route (**N**) (**Level II**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Alpha-2 adrenergic agonists offer benefits in addition to analgesia in children in the perioperative, intensive care and procedural settings. These benefits include anxiolysis, sedation, behavioural modification, reduction of emergence agitation and prevention or treatment of opioid withdrawal (facilitating opioid weaning) (**N**).

9.4.8 Corticosteroids

The impact of systemic corticosteroid use on various outcomes in children post surgery or with acute pharyngitis has been assessed; for data on corticosteroid use in combination with local and regional techniques see Section 9.6.

For pharyngitis (proven bacterial or severe symptoms), oral dexamethasone 0.6 mg/kg (max 10 mg) achieved onset of analgesia 5–24 h earlier than placebo (measured with three different scoring systems), with a single dose as effective as a 3-d course (Korb 2010 **Level I**, 3 RCTs [paediatric], n=393) (see Section 8.6.7.5 for adult data).

Following paediatric dental surgery under general anaesthetic, single-dose dexamethasone IV 0.3 mg/kg (maximum 8 mg) did not improve pain scores or oral intake but reduced postoperative vomiting (McIntyre 2012 **Level II**, n=200, JS 5).

Following paediatric tonsillectomy, a 5-d postoperative course of prednisolone did not improve pain, PONV, return to normal diet or sleep (Macassey 2012 **Level II,** n=215, JS 5).

Beneficial effects upon multiple outcomes are reported for single-dose dexamethasone in children 1 d following tonsillectomy (Steward 2011 **Level I** [Cochrane] 19 RCTs, n=1,756). Compared to placebo, dexamethasone IV 0.15–1.0 mg/kg (maximum 8–25 mg) improved postoperative pain as measured by VAS (MD -1.1/10; 95%CI -1.7 to -0.4) (8 RCTs, n=652), reduced postoperative vomiting (RR 0.49; 95%CI 0.41 to 0.58) (15 RCTs, n=1,273) and resulted in an earlier return to soft diet (RR 1.45; 95%CI 1.15 to 1.83) (5 RCTs, n=452). A sub-analysis to assess dose-dependent effect was not performed. A trial, excluded from this review (due to early termination), compared dexamethasone 0.05, 0.15 and 0.5 mg/kg (maximum 20 mg) and demonstrated a dose-dependent effect for PONV (Czarnetzki 2008 **Level II**, n=215, JS 5). The reason for termination was dose-dependent increase in bleeding in dexamethasone-treated patients (above those ibuprofen-treated).

Four subsequent systematic reviews of dexamethasone have included this RCT and have qualified this finding (Geva 2011 **Level I**, 14 RCTs [11 paediatric], n=1,429; Shargorodsky 2012 **Level I**, 12 RCTs [paediatric] n=1,180; Bellis 2014 **Level I**, 15 RCTs, n=1,693; Plante 2012 **SR Level III-1,** 28 studies, n=2,674). These reviews have 9–14 RCTs overlap. The included studies assess haemorrhage as primary or secondary, requiring readmission, transfusion or reoperation and with 6 h to 14 d follow-up. The largest review includes randomised and nonrandomised studies and reports an overall bleeding rate of 4.4% (Plante 2012 **SR Level III-1,** 28 studies, n=2,674). Dexamethasone does not increase the overall risk of bleeding post tonsillectomy (OR 0.96; 95%CI 0.66 to 1.40)

but reoperation for bleeding is increased in children (OR 3.43; 95%CI 1.29 to 9.13) (8 RCTs) but not in adults (4 RCTs).

Key messages

1. Dexamethasone reduces pain post tonsillectomy, postoperative vomiting and time to soft diet commencement in children (**S**) (**Level I** [Cochrane Review]).
2. Dexamethasone does not increase the overall risk of bleeding post tonsillectomy but increases the risk of reoperation for bleeding in children (**Q**) (**Level I**).
3. Dexamethasone (given in addition to antibiotics) shortens the time to onset of pain relief in pharyngitis in children (**N**) (**Level I**).

9.5 Opioid infusions and PCA

This section incorporates the techniques of parenteral administration of opioids to children via continuous infusion and PCA devices, including a subsection on nurse-controlled and parental proxy. As intermittent IM injections are distressing for children, parenteral administration via the IV route is preferred; if peripheral perfusion is normal, the SC route can be used (McNicol 1993 **Level IV**) with similar safety and efficacy to the IV route (Doyle 1994a **Level II**, n=60, JS 3). Procedure-specific dose recommendations and evidence for the use of these parenteral techniques have been published (APAGBI 2012 **GL**). Large-scale audits (of 10,000+ children) provide data for serious clinical incidents and adverse effects associated with the use of these parenteral opioid techniques (see individual subsections and "Overall safety" at the end of this section).

9.5.1 Opioid infusions

Differences between intermittent bolus doses and continuous infusion of opioid relate more to the total dose than to the administration method (Lynn 2000 **Level III-2**). Comparison in neonates and young infants of the same total dose of morphine given via infusion (10 mcg/kg/h) or bolus (30 mcg/kg every 3 h) found no difference in pain scores (COMFORT scale and observer VAS) (Bouwmeester 2003a **Level II,** n=68, JS 3; van Dijk 2002 **Level II**, n=181, JS 4) or stress response to surgery (Bouwmeester 2001 **Level II**, n=204, JS 4). However, these doses were inadequate in children aged 1–3 y, in whom additional bolus doses were required and the 3-h interval was less effective (possibly due to more rapid clearance) (van Dijk 2002 **Level II**, n=181, JS 4).

Pharmacokinetic data has provided support for aged-based initial dosing recommendations for morphine infusion for postoperative pain: 10 mcg/kg/h in neonates, 15 mcg/kg/h in toddlers and 25 mcg/kg/h in children >5 y (Taylor 2013 **Level IV PK**); 10–40 mcg/kg/h are standard postoperative ward order parameters (APAGBI 2012 **GL**). In ventilated postsurgical neonates, various morphine infusion regimens have been used ranging from 2.5–5 mcg/kg/h (Ceelie 2013 **Level II**, n=71, JS 5) to 10–30 mcg/kg/h (Olischar 2014 **Level II**, n=71, JS 5; Anand 2008 **Level II**, n=1,773, JS 5), with wide variation between centres (Anand 2013 **Level IV**). For control of acute procedural pain in ventilated neonates, opioid infusions have limited efficacy (Anand 2008 **Level II,** n=1,773, JS 5) and other analgesic interventions are recommended (APAGBI 2012 **GL**) (see also Section 9.4.1). Following ureteroneocystostomy, fentanyl loading of 1 mcg/kg and then infusion 0.17 mcg/kg/h was effective, although patients who received continuous ketorolac infusion experienced less frequent bladder spasms (Jo 2011 **Level II**, n=52, JS 5).

9.5.1.1 Adverse effects, complications and outcomes

A prospective multicentre audit has reported on 1,955 opioid infusions (Morton 2010 **Level IV**). This audit reports only two cases of respiratory depression in association with continuous opioid infusion, one requiring naloxone. Sedation scores, oxygen saturations and requirement data were not collected. Programming or prescription errors were the most common reported incidents with continuous opioid infusions (n=9), none of which led to patient harm (see also Section 9.5.2).

The impact of the routine use of morphine infusion in ventilated neonates on neurodevelopmental and other outcomes has been studied and remains of concern (Anand 2004 **Level II**, n=898, JS 4). A meta-analysis found no differences in mortality, duration of ventilation, or improvements in short or long-term neurological outcomes but the analysed outcomes were assessed by small, heterogeneous and usually single trials of low quality (Bellu 2008 **Level I** [Cochrane], 13 RCTs, n=1,505). A study found no overall harm at 8-y follow-up (n=89), with positive effects on higher executive function of low-dose infusions (10 mcg/kg/h) (de Graaf 2013 **Level IV**). The same authors at 5-y follow-up (n=90) had previously suggested a negative association with morphine use and the "visual analysis" intelligence quotient subtest, after adjusting for propensity scores (de Graaf 2011 **Level IV**). Detrimental effects of prolonged sedation and/or analgesia on preterm neonates have also been a research focus (Anand 1999 **Level II**, n=67, JS 5; Anand 2004 **Level II**, n=898, JS 4). A 5-y follow-up of very premature neonates (n=1,572) found morphine and sedative exposure for >7 d was associated with poor neurodevelopmental outcome. This association was abolished once adjusted for gestational age and propensity scores (Roze 2008 **Level III-2**). As studies vary in the degree and manner of correction for confounding factors, follow-up at a later age focussing on higher-order neurocognitive function is necessary.

9.5.1.2 Iatrogenic opioid dependence in hospitalised children

Administration of opioids for as little as 5–7 d can produce opioid dependence. Recognition and management of withdrawal is important to reduce physiological disturbance. This is particularly relevant for intensive care patients receiving opioids for sedation, endotracheal tube tolerance and postoperative pain, where tolerance (particularly to fentanyl) is recognised (Gish 2011 **Level III-3**; Anand 2013 **Level IV**). Weaning 10–20% of total dose every 48 h is recommended (Anand 2013 **Level IV;** Galinkin 2014 **NR**).

9.5.2 Patient-controlled analgesia

Patient-controlled analgesia can provide safe and effective analgesia for children aged as young as 5–6 y and compares favourably with continuous morphine infusion (Morton 2010 **Level IV**). Patient selection is important and depends on the ability of the child and carers to understand the concepts of PCA and the availability of suitable equipment and trained staff.

Compared with continuous IV opioid infusions, PCA provided greater dosing flexibility, and similar analgesia. PCA has been associated with higher opioid consumption but the incidence of adverse effects has varied, depending on the PCA dosing parameters (Bray 1996 **Level III-2**; Peters 1999 **Level II**, n=47, JS 3). PCA can be particularly useful in children with altered opioid requirements. Postoperative PCA morphine requirements in children with sickle-cell disease were almost double those of nonsickle children (Crawford 2006a **Level III-3**). Morphine PCA with bolus and background (mean rate 20 mcg/kg/h) has been used for paediatric sickle cell patients (Jacob 2008 **Level IV**).

Following scoliosis surgery, morphine and hydromorphone by PCA have been used (McDonnell 2012 **Level III-3;** Matava 2014 **Level IV;** Milbrandt 2009 **Level III-3**; Ravish 2012 **Level III-3**). A high early PCA demand ratio predicts higher pain scores, 24 h morphine consumption (Matava 2014 **Level IV**) and the need to rotate to hydromorphone (McDonnell 2012 **Level III-3**). Intraoperative remifentanil was associated with an increase in PCA morphine requirement in the 24 h post scoliosis surgery (Crawford 2006b **Level II,** n=30, JS 5), likely due to acute opioid tolerance or opioid-induced hyperalgesia. Following pectus excavatum surgery, PCA morphine and hydromorphone have been compared to epidural analgesia with minimal advantage of epidural analgesia with regard to pain scores and no other differences (Stroud 2014 **Level III-3 SR**, 6 studies, n=403) (see also Section 9.6.2). PCA morphine with ketoprofen vs placebo has been trialled (Rugyte 2007 **Level II**, n=31, JS 5) and morphine by PCA was similarly effective to morphine by continuous infusion (Rugyte 2010 **Level III-3**). Post tonsillectomy, morphine 2 mg PCA bolus vs tramadol 20 mg PCA bolus were similarly effective (Ozalevli 2005 **Level III-1**).

Fentanyl is a useful alternative opioid, particularly for patients with renal impairment or those experiencing morphine-related adverse effects (Tobias 1992a **Level IV**). Fentanyl PCA has been used safely and effectively following neurosurgery (Chiaretti 2008 **Level IV**), pectus excavatum

surgery (Butkovic 2007 **Level IV**) and for acute cancer-related pain (Ruggiero 2007 **Level IV**) (see also Section 9.8).

As in adults, the use of pethidine should be discouraged in the paediatric setting (Benner 2011 **NR**). Pethidine does not have any advantage over other opioids and neurotoxicity from norpethidine (normeperidine) accumulation has been reported in a healthy adolescent (Kussman 1998 **CR**) (see also Section 4.1.1.2).

9.5.2.1 PCA prescription

A survey of 294 paediatric anaesthetists in the USA found significant variation in standard prescribing practices for PCA (Nelson 2010 **Level IV**). Worldwide, morphine is the medicine used most frequently in paediatric PCA. A bolus dose of morphine 20 mcg/kg is a suitable starting dose (APAGBI 2012 **Level IV**) and is associated with improved pain scores during movement compared with 10 mcg/kg (Doyle 1994b **Level II**, n=40, JS 3). The addition of a background infusion is more common in children than adults, tends to be reserved for more painful surgeries or conditions such as scoliosis and mucositis, and may be time limited postoperatively eg first 12–48 h. Morphine 0–4 mcg/kg/h is recommended (APAGBI 2012 **Level IV**). Higher background rates are also prescribed (Nelson 2010 **NR**). A meta-analysis, incorporating data from three small paediatric trials, reports that the addition of a background infusion increases the odds for respiratory depression in adults (see Section 6.4.3) but not in children (George 2010 **Level I**, 3 RCTs [paediatric], n=122). The combined ORs for sedation and pruritus were not significantly different and nausea and vomiting as an outcome could not be assessed. Although use of a background infusion was associated with increased sleep disturbance in one audit (calculated from the number of hours PCA presses were required), numbers were too small to fully investigate the contribution of the kind of surgery (Kelly 2006 **Level IV**). Morphine PCA 20 mcg/kg bolus with 5–20 mcg/kg/h background infusion has been used for children (>7 y) having laparoscopic appendectomy (Liu 2013 **Level IV**). Surveyed anaesthetists reported fentanyl prescriptions of 0.2–0.4 mcg/kg boluses and hydromorphone of 1–3 mcg/kg (with similar background infusion rates) (Nelson 2010 **NR**). Hydromorphone was dosed in a paediatric series as 3 mcg/kg PCA boluses and had similar efficacy and adverse-effect profile to morphine 15 mcg/kg boluses (Karl 2012 **Level III-1**). Hydromorphone IV PCA 2 mcg/kg bolus with 2 mcg/kg/h background has been compared with PCEA bupivacaine/hydromorphone in scoliosis surgery (Gauger 2009 **Level II**, n=38, JS 3).

9.5.2.2 Adverse effects, complications and outcomes

Nausea and vomiting occurs in 30–45% of children using morphine PCA and can be reduced by prophylactic antiemetics (Carr 2009 **GL**). Adding antiemetics directly to PCA solutions for children was not effective (Munro 2002 **Level II**, n=60, JS 5). Addition of a low-dose naloxone infusion (0.25 mcg/kg/h) did not impair analgesia but decreased pruritus and nausea in postoperative children treated with PCA (Maxwell 2005 **Level II**, n=46, JS 5). Naloxone 1 mcg/kg/h more effectively decreased pruritus than 0.25 mcg/kg/h in children requiring morphine infusions during a sickle cell crisis (Koch 2008 **Level IV**). The suggested optimal dose of IV naloxone by continuous infusion (n=59; determined by up titration from 0.05 to 1.65 mcg/kg/h) is approximately 1 mcg/kg/h (Monitto 2011 **Level IV**).

Recognition of potential complications of PCA use was enhanced by providing set instructions for monitoring, and by APS support (Wrona 2007 **Level III-2**). A large UK audit has included prospective data for PCA (n=5,065) (Morton 2010 **Level IV**). No incident of permanent harm occurred, with a very low incidence (approximately 1 in 500) of "harm with full recovery", including respiratory depression requiring naloxone (1), urinary retention (4), nausea/vomiting (5) and itch (3). Sedation scores were not collected. These adverse effects were defined by "requiring cessation of or change in technique", which explains why rates were lower than reported in case-control series and trials. Seven programming and prescribing errors that did not lead to harm were also reported.

Compartment syndrome in children occurs infrequently (1.3–3%), usually diagnosed at a mean of 19 h (range 1.5–65) post fracture or surgery of the distal limb (Ferlic 2012 **Level IV**). Pain as one of the "5P hallmarks" can be further qualified as pain escalation at rest as well as

with passive movement, unrelieved by plaster splitting and with increased analgesic request. Escalation in PCA demands may occur as reported in two paediatric patients (Yang 2010 **Level IV**).

9.5.3 Nurse-controlled analgesia

In younger children and infants, "PCA" pumps have been used by nurses to administer intermittent bolus doses (with or without a background infusion), a technique termed "nurse-controlled analgesia" (NCA). This technique may increase ease of administration particularly prior to movement or procedural interventions, increase dose flexibility and improve parent and nurse satisfaction. Dose recommendations for morphine are generally 5–40 mcg/kg/h with 10–20 mcg/kg nurse-initiated boluses (Howard 2010 **Level IV**). NCA has also been used in older children in intensive care who are unable to activate a conventional PCA device. Adequate analgesia comparable to PCA was reported but efficacy was dependent on accurate nurse assessment of pain (Weldon 1993 **Level III-2**). The technique has also been used in open vs laparoscopic Nissen fundoplication surgery (McHoney 2011 **Level II**, n=39, JS 5) and for fast-track cardiac surgical patients (Iodice 2011 **Level IV**). In intubated patients post cardiac surgery, tramadol NCA in comparison to morphine NCA provided minor improvements in time to extubation (Chu 2006 **Level II**, n=40, JS 4). Fentanyl NCA with paracetamol (or placebo) has been used in young children (<2 y) post ureteroneocystostomy (Hong 2010b **Level II**, n=63, JS 5).

9.5.3.1 Adverse effects, complications and outcomes

The incidence of adverse effects was similar in children self-administering conventional PCA and those receiving NCA (Voepel-Lewis 2008 **Level III-2**; Morton 2010 **Level IV**). Rescue events (requiring naloxone, airway management or admission to high dependency/ICU) were more common in the NCA (and parental proxy) group but this group was also younger and had a higher prevalence of comorbidities (Voepel-Lewis 2008 **Level III-2)**. Cognitive impairment and high opioid dose requirements on d 1 were associated with increased adverse effects. Two large prospective audits in institutions with APS oversight affirm NCA use (mostly morphine; total n=13,706) as safe and effective for postoperative analgesia in children (Howard 2010 **Level IV**; Morton 2010 **Level IV**). The multicentre 2007–2008 UK audit reports one incident of harm overall, which was with the NCA technique (cardiac arrest in a 2.5 kg neonate), and eleven respiratory depression events (0.3% of 3,706) with "harm but full recovery", six requiring naloxone (Morton 2010 **Level IV)**. The single centre 1996–2008 audit reports no deaths but a similar rate of 0.4% for serious potentially life-threatening events of oversedation or respiratory depression requiring active resuscitation and naloxone (Howard 2010 **Level IV**). This audit provided rates for respiratory depression and sedation at 4.5% (with 91% improving with temporary cessation or adjustment of technique), PONV 25% (severe for 14%) and itching 9.4% (severe for 4%). The incidences varied with age, morphine dose, and type of surgery. Notably both audits report higher incidences of serious adverse effects with NCA in neonates than children aged >1 mth: 0.8 vs 0.4% (Morton 2010 **Level IV)** and 2.5 vs 0.27% (Howard 2010 **Level IV**).

9.5.4 PCA by proxy

Administration by a nurse trained in pain assessment, rather than parents, is recommended in most centres (Howard 2010 **Level IV**). Confusingly the term "PCA by proxy" has been used to describe administration by both nurses and/or parents. The Joint Commission on Accreditation of Healthcare Organisations issued a sentinel alert cautioning against the practice of parental proxy in 2004. In response, some US centres ceased to use parental proxy (reported by 11% of surveyed anaesthetists) (Nelson 2010). However, many centres continue this practice and, as for the conventional PCA technique, selection criteria, education and guidelines should be followed (Chidambaran 2012 **NR**). In a prospective series of PCA by proxy (parents or health care providers), effective analgesia was achieved in 81–95% of children <6 y of age; 25% required supplemental oxygen, and 4% required naloxone for respiratory depression (Monitto 2000 **Level IV**). In a retrospective series, PCA by proxy resulted in low pain scores, while somnolence or respiratory depression requiring naloxone occurred in 2.8% of children with developmental delay (Czarnecki 2008 **Level IV**) and 1.9% of infants and

preschoolers (Czarnecki 2011 **Level IV**). PCA by proxy vs conventional PCA in children with cancer pain was associated with comparable (Anghelescu 2005 **Level III-3**) and lower complication rates in a follow-on series (Anghelescu 2012 **Level IV**).

Comparison of morphine and hydromorphone via PCA, NCA and PCA by proxy (with a background infusion ≈70%) has been described (Voepel-Lewis 2008 **Level III-3**). Fentanyl PCA was administered by parental proxy (initial settings 0.075 mcg/kg bolus and background 0.3 mcg/kg/h) for toddlers for 48 h post cleft palate repair to establish an ED50–95 of 0.63–0.83 mcg/kg/h (Choi 2008 **Level IV**).

9.5.5 Overall safety of parenteral opioid use in children

Overall, parenteral opioid techniques are safe in children as long as administered in appropriate settings. Of 294 surveyed paediatric anaesthetists (representing 252 USA institutions with 51% having APS oversight), 8 recalled deaths (in the preceding 5 y) in association with these techniques and 42 recalled cardiorespiratory events requiring naloxone (in the year prior; denominator unknown) (Nelson 2010 **Level IV**). The incidence rates of respiratory depression in the various paediatric studies will vary depending upon how it is defined; degree of desaturation, requirement for supplemental oxygen, suspension/ cessation of opioids, requirement for naloxone or respiratory intervention including ventilation. The studies done to date are generally underpowered to detect differences in the incidence of respiratory depression. The large UK prospective audit of parenteral opioids delivered by the above techniques reports an overall ≈1 in 10,000 incidence of serious harm and 0.13% incidence of respiratory depression (requiring intervention with respiratory support, naloxone or opioid cessation) (Morton 2010 **Level IV)**. Importantly, these low rates occurred in UK centres with 100% oversight by a paediatric APS and with institutional guidelines in place. Safety can be improved through avoidance of concurrent sedatives or opioids by other routes, awareness of comorbidities posing extra risk and by careful dosing, with heightened monitoring in infants. Opioid prescription and pump programming errors were an issue (1 in 631 infusions or 0.16%) and can be minimised through adherence to guidelines and careful cross-checking (Morton 2010 **Level IV**).

Key messages

1. In ventilated preterm neonates, routine use of morphine infusions does not affect mortality, duration of ventilation or neurological outcomes (**Q**) (**Level I** [Cochrane Review]), including when followed up as older children (**N**) (**Level III-3**).
2. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**U**) (**Level II**).
3. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).
4. Patient-controlled analgesia (PCA) can provide safe and effective analgesia for children as young as 5 years old (**S**) (**Level III-3**).
5. Intravenous opioids via continuous infusion, nurse-controlled analgesia and parental proxy use of PCA devices can be used effectively in children of all ages (**S**) (**Level III-2**).
6. Nurse-controlled analgesia (**N**) (**Level III-2**) and parental proxy use of PCA devices in children (**N**) (**Level III-3**) may require more rescue interventions (such as naloxone, airway management or intensive care) but this may reflect the younger patient population where this technique is offered.

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Initial doses of opioid should be based on the age, weight and clinical status of the child and then titrated against the individual's response (**U**).
- ☑ Effective PCA prescription in children incorporates a bolus that is adequate for control of movement-related pain, and may include a low-dose background infusion (**W**).

9.6 Regional analgesia

Regional analgesia, incorporating peripheral and central block or catheter techniques, is typically performed in children under general anaesthesia. Large-scale prospective multicentre audits of these techniques (French, UK and the USA Pediatric Regional Anesthesia Network [PRAN]) have provided quality outcome and safety data (Llewellyn 2007 **Level IV**; Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**; Taenzer 2014 **Level IV**). Data collection and publication by PRAN is ongoing.

9.6.1 Continuous and single-injection peripheral nerve blocks

Peripheral local anaesthetic techniques are an effective and safe adjunct for the management of procedural, perioperative and injury-related acute pain (Giaufre 1996 **Level IV**; Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**; Bosenberg 2013 **NR**; Taenzer 2014 **Level IV**) (see also Section 5.8). PNBs are being increasingly performed in paediatrics with a trend away from central blocks (Bosenberg 2013 **NR**), particularly in older children/ adolescents (Kuo 2012 **Level IV**; Taenzer 2014 **Level IV**). The efficacy of specific local anaesthetic blocks for common paediatric surgical conditions has been assessed (see below). Differences between groups can be difficult to detect if the sample size is small or the outcome measure is relatively insensitive (eg supplemental analgesic requirements following procedures with low ongoing pain).

9.6.1.1 Continuous peripheral nerve blocks

The use of CPNB catheters and plexus techniques in children has increased significantly (Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**; Kuo 2012 **Level IV**). Prospective audits confirms efficacy (Ganesh 2007 **Level IV**; Ludot 2008a **Level IV**; Dadure 2009 **Level IV**; Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**; Gurnaney 2014 **Level IV**; Taenzer 2014 **Level IV**). Patients have been discharged home (d 0–3 postoperatively) with CPNB catheters and elastomeric pumps providing analgesia for 2–7 d with variable opioid requirements (Ludot 2008a **Level IV**; Ganesh 2007 **Level IV**; Gurnaney 2014 **Level IV**). These series total approximately 1,865 catheters in approximately 1,549 paediatric patients; the majority (92%) were discharged home with CPNB *in situ*. Infusion rates were 2–10 mL/h of ropivacaine (0.1–0.2%) or bupivacaine (0.1–0.125%). CPNB catheters have also been used to manage a few patients with complex pain due to pathological limb fracture (Burgoyne 2012 **Level IV**) and forequarter amputation (Kaddoum 2013 **Level IV**).

9.6.1.2 Safety and complications of peripheral nerve blocks

Two large regional block audits confirm the safety of PNBs (single injection and continuous n=46,927) (Ecoffey 2010 **Level IV**; Taenzer 2014 **Level IV**) with a six-fold lower complication rate of PNBs (0.05%; 95%CI 0.03 to 0.1) (n=20,576) vs central blocks (0.29%; 95%CI 0.21 to 0.43) (n=10,556) (Ecoffey 2010 **Level IV**). The PNBs in these audits were mostly performed under general anaesthesia (see further commentary in Section 9.6.2.4 Overall complications) and with US guidance (see below) (Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**).

Prospective audits confirm the safety of CPNBs (Ganesh 2007 **Level IV**; Ludot 2008a **Level IV**; Dadure 2009 **Level IV**; Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**; Gurnaney 2014 **Level IV**; Taenzer 2014 **Level IV**). Reported complications included primary failure of the technique at insertion (generally ≤2%; higher for upper limb 7.6%), recognised vascular puncture (2–3%), and secondary failure 2–20% (catheter kinking, dislodgement, leak, disconnection, malfunction) with rare occurrence of site infection requiring antibiotics (≤0.5–0.9%) and local anaesthetic systemic toxicity (≤0.3%) (Ganesh 2007 **Level IV**; Ludot 2008a **Level IV**; Dadure 2009 **Level IV**; Polaner 2012 **Level IV**; Gurnaney 2014 **Level IV**). In the series where patients were discharged home, the families received education in catheter clamping in the event of adverse effects and most had no difficulty with catheter removal. With low concentration and low infusion rates (see above), reported rates of motor block were 10 (Ganesh 2007 **Level IV**) to 20% (Dadure 2009 **Level IV**), resolving within 3 h of catheter clamping (Gurnaney 2014 **Level IV**).

Compartment syndrome

There were three case reports of compartment syndrome in adolescents that was not masked by CPNB (Cometa 2011 **CR**; Walker 2012a **CR**; Munk-Andersen 2013 **CR**). This highlights the need for clinical monitoring and early review in the event of breakthrough pain following high-risk injury or surgery.

9.6.1.3 Ultrasound guidance impact on safety and success

To date, paediatric trials are insufficient in number, size and power to evaluate whether US-guidance reduces adverse effects such as intravascular injection or nerve injury. US guidance for PNBs reduces onset time, improves block success in the upper extremity and trunk, improves block quality and reduces the local anaesthetic dose required (Tsui 2010 **Level I** [PRISMA], 6 RCTs [paediatric], n unspecified); there are no paediatric trials assessing whether US reduces block performance time.

9.6.1.4 Specific peripheral nerve blocks

Lower limb blocks

Femoral nerve or fascia iliaca compartment blocks provided analgesia for surgery on the anterior aspect of the thigh and reduced pain associated with femoral fractures (Paut 2001 **Level IV**) and were equivalent for adolescent reconstructive knee surgery (Farid 2010 **Level II**, n=23, JS 3).

For lower limb surgery, lumbar plexus block or catheter insertion using a landmark technique with peripheral nerve stimulator is described (Walker 2011 **Level IV**) and psoas compartment block may be a useful alternative to neuraxial techniques (Omar 2011 **Level II**, n=40, JS 3; Dadure 2004 **Level IV**) although, when performed by trainee anaesthetists unfamiliar with the technique, vascular puncture occurred in 16% (Schuepfer 2005 **Level IV**).

For children undergoing major foot and ankle surgery, continuous popliteal nerve block with 0.2% ropivacaine produced comparable analgesia with fewer adverse effects (PONV, urinary retention, early discontinuation) than continuous epidural infusion (Dadure 2006 **Level II**, n=52, JS 3).

Upper limb blocks

Axillary brachial plexus blocks provided satisfactory analgesia for hand and forearm surgery in 75–94% of cases (Fisher 1999 **Level IV**; Dadure 2009 **Level IV**; Polaner 2012 **Level IV**; Gurnaney 2014 **Level IV**; Taenzer 2014 **Level IV**). Adding clonidine 1 mcg/kg did not confer additional benefit (Trifa 2012 **Level II**, n=60, JS 5). The use of US guidance has led to new approaches to brachial plexus anaesthesia in children (Fleischmann 2003 **Level II**, n=40, JS 5; Ganesh 2007 **Level IV**; Ponde 2008 **Level IV**; Dadure 2009 **Level IV**; Polaner 2012 **Level IV**) with improved success rates (Marhofer 2004 **Level II**, n=36, JS 3; De Jose Maria 2008 **Level II**, n=80, JS 1; Dadure 2009 **Level IV**; Polaner 2012 **Level IV**; Taenzer 2014 **Level IV**). Infraclavicular blocks are as safe as other approaches to the brachial plexus, with lower incidence of tourniquet pain and more reliable musculocutaneous nerve block compared to axillary block (Chin 2013 **Level I** [Cochrane] 3 RCTs [paediatric], n=156).

Wrist block vs intraoperative alfentanil for distal hand surgery in young children under general anaesthesia improved postoperative pain scores, decreased PONV and shortened postoperative recovery time (De Windt 2010 **Level II**, n=60, JS 3).

Paravertebral blocks

Paravertebral local anaesthetic injection or catheter infusion is reported in paediatric perioperative management (Polaner 2012 **Level IV**). Single injection has provided effective analgesia for several hours after renal surgery (Berta 2008 **Level IV**), inguinal hernia repair (Naja 2005 **Level IV**), aortic coarctation repair (Turkoz 2013 **Level IV**) and Nuss procedure (Qi 2014 **Level II**, n=30, JS 3). Continuous unilateral paravertebral/extrapleural infusions provided effective analgesia following thoracotomy in term neonates (Palmer 2012 **Level IV**), infants and older children (Di Pede 2014 **Level III-3)** and were equivalent to thoracic epidural analgesia in children under 2 y (El-Morsy 2012 **Level II**, n=60, JS 5). Bilateral PVB infusion also provided

equivalent analgesia to thoracic epidural catheters infusion for the Nuss procedure (Hall Burton 2014 **Level III-2**).

Transversus abdominis plane blocks

US-guided TAP blocks provided abdominal wall sensory block below T10 with 0.4 mL/kg local anaesthetic injection (Palmer 2011 **Level IV**). For inguinal hernia repair, TAP blocks with 0.25% bupivacaine 0.5 mL/kg were superior to wound infiltration with of 0.25% bupivacaine 0.2 mL/kg with reduced pain scores and analgesic consumption during the first 24 h postoperatively (Sahin 2013 **Level II**, n=57, JS 5). However, lower volume TAP blocks using lignocaine 0.5%/ropivacaine 0.5% 0.3 mL/kg were inferior to US-guided ilioinguinal block in terms of pain frequency and ibuprofen use prior to but not following discharge (Fredrickson 2010 **Level II**, n=41, JS 3). Bilateral US-guided TAP blocks (ropivacaine 0.2%, 0.5 mL/kg) in addition to local anaesthesia and paracetamol for laparoscopic appendectomy provided no additional benefit beyond lower initial pain scores in PACU (Sandeman 2011 **Level II**, n=87, JS 5). In this study, more patients in the TAP group had complicated appendicitis (31 vs 11%; p=0.02). In contrast, morphine requirements were reduced following ipsilateral TAP vs saline block in open appendectomy, where perforation and positive histopathology rates were similar (Carney 2010 **Level II**, n=40, JS 5).

The PRAN consortium reported a very low incidence of complications (0.1%; 95%CI 0.02 to 0.3%) with TAP blocks (n=1,994; 95% US-guided) (Long 2014 **Level IV**). Notably, bupivacaine dosing varied widely (mean 1 mg/kg, range 0.47–2.29 mg/kg) with 7% of patients receiving potentially toxic doses (>2 mg/kg); these tended to be younger children highlighting the need to dose according to weight. No local anaesthetic systemic toxicity events were reported.

TAP block catheters have been employed in small children (weighing <10 kg) where epidural use was contraindicated or refused (Visoiu 2012 **Level IV**).

9.6.1.5 Use of peripheral nerve blocks in specific surgical procedures

Circumcision

In boys (infants to adolescent) who also received a general anaesthetic, a dorsal penile nerve block provided similar analgesia to a caudal block (Cyna 2008 **Level I** [Cochrane], 4 RCTs [penile block], n=336) and a longer duration of effect than application of a topical local anaesthetic cream (EMLA®)(Choi 2003 **Level II**, n=60, JS 5). When compared to parenteral analgesia, caudal analgesia does not reduce PONV (RR 0.61; 95%CI 0.36 to 1.05) or the need for early rescue or other analgesia (RR 0.41; 95%CI 0.12 to 1.43) (Cyna 2008 **Level I** [Cochrane], 4 RCTs [parenteral], n=235). A study comparing US- and landmark-based techniques for dorsal penile nerve block found no difference in intraoperative fentanyl requirements but increased postoperative codeine administration in the landmark group (38 vs 6%) (O'Sullivan 2011 **Level II**, n=66, JS 5).

There are insufficient controlled trials to adequately rank the efficacy of all local anaesthetic techniques for circumcision in awake neonates but as topical local anaesthetic cream only partially attenuates the pain response to circumcision, more effective analgesic techniques such as dorsal penile nerve block are recommended (Brady-Fryer 2004 **Level I** [Cochrane], 35 RCTs n=1,984). Nerve stimulator-guided pudendal nerve block had lower pain scores, reduced analgesic requirement and provided longer duration of analgesia vs dorsal penile nerve block for circumcision (Naja 2011 **Level II**, n=60, JS 4) and vs caudal block for hypospadias repair (Naja 2013 **Level II**, n=80, JS 5).

Policy statements from the Royal Australasian College of Physicians (RACP 2010 **GL**) and British Association of Paediatric Urologists (BAPU 2007 **GL**) emphasise the need for adequate analgesia for neonatal circumcision.

Inguinal and umbilical surgery

Similar analgesic efficacy following inguinal hernia repair has been found with wound infiltration, ilioinguinal/iliohypogastric nerve block or caudal analgesia (Splinter 1995 **Level II**, n=200, JS 5; Machotta 2003 **Level II**, n=58, JS 4). Ilioinguinal block is inherently safe but US guidance may improve safety and efficacy (Willschke 2005 **Level II**, n=100, JS 3; Weintraud 2008

Level IV). Addition of clonidine to bupivacaine for ilioinguinal block did not improve duration or quality of analgesia (Kaabachi 2005 **Level II**, n=98, JS 4).

In a small umbilical hernia repair study, rectus sheath block (RSB) using anatomical landmarks offered no benefit over wound infiltration using bupivacaine 0.25% with adrenaline, with similar PACU morphine requirement, pain and sedation scores (Isaac 2006 **Level II**, n=13, JS 5). In contrast, US-guided RSB was effective (Willschke 2006a **Level IV**) and, when compared with wound infiltration using lower volumes of bupivacaine 0.25%, halved perioperative opioid requirements (Gurnaney 2011 **Level II**, 52 patients, JS 5) with a longer time to rescue morphine with higher, but safe, plasma levels (Flack 2014 **Level II**, n=40, JS 5).

Tonsillectomy

The assessment and comparison of efficacy of analgesia in tonsillectomy trials is challenged by the variation in surgical technique within and between trials. Due to the proximity of significant vascular structures and nerves, peritonsillar infiltration and nerve block has inherent risks. Trials of infiltration with agents that are effective systemically must have a systemic arm for comparison that permits assessment of additive risk vs analgesic benefit

Various local anaesthetics by infiltration (5 RCTs) or topical application (2 RCTs) (see Section 9.6.3) produced modest reductions in pain (mean reduction 7–19/100) compared to placebo following tonsillectomy (Grainger 2008 **Level I,** 7 RCTs [paediatric], n≈356). Bupivacaine 0.25%/pethidine infiltration reduced analgesic requirements at rest compared with saline but did not affect other pain outcomes following tonsillectomy in children (Nikandish 2008 **Level II**, n=80, JS 5).

Peritonsillar infiltration with ketamine (0.5 or 1.0 mg/kg) reduced pain and analgesic requirements compared to peritonsillar pethidine (El Sonbaty 2011 **Level II,** n=100, JS 1) and placebo for up to 24 h post tonsillectomy in children (Honarmand 2008 **Level II**, n=75, JS 5; Erhan 2007 **Level II**, n=60, JS 2; Siddiqui 2013 **Level II**, n=75, JS 4) but was similar to placebo and inferior to tramadol infiltration in a further trial (Ayatollahi 2012 **Level II**, n=126, JS 4). Preoperative infiltration was more (Khademi 2011 **Level II**, n=78, JS 5) or no more effective (Dal 2007 **Level II**, n=90, JS 5) than the same dose 0.5 mg/kg IV, using the same surgical technique. Ketamine 0.5 mg/kg IV with peritonsillar bupivacaine was more effective than placebo IV/bupivacaine infiltration and placebo IV/infiltration (Inanoglu 2009 **Level II**, n=90, JS 5).

The combination of glossopharyngeal nerve block with dexamethasone IV (0.15 mg/kg; maximum 8 mg) for tonsillectomy was superior to either in isolation (Mohamed 2009 **Level II,** n=150, JS 3). However, glossopharyngeal nerve block in children has been associated with postoperative airway obstruction (Bean-Lijewski 1997 **Level III-3**).

Head and neck surgery

Blocks of scalp branches of the frontal (supraorbital, supratrochlear), maxillary (zygomaticotemporal) and auriculotemporal nerves as well as branches of the superficial cervical plexus (greater auricular and occipital nerves) have been used in a small number of children, supplementing postoperative opioids, following craniosynostosis repair (Pardey Bracho 2014 **Level IV**) and neurosurgery (Pardey 2008 **Level IV**) (see also Section 8.1.8).

Superficial cervical plexus block has provided pain relief for internal jugular haemodialysis catheter insertion (Ciftci 2014 **Level IV)** and cochlear implant (Merdad 2012 **Level III-3**).

Greater auricular nerve block (GANB) provided similar analgesia with reduced PONV compared with morphine following tympanomastoid surgery (Suresh 2002 **Level II**, n=40, JS 4). Administration preincision vs placebo did not add to GANB performed at surgery completion (Suresh 2004 **Level II**, n=40, JS 4). A combination of GANB and lesser occipital nerve block for otoplasty provided similar analgesia to local infiltration (Cregg 1996 **Level II**, n=43, JS 2). Otoplasty for paediatric patients (aged 4–17 y) under local anaesthetic infiltration only had reduced PONV rates vs with local/general anaesthesia combined (Lancaster 2003 **Level III-3**).

For paediatric cleft lip repair, infraorbital nerve block was superior to IV fentanyl (Rajamani 2007 **Level II**, n=82, JS 5) and placebo block (Takmaz 2009 **Level II**, n=40, JS 5). Adding clonidine 1 mcg/kg to bilateral infraorbital nerve block with bupivacaine decreased intraoperative

opioid requirement and prolonged duration of analgesia (11.1 vs 9.3 h) (Jindal 2011 **Level II**, n=50, JS 5); however, the control group received no systemic clonidine. Adding opioids, fentanyl and pethidine, to bupivacaine also increased the duration of analgesia of infraorbital nerve block from 18 h to 24 h and 35 h respectively (Mane 2011 **Level II**, n=45, JS 5); again no systemic comparators were used. For cleft palate repair, bilateral suprazygomatic maxillary nerve block with ropivacaine vs saline halved the postoperative 48 h IV morphine requirement and the need for continuous morphine infusion (Chiono 2014 **Level II**, n=57, JS 4).

Compared with intraoperative opioids, peribulbar and sub-Tenon's blocks following strabismus surgery reduced intraoperative oculocardiac reflexes and PONV, but effects on postoperative analgesic requirements were variable (Steib 2005 **Level II**, n=40, JS 5; Chhabra 2005 **Level III-1**; Gupta 2007 **Level II**, n=45, JS 2; Kachko 2010 **Level II**, n=53, JS 1; Ramachandran 2014 **Level II**, n=67, JS 3). Sub-Tenon's block provided more effective analgesia than IV fentanyl for paediatric vitreoretinal surgery (Chhabra 2009 **Level II**, n=196, JS 5). Sub-Tenon's blocks reduced emergence agitation after strabismus surgery (Seo 2011 **Level II**, n=250, JS 5) and have been used for paediatric cataract surgery (Ghai 2010 **Level II**, n=120, JS 4). The relative risks of the different eye block approaches have not been fully evaluated.

Local anaesthetic infiltration reduced pain following dental extractions (Anand 2005 **Level III-2**) but addition of a small dose of morphine (25 mcg/kg) to the local anaesthetic did not improve the quality or duration of analgesia (Bhananker 2008 **Level II**, n=42, JS 3). Use of a computer-controlled local anaesthetic delivery device compared to conventional infiltration was not painful, with similar onset of effect for submucosal and buccal injection for 1st permanent molar work (Kandiah 2012 **Level II**, n=30, JS 3) and less painful for buccalpalatal injection (Feda 2010 **Level II**, n=40, JS 1). A vibrating device did not affect pain scores during local anaesthetic injection (Roeber 2011 **Level II**, n=90, JS 4). A needleless jet system was inferior to standard local anaesthetic infiltration, as it required more local anaesthetic supplementation and more patients reported postprocedure pain (Arapostathis 2010 **Level III-2**). The addition of local anaesthetic to IV ketorolac in dental restorations or extractions under general anaesthetic does not improve quality of recovery vs IV ketorolac alone and young children may bite or chew the anaesthetic cheek or lip (Townsend 2009 **Level II**, n=27, JS 5).

9.6.2 Neuraxial blocks

Central neural block is used in paediatric patients to provide postoperative analgesia and to supplement intraoperative anaesthesia. Patient selection, technique, choice of medicines, availability of experienced staff for performing blocks, an APS or outpatient resources and adequacy of follow-up vary between centres (Williams 2003 **NR**).

9.6.2.1 Caudal analgesia

Despite the current trend towards PNB (Taenzer 2014 **Level IV**), caudal analgesia remains a commonly performed regional technique (comprising 27–40% of audited blocks), especially in the smaller paediatric patient (Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**). Single-injection caudal block provides intra and postoperative analgesia and is generally used for surgery on the lower abdomen, perineum and lower limbs (see Table 9.6 and Section 9.6.2.3). Large series have reported a high success rate (particularly in children aged <7 y) and a low incidence of serious complications (Giaufre 1996 **Level IV**; Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**; Taenzer 2014 **Level IV**).

Caudal bupivacaine, levobupivacaine and ropivacaine produced similar times to onset of block and quality of postoperative analgesia (Ivani 2005 **Level II**, n=60, JS 5; Breschan 2005 **Level II**, n=182, JS 3; Frawley 2006 **Level II**, n=310, JS 5; Ingelmo 2006 **Level II**, n=86, JS 5).

Concentration-dependent differences have been noted for individual agents. Ropivacaine 0.175% was superior to lower concentrations and was as effective as a 0.2% solution but produced less motor block (Khalil 2006 **Level II**, n=74, JS 5). In children aged 1–3 y having inguinal surgery, six concentrations of levobupivacaine were administered (0.08–0.18%, 1 mL/kg) (Yao 2009 **Level II**, n=60, JS 5); for caudal analgesia, this study established the EC50 as 0.109% (95%CI 0.098 to 0.120) and the EC95 as 0.151% (95%CI 0.135 to 0.193).

The volume administered influences the height of block achieved. The spread of caudal block has been measured clinically (assessing dermatomes and myotomes) and the vertebral height measured by US and contrast studies (see Table 9.6). Dosing in volume based on weight is practical. For effective caudal analgesia, volumes of 0.5–0.7 mL/kg are used for sacral dermatome surgery and 0.8–1 mL/kg for lumbar and lower abdominal dermatome surgery. Higher volume 1.2–1.5 mL/kg blocks are effective for abdominal and thoracic surgery; spread above the T12 dermatome occurs most reliably in neonates and infants.

Table 9.6 Block height following caudal injection in children using different formulae

Surgery type Patient number and age	Local anaesthetic agent (%) and additives	Volume used vs suggested formula	Block height achieved
Clinical			
Study	McGown 1982 **Level IV**		
Upper abdominal; lower abdominal; lumbosacral; sacral n=500 Height assessed in 360 aged 6 mth–10 y	Lignocaine 1% (with adrenaline 5 mcg/mL)	1.65 mL/kg 1.1 mL/kg 0.55 mL/kg	T2–T8 T8–T12 L1–S3
Outcome/conclusion	Volume/weight calculation successful for 430 (86%)		
Study	Satoyoshi 1984 **Level IV**		
Abdominal Paediatric cadaver radio-opaque contrast study: n=16 Clinical: n=21 Aged 1 mth–11 y	Bupiv 0.25–0.375% or Mepiv 0.75–1.5%	1 mL/kg or Spiegel formula (x1–1.5) Developed new formula: mL=[(cm in distance from C7 to sacral hiatus) – 13]	New formula achieved T4–5 height assessed by response to painful stimulus
Outcome/conclusion	Reduced thoracoabdominal musculature movement; abdominal surgery successfully completed		
Study	Coad 1989 **Level II**, n=60, JS 3		
Inguinal n=48 (including 2 failures); mean age 2+/-1 y	Bupiv 0.25% Bupiv 0.25% Bupiv 0.5%	1 mL/kg vs formula ((Age in years) +2)mL	
Outcome/conclusion	No difference found for weight- vs formula-based dosing with similar postoperative pain scores.		
Study	Verghese 2002 **Level II**, n=50, JS 4		
Orchidopexy n=50 aged <6 y	Bupiv 0.25% Vs Bupiv 0.2% (both with adrenaline 5 mcg/mL and sodium bicarbonate 8.4% 0.1 mL/10 mL)	0.8 mL/kg vs 1 mL/kg	35% to T 10 vs 70% to T10 (assessed with spermatic cord traction test)
Outcome/conclusion	Higher volume lower concentration had less response to spermatic cord traction. The sample was too small to detect a difference in postoperative rescue analgesia (fentanyl 7 vs 17% p=0.4; paracetamol 59 vs 74% p=0.37).		

Surgery type Patient number and age	Local anaesthetic agent (%) and additives	Volume used vs suggested formula	Block height achieved
Ultrasound			
Study	Lundblad 2011 **Level IV**		
Subumbilical surgery: urogenital, anal, foot, and inguinal n=50 aged 0–4 y	Ropiv 0.2%	All received 1.5 mL/kg with volume/kg noted once T12 reached: Formula generated by US was lower than studies with dermatomal testing: mL per spinal segment= (0.154 x kg) minus 0.094	Block ≥T12 vertebral level on US in 93% neonates, 73% infants and 25% young children.
Outcome/conclusion	Inverse relationship with age (r=0.8) and weight (r=1.0).		
Study	Brenner 2011 **Level II**, n=75, JS 5		
Anal, penile and inguinal n=75, median age 21–32 mth	Ropiv 0.2% if <12 mth Ropiv 0.35% if >12 mth	0.7 mL/kg 1.0 mL/kg 1.3 mL/kg	Median vertebral height L2; same for age <12 or >12 mth.
Outcome/conclusion	Weak inverse correlation with weight, height, BMI.		
X-ray contrast study			
Study	Hong 2009 **Level II**, n=73, JS 4		
Orchidopexy n=73; aged 1–5 y	Ropiv 0.225% vs 0.15%	1 mL/kg 1.5 mL/kg	Median height (range) T6 (T3–11) T11 (T8–L2);
Outcome/conclusion	No difference in recovery times, postoperative pain scores or adverse effects Higher volume/lower concentration had longer time to acetaminophen rescue (9.2 vs 6.1 h; p<001) and reduced requirement (50 vs 76%; p=0.03).		
Study	Koo 2010 **Level III-2**		
Perineal, inguinal, orchidopexy n=87 recruited: 83 had caudal aged 6 mth–4.5 y	Ropiv 0.2%	0.5 mL/kg 1 mL/kg 1.25 mL/kg	Median height (range) L2 (L4–T12) T12 (L1–T8) T10 (L2–T7)
Outcome/conclusion	More segments were covered per mL administered with younger age: mean number of segments (SD) of 1.3 (0.4) for <1 y, 1.1 (0.3) for 1–3 y and 0.8 (0.4) for >3 y. Dosed according to surgical type; effective for surgery in 100%, with low median postoperative pain scores (>2 h), 4% required analgesic rescue.		
Study	Thomas 2010 **Level III-2**		
Perineal/lower limb, inguinal n=45; aged 1–7 y abdominal	Bupiv 0.25%	0.5 mL/kg 0.75 mL/kg 1 mL/kg	Median height (SEM) L2+/-0.44 L1 +/-0.32 T12+/-0.43
Outcome/conclusion	Contrast study 1 mL/kg of caudal injectate reliably achieved one vertebral level higher than 0.5 mL/kg (L2 vs L3 for 93% of patients)		

Caudal adjuvants

Opioid and nonopioid adjuvants have been added to caudal local anaesthetic with the aim of improving the efficacy or duration of analgesia. The neurotoxicity of nonopioid spinal additives has not been systematically evaluated in neonates and children (Walker 2012b **NR**).

Opioids

Addition of morphine to caudal local anaesthetic prolonged analgesia but dose-related adverse effects were relatively common (Bozkurt 1997 **Level IV**; Cesur 2007 **Level II**, n=135, JS 5). Morphine 7.5 mcg/kg added to 0.125% levobupivacaine resulted in a lower incidence of vomiting than higher morphine doses and provided effective postoperative analgesia (Dostbil 2014 **Level II**, n=240, JS 5). Morphine 20 mcg/kg added to bupivacaine 0.166% (with adrenaline 1:600,000) 1 mL/kg was more effective (lower pain scores and fewer patients requiring rescue analgesics) than bupivacaine/adrenaline alone or with clonidine 1 mcg/kg, although with higher rates of PONV (Fernandes 2012 **Level II**, n=80, JS 5).

Clinically significant respiratory depression has been reported, particularly with higher morphine doses and in younger patients (de Beer 2003 **NR**). Adverse effects are potentially fewer with lipid soluble opioids but, while fentanyl may prolong caudal analgesia (Constant 1998 **Level II**, n=59, JS 5), others have shown no benefit (Joshi 1999 **Level II**, n=56, JS 2; Baris 2003 **Level II**, n=75, JS 3; Kawaraguchi 2006 **Level II**, n=35, JS 3).

Adrenaline (epinephrine)

Adding adrenaline (epinephrine) to bupivacaine has minimal effect on the duration of analgesia, particularly in older children (Ansermino 2003 **Level I**, 3 RCTs, n=407). The influences of caudal adrenaline and/or clonidine on the absorption characteristics of caudal levobupivacaine were evaluated in 240 paediatric patients (Chalkiadis 2013 **Level IV**). Adrenaline (5 mcg/mL) decreased the rate of levobupivacaine systemic absorption, reducing peak concentration by half but with minimal impact on levobupivacaine's time-concentration profile. Adrenaline (2.5 mcg/mL) addition to caudal ropivacaine slowed the T_{max}, and reduced the peak ropivacaine concentration by 35% (Van Obbergh 2003 **PK**).

Alpha-2 agonists

Addition of clonidine (1–2 mcg/kg) to caudal local anaesthetic, as assessed by two systematic reviews (with overlap of 14 RCTs), prolongs analgesia by a mean difference of 3.7 to 4 h (95%CI 2.7 to 4.7 and 2.8 to 5.1) with fewer patients requiring rescue analgesics (RR 0.72; 95%CI 0.57 to 0.90) (Schnabel 2011b **Level I** [PRISMA], 20 RCTs, n=993) and (OR 0.22; 95%CI 0.13 to 0.37) (Engelman 2013 **Level I** [PRISMA], 18 RCTs, n=782). In assessing the sedative effects of clonidine as a caudal additive, these systematic reviews conflict; one finding positive association (OR 2.48; 95%CI 1.62 to 3.69) (Engelman 2012 **Level I** [PRISMA], 3 RCTs [sedation], n unspecified) and the other none (RR 4.76; 95% CI 0.24 to 93.19) (Schnabel 2011b **Level I** [PRISMA], 4 RCTs [sedation], n=142). Both found no reduction of PONV. Caudal clonidine 1, 2 and 3 mcg/kg dose dependently spared levobupivacaine (from 0.2% to ED50s of 0.11, 0.08 and 0.04% respectively) (Disma 2011 **Level II**, n=120, JS 4). The optimal dose was 2 mcg/kg with less emergence agitation, longer time to first analgesic rescue and reduced rescue analgesic requirement vs 1 mcg/kg and more patients were sedated in the 3 mcg/kg group (12/40 vs 4/40 vs 0/40). Added to ropivacaine 0.25%, clonidine 2 mcg/kg had similar analgesic efficacy to fentanyl 1 mcg/kg, with more episodes of postoperative vomiting, desaturation and bradycardia occurring in the fentanyl group (Shukla 2011 **Level II**, n=90, JS 4). Interestingly, clonidine (2 mcg/mL) differed from adrenaline with faster systemic absorption of levobupivacaine but both agents had minimal impact upon levobupivacaine's time-concentration profile overall (Chalkiadis 2013 **PK**).

Dexmedetomidine 2 mcg/kg added to caudal bupivacaine prolonged analgesic effect (median 16 h; 95%CI 14 to 18) similar to clonidine 2 mcg/kg (12 h; 95%CI 3 to 21) compared to placebo (5 h; 95%CI 4 to 6) for lower abdominal surgery (El-Hennawy 2009 **Level II**, n=60, JS 4). This was also found for dexmedetomidine 1 mcg/kg added to caudal bupivacaine vs bupivacaine alone for inguinal surgery and orchidopexy (Saadawy 2009 **Level II**, n=60, JS 4; Xiang 2013 **Level II**, n=60, JS 5). Following cardiac surgery, dexmedetomidine 0.5 mcg/kg added to bupivacaine 0.25%

1 mL/kg compared with fentanyl/bupivacaine achieved lower pain scores for 8 h, with no IV comparator (Nasr 2013 **Level II**, n=40, JS 5).

Dexamethasone

For paediatric day-stay orchidopexy, adding dexamethasone (0.1 mg/kg) to ropivacaine (0.15%, 1.5 mL/kg) via caudal route significantly improved the quality and duration of analgesia with lower pain scores at 6 and 24 h, more pain-free patients over 48 h, reduced rescue analgesic use and longer time to first analgesic request but with no IV comparator (Kim 2014 **Level II**, n=80, JS 5). This was also true for IV dexamethasone (0.5 mg/kg, maximum 10 mg) as a supplement to caudal analgesia, with reduced rescue fentanyl and paracetamol requirement and longer time to first analgesic request (10.8 vs 7.2 h) (Hong 2010a **Level II**, n=77, JS 5).

Ketamine

Ketamine 0.25–0.5 mg/kg added to caudal bupivacaine or ropivacaine prolongs time to first analgesic request compared with a local anaesthetic alone (MD 5.6 h; 95%CI: 5.45 to 5.76) without prolonged motor block (Schnabel 2011a **Level I** [PRISMA], 13 RCTs [paediatric], n=584). A second meta-analysis of 13 RCTs (overlapping by 6 RCTs) reports increased duration of block with ketamine 0.5 mg/kg (SMD 2.25; 95%CI 1.53 to 3) (Dahmani 2011 **Level I** [QUORUM] 10 RCTs [paediatric], n=686) and reduced postoperative analgesic requirements (OR 0.26; 95%CI 0.1 to 0.7). Some adverse effects were more frequent in the ketamine group (eg PONV, hallucinations, sedation) but not significantly different to placebo for PONV (OR 1.17; 95%CI 0.7 to 2) (Schnabel 2011a **Level I** [PRISMA], 13 RCTs [paediatric], n=584) or for psychomimetic effects (OR 1.72; 95%CI 0.7 to 4.3) (Dahmani 2011 **Level I** [QUORUM] 10 RCTs [paediatric], n=686). A subanalysis of S-ketamine added to caudal anaesthesia was performed showing similar prolongation of block compared to racemic (Dahmani 2011 **Level I** [QUORUM] 4 RCTs [S-ketamine], n unspecified). A significant concern that continues to limit the use of neuraxial ketamine is local neurotoxicity *in vitro* (Werdehausen 2011 **BS**; Walker 2012b **NR**).

Tramadol, neostigmine and midazolam

Tramadol 1–2 mg/kg added to local anaesthetic prolongs the time to first rescue analgesic (4.5 h: 95%CI 2.8 to 6.1) at the expense of increased vomiting (OR 2.5; 95%CI 1.3 to 4.6), with no IV comparator (Engelman 2012 **Level I** [PRISMA], 9 RCTs [tramadol], n=258). Caudal tramadol 2 mg/kg added to bupivacaine and levobupivacaine was similarly effective for inguinoscrotal surgery (Sezen 2014 **Level II**, n=68, JS 5).

Neostigmine added in doses of 1–4 mcg/kg extends the time to first analgesic rescue request by 2.5 times that of clonidine (MD 10 h; 95%CI 7.8 to 12.2) without any dose-dependent effect evident. This is at the expense of increased vomiting (OR 1.8; 95%CI 1.1 to 2.8) (Engelman 2012 **Level I**, 7 RCTs [neostigmine], n=533). Neostigmine (administered with 5 mcg/mL adrenaline) without local anaesthetic demonstrated analgesic efficacy for 20–50 mcg/kg but not 10 mcg/kg with a dose-dependent increase in PONV (Batra 2003 **Level II**, n=120, JS 2).

Midazolam 50 mcg/kg caudal addition was similar to added fentanyl 1 mcg/kg and plain bupivacaine caudal groups regarding 24 h postoperative analgesic requirement, with higher sedation scores over the initial 90 min (Baris 2003 **Level II**, n=75, JS 3). This dose added to bupivacaine prolonged time to first rescue analgesic (similar to neostigmine 2 mcg/kg and ketamine 0.5 mg/kg) with no difference in sedation scores over 24 h compared to plain bupivacaine (Kumar 2005 **Level II**, n=80, JS 4). Compared to plain bupivacaine, midazolam 50 mcg/kg vs morphine 50 mcg/kg added to bupivacaine prolonged the duration of analgesia (mean duration 8 vs 21 vs 15 h respectively) with similar prolongation of sedation to 12 h (Gulec 1998 **Level II**, n=60, JS 1).

9.6.2.2 Epidural analgesia

As the epidural space is relatively large with loosely packed fat in neonates, catheters can be threaded from the sacral hiatus to lumbar and thoracic levels (Tsui 2004 **Level IV**). In older infants, various techniques have been suggested to improve correct placement including US, nerve stimulation and ECG guidance (Tsui 2002 **Level IV**; Tsui 2004 **Level IV**; Willschke 2006b

Level IV). US provides visibility of the dura mater and ligamentum flavum, especially in infants and younger children. It is a good predictor of depth to loss of resistance, offers visibility of the needle and catheter and may reduce bone contacts (Tsui 2010 **Level IV SR** [PRISMA], 12 studies, n unspecified). Insertion of epidural catheters at the segmental level required for surgery was more reliable in older children, and has been shown to be safe in experienced hands with appropriately sized equipment (Giaufre 1996 **Level IV**; Llewellyn 2007 **Level IV**).

Local anaesthetics

Continuous epidural infusions of bupivacaine are effective and safe in children (Llewellyn 2007 **Level IV**; Ecoffey 2010 **Level IV;** Wong 2013a **Level IV;** Taenzer 2014 **Level IV**). Epidural infusions provide similar levels of analgesia to systemic opioid, with similar safety profiles. In children <4 y having abdominal surgery, epidural infusion was similarly effective compared to morphine infusion (Wolf 1993 **Level II**, n=32, JS 3). Epidural analgesia compared to PCA for Nuss surgery reduced pain scores modestly (WMD: 0.5–1.1/10) over 0–48 h, with no differences between secondary outcomes (Stroud 2014 **Level III-3 SR**, 6 studies, n=403). In children aged 7–12 y, PCEA provided analgesia similar to a continuous epidural infusion (Antok 2003 **Level II**, n=48, JS 2). Total local anaesthetic dose was reduced with PCEA but no differences in adverse effects were detected.

Due to reduced clearance and the potential for accumulation of bupivacaine, the hourly dose should be reduced and the duration of therapy limited to 24–48 h in neonates (Larsson 1997 **Level IV**). Postnatal age and weight influence the pharmacokinetic profile of levobupivacaine, with slower absorption and clearance in neonates and infants (Chalkiadis 2006 **Level IV**). Although plasma concentrations increased, they remained low after 24 h of epidural levobupivacaine infusion in children aged >6 mth (Lerman 2003 **Level II**, n=120, JS 5). Epidural infusions of ropivacaine were effective and safe in neonates (Bosenberg 2005 **Level IV**) and children (Berde 2008 **Level IV**) with minimal drug accumulation.

Epidural opioids alone

Epidural opioids alone have a limited role. Epidural morphine provided prolonged analgesia but no improvement in the quality of analgesia compared with systemic opioids (Bozkurt 2004 **Level II**, n=32, JS 1). Without systemic or epidural local anaesthetic comparator, epidural morphine 0.1 mg/kg compared to epidural tramadol 2 mg/kg had similar pain scores and time to first rescue analgesic but with higher rates of adverse effects (Demiraran 2005 **Level II**, n=80, JS 3). Epidural fentanyl 1 mcg/mL alone was less effective than both levobupivacaine 0.0625 and 0.125% alone and levobupivacaine/fentanyl combined (Lerman 2003 **Level II**, n=114, JS 5). Bolus doses of epidural morphine 20–30 mcg/kg were less effective than epidural infusions of fentanyl 1–2 mcg/mL and local anaesthetic (Reinoso-Barbero 2002 **Level II**, n=30, JS 1; Kart 1997 **Level II**, n=30, JS 5). Ketoprofen IV improved analgesia vs saline when given in conjunction with epidural sufentanil (Kokki 1999 **Level II**, n=54, JS 5).

Local anaesthetic and opioid or other adjuvant in combination

A combination of local anaesthetic and opioid is frequently used in epidural infusions but there are limited data available to assess the relative merits of different regimens. Fentanyl 1–2 mcg/mL addition to local anaesthetic infusions has both improved analgesia (less IV opioid rescue) (Lovstad 2001 **Level III-2**) and had similar analgesic effect (Lerman 2003 **Level II**, n=114, JS 5) but increased nausea and vomiting (Lovstad 2001 **Level III-2**; Cho 2009 **Level II**, n=108, JS 5). Addition of fentanyl 5 mcg/mL to bupivacaine 0.1% provided similar analgesia but increased adverse effects compared with clonidine 1.2 mcg/mL with bupivacaine 0.1% (Cucchiaro 2006 **Level II**, n=47, JS 3). Addition of morphine 10 mcg/mL to an epidural local anaesthetic infusion was more effective than clonidine 0.6 mcg/mL (Cucchiaro 2003 **Level II**, n=26, JS 5) but higher doses of clonidine improved analgesia when added to epidural ropivacaine infusion (De Negri 2001 **Level II,** n=60, JS 4). Epidural sufentanil (0.015 mcg/kg/mL with ropivacaine 0.15%) achieved similar pain scores following paediatric urological surgery with reduced rescue analgesic use but more pruritus vs fentanyl (0.1 mcg/kg/mL)/ropivacaine (Cho 2008 **Level II**, n=64, JS 4). Tramadol 2 mg/kg has been added to ropivacaine 0.2% via the epidural route and was superior to ropivacaine alone (Inanoglu 2010 **Level II**, n=44, JS 5).

9.6.2.3 Outcomes

Perioperative regional analgesia modifies the stress response to surgery in children (Wolf 1998 **Level II**, n=26, JS 1; Humphreys 2005 **Level II**, n=59, JS 2; Nasr 2013 **Level II**, n=40, JS 3). Suppression of the stress response may necessitate a local anaesthetic block that is more intense or extensive than required for analgesia, and therefore the risks of increased adverse effects or toxicity must be balanced against any potential benefit (Wolf 1998 **Level II**, n=26, JS 1). Use of caudal opioids alone (morphine 30 mcg/kg) was less effective than plain bupivacaine 0.25% in attenuating cortisol and glucose responses following hypospadias surgery (Teyin 2006 **Level II**, n=28, JS 3). Sufentanil added to bupivacaine modified the stress response to cardiac surgery (Sendasgupta 2009 **Level II**, n=30, JS 3).

Improvements in respiratory outcome with regional analgesia have not been established in controlled comparative trials. Reductions in respiratory rate and oxygen saturation were less marked during epidural analgesia compared with systemic opioids but the degree of difference was of limited clinical significance (Wolf 1993 **Level II**, n=32, JS 2). Case series report improvements in respiratory function and/or a reduced need for mechanical ventilation with regional analgesia techniques (McNeely 1997 **Level IV**; Hodgson 2000 **Level IV**; Raghavan 2008 **Level IV**; Aspirot 2008 **Level IV**). A review summarises the use of awake caudal or combined spinal epidural vs epidural as a supplement to general anaesthesia in 560 neonates having multiple surgery types with multiple outcomes (surgical efficacy, postoperative respiratory events, other) (Maitra 2014 **NR**). A meta-analysis of spinal vs general anaesthesia for inguinal herniorrhaphy in premature infants reported a reduction in postoperative apnoea in the spinal group (when infants having preoperative sedation were excluded) and a reduced need for postoperative ventilation (of borderline statistical significance) (Craven 2003 **Level I** [Cochrane], 3 RCTs, n=108). A subsequent large multicentre RCT assessing infant hernia repair under awake spinal anaesthetic vs <1 h of sevoflurane anaesthesia further qualifies this. Prematurity predicted apnoea (OR 22; 95%CI 4 to 109), but regional techniques reduced only early 0–30 min apnoea (1 vs 3%, OR 0.20; 95%CI 0.05 to 0.91; p=0.037) with no difference in later apnoea incidence (2%) (Davidson 2015b, **Level II**, n=722 ,JS 3). Neurodevelopmental outcome between the two techniques at 2 y also did not differ (Davidson 2015a, **Level II**, n= 532 analysed, JS 3).

9.6.2.4 Complications

Overall complications

The safety of performing paediatric regional anaesthesia under general anaesthesia or deep sedation has been demonstrated in five large prospective multi-regional audits (Giaufre 1996 **Level IV**; Llewellyn 2007 **Level IV**; Ecoffey 2010 **Level IV**; Polaner 2012 **Level IV**; Taenzer 2014 **Level IV**; Wong 2013a **Level IV**) (see Table 9.7). Placement of regional anaesthesia/analgesia under general anaesthesia is confirmed to be as safe as placement in sedated and awake children (Taenzer 2014 **Level IV**). Reported rates of overall complications for regional analgesia were 0.09% (Giaufre 1996 **Level IV**), 0.12 % (95%CI 0.09 to 0.17) (Ecoffey 2010 **Level IV**), 0.2% (PRAN n=14,917 blocks) (Polaner 2012 **Level IV**) and 1.2% (95%CI 1.1 to 1.3) (PRAN cumulative n=53,564 blocks) (Taenzer 2014 **Level IV)**. Infants were more likely to have complications: 0.4% <6 mth (3,860 blocks) vs 0.1% >6 mth of age (27,272 blocks) (Ecoffey 2010 **Level IV**). In a separate audit, neonates had higher complication rates of 1.13% vs older children 0.3–0.8% (p=0.025) (10,633 epidurals), particularly dosing error (0.3% <12 mth vs 0.07% >12 mth) (Llewellyn 2007 **Level IV**). A retrospective audit also found that complications were more common in neonates and infants than in older children (OR 2.9; 95%CI 1.2 to 7.0) (Wong 2013a **Level III-2**).

Table 9.7 Incidence of adverse effects in large-scale audits of paediatric regional analgesia

Study	Taenzer 2014		
Denominator	53,564 blocks; general anaesthesia 94%; 27,213 neuraxial	*Years audited*	PRAN: Apr 2007–Dec 2012
Adverse effects type and incidence			
LAST	LAST 1 in 10,000: 2 seizures; 1 hypotension; 2 cardiac arrests	*Dural tap, PDPH*	2
PONS	Short duration: 1.3 in 1,000 (95%CI 1–1.7) Long duration: 1 in 50,000 (95%CI 0–10)	*Drug error*	NS
Death, cardiac arrest	0 deaths (2 cardiac arrests associated with LAST)	*Pressure sore*	NS
Bleeding	NS	*Compartment syndrome*	NS
Infection	4 that led to prolonged inpatient stay		
Study	Polaner 2012		
Denominator	14,917 blocks in 13,725 patients; 9,156 neuraxial; (2,946 neuraxial catheters)	*Years audited*	PRAN: Apr 2006–Mar 2010
Adverse effects type and incidence			
LAST	0 (95%CI 0 to 2 in 10,000); 60 positive test doses or vascular puncture	*Dural tap, PDPH, blood patch*	26 dural puncture (0.9% 95% CI 0.6 to 1.3); 4 developed PDPH +1 further (d 2 attributed to erosion by catheter); all 5 requiring blood patch
PONS	Epidural: 4 Horners (resolved with rate change); 3 paraesthesiae (resolved); 1 of these also had allodynia and received gabapentin, symptoms resolved while inpatient; Lumbar plexus catheter: 1 paraesthesia and numbness of long duration (<3 mth)		
Death,cardio-respiratory event/arrest	0 deaths (95%CI 0 to 3.3 in 10, 000); 5 episodes of respiratory depression (responding to reduction/removal of epidural opioid)	*Drug error*	NS
Bleeding	0 epidural haematoma	*Pressure sore*	NS
Infection	Central 32, 3 needing antibiotics; 0 epidural abscess/deep infection/ meningitis; Peripheral 3 needing antibiotics	*Compartment syndrome*	NS
Study	Ecoffey 2010		
Denominator	31,142 blocks; GA 96%; 11,418 neuraxial	*Years audited*	(ADARPEF II) Nov 2005–Oct 2006
Adverse effects type and incidence			
LAST	5.1 in 10,000; (95%CI 3–8); 1 convulsion; 15 cardiac: 2 ECG change, 13 arrhythmia; (Positive test doses within 134 reports excluded from adverse event assessment)	*Dural tap, PDPH, total spinal anaesthesia*	10 dural taps 0 PDPH 1 total spinal anaesthesia
PONS	5 of short duration (18 h–3 wk); 0 permanent	*Drug error*	1 leading to LAST in infant
Death, cardio-respiratory event/arrest	0 deaths/cardiac arrests; 1 total and 2 high spinals: requiring short term ventilation <12 h	*Pressure sore*	NS
Bleeding	NS	*Compartment syndrome*	NS
Infection	1 local		

Study	Llewellyn 2007		
Denominator	10,633 epidurals	*Years audited*	Mar 2001–Dec 2005
Adverse effects type and incidence			
LAST	1 seizure post 2 boluses; 1 seizure/LAST at 24 h high end dosing	*PDPH, blood patch*	5 PDPH, 1 blood patch
PONS	1 permanent (peripheral nerve); 1 cauda equina; 5 resolved over 4–10 mth (2 concurrent spinal cord insult: 1 haematoma with rods, 1 impaired blood supply)	*Drug error*	13
Death, cardio-respiratory event/ arrest	0 deaths/cardiac arrests; 2 respiratory arrests 1 total spinal and 1 with opioid and epidural bolus; ventilated <24 h	*Pressure sore*	33
Bleeding	(1 possible haematoma mentioned above in PONS in patient with 2 epidural catheters attributed to rod placement in scoliosis surgery)	*Compartment syndrome*	4 (not masked by epidural)
Infection	2 epidural abscess; 1 meningism; 25 local		
Study	Giaufre 1996		
Denominator	24,409 blocks; 15,013 neuraxial	*Years audited*	May 1993–April 1994 (ADARPEF I)
Adverse effects type and incidence			
LAST	7 LAST: 2 convulsions; 1 arrhythmia; 2 delayed arrhythmia (with overdose); 2 "subclinical"	*Dural tap, PDPH*	2 dural puncture; 2 PDPH; 4 total spinal
PONS	2 transient <8 h	*Drug error*	NS
Death, cardio-respiratory event/ arrest	1 apnoea secondary to excess epidural morphine	*Pressure sore*	NS
Bleeding	NS	*Compartment syndrome*	NS
Infection	1 local burn from skin preparation solution/ heated mattress; 1 rectal puncture (with caudal) without sequelae		
Study	Wong 2013a		
Denominator	3,152 epidurals	*Years audited*	Jan 1997–Dec 2011
Adverse effects type and incidence			
LAST	0 (1 intravascular catheter; unrecognised)	*Dural tap, PDPH, intrathecal placement*	1 PDPH; blood patch NS; 1 IT placement-unrecognised
PONS	1 permanent with residual left sided 3–4/5 weakness of L5S1 (blood staining of dural sac)	*Drug error*	3
Death, cardio-respiratory event/arrest	1 fatal cardiac arrest; 1 respiratory depression	*Pressure sore*	3
Bleeding	NS (bar that in patient with PONS above)	*Compartment syndrome*	1
Infection	11 local of skin: 5 required antibiotics		

Notes: *ADARPEF: French-Language Society of Paediatric Anaesthesiologists; LAST: local anaesthetic systemic toxicity; NS: none specified; PDPH: postdural puncture headache; PONS: postoperative neurological symptoms.*

Local anaesthetic systemic toxicity

Accidental intravascular injection and local anaesthetic toxicity remains a high-risk complication of caudal and epidural analgesia. It is reported as occurring rarely: 1 to 5 in 10,000 (see Table 9.7). As the sacrum is largely cartilaginous during infancy and early childhood, vascular puncture can occur (38 in 6,011) (Polaner 2012 **Level IV**) and there is an increased risk of injecting local anaesthetic into the highly vascular medullary space of the sacrum (Veyckemans 1992 **Level IV**). Sevoflurane attenuated cardiovascular responses to adrenaline 0.5 mcg/kg IV less than halothane, and may be a better agent to facilitate detection (Kozek-Langenecker 2000 **Level III-2**). Changes in T-wave amplitude can be observed in 91% of patients within 1 min of IV injection of 0.1 mL/kg of lignocaine 1%/adrenaline 5 mcg/mL (and >25% change measured in 94%) (Varghese 2009 **Level II,** n=68, JS 4); this is a sensitive way of detecting intravascular injection. Almost all regional blocks are performed under general anaesthesia in children but there is no clear evidence that this obscures early signs of systemic local anaesthetic toxicity (Bernards 2008 **Level IV**; Taenzer 2014 **Level IV**).

Lipid emulsion infusion has been shown to be of value in managing acute cardiovascular toxicity due to accidental intravascular injection of local anaesthetics in children (Ludot 2008b **CR**) and is recommended as an early intervention (see also Section 4.4.3). Dosing recommendations are the same as for adults: 1.5 mL/kg over 1 min, then 0.25 mL/kg/min (to 0.5 mL/kg/min if hypotension persists), continuing for 10 min after attaining circulatory stability, maximum 10 mL/kg over the first 30 min (AAGBI 2010 **GL**; Neal 2010 **GL**)

Postoperative neurological symptoms

Neurological damage attributable to paediatric regional analgesia is rare (see Table 9.7). The most recent PRAN publication reports a low overall incidence (1.3 in 1,000) of PONS of short duration and one sensory deficit only persisting beyond 6 mth (incidence 1 in approximately 50,000) (Taenzer 2014 **Level IV**). Specifically, PONS occurred less commonly when performed under general anaesthesia at 0.93 per 1,000 (95%CI 0.7 to 1.2) compared with 6.82 per 1, 000 (95%CI 4.2 to 10.5) in sedated and awake patients. This supports the benefit of having an immobile child outweighing the risk of performing regional anaesthesia under general anaesthesia in children.

The UK audit reports a similar incidence of PONS with two events with residual symptoms at 12 mth: one cauda equina syndrome resulting from a drug volume error and one peripheral nerve injury (Llewellyn 2007 **Level IV**). Five other cases of peripheral or nerve root damage were of short duration: three resolved spontaneously, two required chronic pain referral and gabapentin but resolved by 10 mth. The two previous audits of mainly French centres report only transient PONS events (Ecoffey 2010 **Level IV**, Giaufre 1996 **Level IV**); a single centre audit reports one permanent PONS event likely related to epidural insertion (Wong 2013a **Level IV**) and a survey reports two permanent events in two infants (Flandin-Blety 1995).

Care of insensate body regions is important as prolonged block and immobility may result in nerve compression accompanied by neurological deficit or neuropathic pain (Symons 2008 **CR**).

Deaths associated with epidural use

One survey (n=24,005) (Flandin-Blety 1995 **Level IV**) and one retrospective audit (n=3,152) (Wong 2013a **Level IV**) have reported deaths in association with neuraxial block insertions: three infants — one related to LAST, one possibly due to cerebral air embolism, one due to spinal cord ischaemia — and one child aged 6 y with cerebral palsy and carnitine deficiency, who had cardiac arrest with intravascular catheter migration of an epidural catheter and presumed bupivacaine toxicity (Wong 2010 **CR**). No deaths have been reported in the prospective audits (see Table 9.7).

Bleeding/epidural haematoma

Vascular puncture is reported, generally without consequence. One audit includes removal of an epidural catheter in a coagulopathic patient without comment on the consequence (Wong 2013a **Level IV**). The audits report no major bleeding in association with regional insertion and use. However, two audits report on epidural/dural sac blood with neurological sequelae; the former related to surgical rod placement (Llewellyn 2007 **Level IV**) and the latter attributed to

epidural placement (Wong 2013a **Level IV**). Otherwise, spinal epidural haematoma is a rare entity in children and occurs more commonly spontaneously (40–50%), associated with anticoagulants (25–30%) and rarely in association with trauma (usually falls) (Sim 2010 **CR**) (see also Section 5.6.5).

Dural puncture

The audits report variably on dural puncture and resultant total spinal or postdural puncture headache and the need for respiratory or blood patch intervention (see Table 9.7).

Infection

Local skin infection is variably reported (see Table 9.7), with *Staphylococcus aureus* the most commonly identified organism (Llewellyn 2007 **Level IV**). The UK audit reported three serious infections (n=10,633 paediatric epidurals): two epidural abscesses and one meningism.

Bacterial colonisation of catheters was more commonly associated with caudal than lumbar catheters (Kost-Byerly 1998 **Level IV**), however documented superficial infection rates were higher for both caudal 0.15% (95%CI 0.08 to 0.27) and thoracic 0.17% (95%CI 0.09 to 0.3) vs lumbar epidural catheters 0.06% (95%CI 0.03 to 0.11) (Polaner 2012 **Level IV**). Deep tissue or epidural space infection is rare in the absence of prolonged or repeated insertion or immunodeficiency syndromes (Strafford 1995 **Level IV**; Llewellyn 2007 **Level IV**; Polaner 2012 **Level IV**). Infection related to regional analgesia is a documented cause of extended hospital stay with an incidence of 3.3 in 10,000 (Taenzer 2014 **Level IV)**.

Compartment syndrome and pressure sores

Compartment syndrome was reported in several children; importantly, the symptoms were not masked by the epidural infusions (see Table 9.7) (Wong 2013a **Level IV**; Llewellyn 2007 **Level IV**). Avoiding dense sensory or motor block and unnecessary sensory block remote to the surgical site allows full assessment and may prevent delay in diagnosis of compartment syndrome (Johnson 2009 **Level IV**). Appropriate education of staff regarding pressure care and vigilant monitoring for pressure areas to prevent sores is essential for the management of patients receiving continuous regional analgesia (Llewellyn 2007 **NR**).

9.6.2.5 Intrathecal opioids

Following cardiac surgery, IT morphine 20 mcg/kg prolonged time to first analgesia and decreased postoperative morphine requirements but did not alter time to discharge from intensive care (Suominen 2004 **Level II**, n=80, JS 5). Addition of IT tetracaine and morphine to IV remifentanil decreased pain scores and analgesic requirements after early extubation (Hammer 2005 **Level II**, n=45, JS 3). Low-dose spinal morphine 2 mcg/kg vs placebo added to bupivacaine reduced time to first rescue analgesic (6 h±3.2 vs 8 h±3.5) and need for supplementary analgesia (17 vs 60%) following hypospadias repair (Apiliogullari 2009 **Level II**, n=54, JS 5). In infants undergoing lower abdominal and urological surgery, addition of fentanyl 1 mcg/kg (but not lower doses) to IT local anaesthetic prolonged the duration of analgesia and reduced supplemental analgesic requirements (Batra 2008 **Level II**, n=58, JS 5). Fentanyl 0.2 mcg/kg added to local anaesthetic prolonged block duration and reduced analgesic requirements after hernia repair in infants (Duman 2010 **Level II**, n=50, JS 4). Dose-responsiveness for IT opioids is not evident in adults; studies are too few to assess this in children.

9.6.2.6 Regional analgesia use in paediatric spinal fusion

Low-dose IT opioids given preoperatively reduced blood loss and provided good analgesia in the immediate perioperative period: morphine 5–15 mcg/kg +/- sufentanil 1 mcg/kg (Eschertzhuber 2008 **Level II**, n=46, JS 5) and morphine 12 mcg/kg (Lesniak 2013 **Level III-3**). IT morphine (3–7 mcg/kg) combined with 2–5 d epidural infusion of ropivacaine +/- fentanyl (Ravish 2012 **Level III-3**) or bupivacaine/hydromorphone epidural infusion (Milbrandt 2009 **Level III-2**) provided superior analgesia compared with IV-PCA opioid alone.

The addition of epidural local anaesthetic (+/-fentanyl) infusion to IV-PCA morphine compared with IV-PCA morphine alone improves VAS scores for up to 72 h, decreases postoperative nausea and improves patient satisfaction (Taenzer 2010 **Level I**, 4 RCTs, n=120). Hydromorphone

10 mcg/mL added to epidural bupivacaine 0.1% via PCEA vs IV-PCA hydromorphone reduced postoperative pain scores, muscle spasms and diazepam requirements (Gauger 2009 **Level II**, n=38, JS 3). Dual epidural catheter techniques improved dermatomal spread and were effective after combined surgical approach (Ekatodramis 2002 **Level IV**), improving analgesia at rest and on movement after anterior (Blumenthal 2006 **Level II**, n=30, JS 3) and posterior surgical approach (Blumenthal 2005 **Level II**, n=30, JS 3; Lavelle 2010 **Level III-2**). PCEA was effective with a high level of patient satisfaction in selected cases (Saudan 2008 **Level IV**; Lavelle 2010 **Level III-2**). There is however a significant epidural failure rate within 24 h of 8.5–37% due to incorrect placement, patency issues and the long wound length (Gauger 2009 **Level II**, n=38, JS 3; Ravish 2012 **Level III-3**).

Continuous bupivacaine infusion via a wound catheter reduced basal morphine use in idiopathic scoliosis surgery (Ross 2011 **Level III-3**).

9.6.3 Topical therapies

9.6.3.1 Tonsillectomy

Following tonsillectomy, topical application of bupivacaine and ropivacaine reduces pain scores at 4–6 h compared to saline (-1.3/10; 95%CI -1.67 to -0.9) (Grainger 2008 **Level I,** 2 RCTs [paediatric], n=71). A small tonsillectomy study demonstrated no benefit on d 1 following single topical application of tramadol 5% but thereafter pain scores were reduced for 7 d (Akbay 2010 **Level II**, n=40, JS 5). Tonsillar applications of tramadol 40 mg and ketamine 20 mg were superior to placebo, with similar pain scores and rescue analgesic requirements on d 1 (Tekelioglu 2013 **Level II**, n=60, JS 5).

9.6.3.2 Acute otitis media

Acute otitis media is common in children. Topical local anaesthetic drops (benzocaine/antipyrine or lignocaine) used in acute otitis media, in addition to oral analgesia, are effective compared with saline at 10 and 30 min after installation (Foxlee 2006 **Level I** [Cochrane], 1 RCT [vs saline], n=54; Bolt 2008 **Level II**, n=63, JS 5). Superiority of local anaesthetic (amethocaine/antipyrine) over naturopathic drops (3–4 herbal extracts in olive oil) is not established in three RCTs (in addition to paracetamol in one RCT and amoxicillin in one RCT) (Foxlee 2006 **Level I** [Cochrane], 3 RCTs [vs naturopathic drops], n=274 [analysed]).

9.6.3.3 Acute mouth ulceration

In painful acute mouth ulceration in children, topical lignocaine 2% did not improve oral intake, with similar requirement for rescue analgesic at 60 min vs placebo (Hopper 2014 **Level II**, n=100, JS =5)

9.6.3.4 Nasogastric tube insertion

See Sections 9.7.1 and 9.7.2.

Key messages

1. Topical local anaesthetic does not adequately control pain associated with circumcision in awake neonates (**U**) (**Level I** [Cochrane Review]).
2. Caudal local anaesthetic and dorsal penile nerve block provide perioperative analgesia for circumcision in infants to adolescents (**U**) (**Level I** [Cochrane Review]).
3. Caudal local anaesthetic in addition to general anaesthesia for circumcision does not reduce postoperative nausea and vomiting or the need for early rescue or other analgesia in (infant to adolescent) boys, when compared to parenteral analgesia (**N**) (**Level I** [Cochrane Review]).
4. In acute otitis media, topical local anaesthetic drops are effective in children compared to placebo and equivalent to naturopathic drops (**N**) (**Level I** [Cochrane Review]).

5. Ketamine added to caudal local anaesthetic for paediatric day-stay surgery prolongs analgesia but not motor block (**N**) (**Level** I [PRISMA]); however concerns regarding neurotoxicity remain.
6. Clonidine improves analgesia in children when added to caudal local anaesthetic blocks (**S**) (**Level I**) [PRISMA] and epidural local anaesthetic infusions (**U**) (**Level II**).
7. In children having scoliosis surgery, the addition of epidural local anaesthetic infusion to IV PCA morphine improves pain scores and patient satisfaction (**N**) (**Level I**) and decreases postoperative nausea (**N**) (**Level II**).
8. Wound infiltration, peripheral nerve blocks, and caudal local anaesthetic provide effective analgesia after day-case paediatric inguinal surgery (**U**) (**Level II**).
9. Epidural infusions of local anaesthetic in children provide similar levels of analgesia compared to systemic opioid infusion (**U**) (**Level II**) and intravenous patient-controlled analgesia (**N**) (**Level III-3 SR**).
10. Epidural opioids alone are less effective than local anaesthetic or combinations of local anaesthetic and opioid in children (**U**) (**Level II**).
11. Intrathecal opioids provide prolonged analgesia after surgery in children and reduce blood loss during paediatric spinal fusion (**U**) (**Level II**).
12. Continuous epidural infusions provide effective postoperative analgesia in children of all ages (**S**) (**Level III-2**).
13. Continuous epidural infusions are safe in children of all ages (**S**) (**Level III-2**) if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**S**) (**Level IV**).
14. Complications of epidural infusions are rare; the rates are slightly higher in neonates and infants versus older children (**N**) (**Level III-2**).
15. Peripheral nerve and neuraxial blocks (as single injections and continuous catheters) are safe and effective analgesic techniques in children (**N**) (**Level IV**).
16. Placement of neuraxial blocks in children under general anaesthesia is not associated with an increased rate of complications (**N**) (**Level IV**).
17. Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery and have a low incidence of serious complications (**S**) (**Level IV**).

9.7 Management of procedural pain in children

Procedure-related pain is a frequent and distressing component of medical care for children, their families and hospital staff (Kennedy 2008 **NR**; Atkinson 2009 **NR**). Repeated interventions are often required and the level of pain and memory of the first procedure affect the pain (Taddio 2009b **Level II**, n=240, JS 5; Noel 2012 **Level IV**), fear (de Vos 2012 **Level IV**) and distress (Chen 2000 **NR**) associated with subsequent procedures (Kennedy 2008 **NR**). Studies suggest that gaps exist in that minor procedures are still undertaken in children, particularly neonates and infants, in the elective and emergency hospital setting without evidence-supported pain management interventions (MacLean 2007 **Level IV;** Harrison 2009 **Level IV**; Hoyle 2011 **Level IV**; Losacco 2011 **Level IV**; Codipietro 2011 **Level IV**; Ali 2014 **Level IV**).

The aim of procedural pain management is to minimise physical discomfort, pain, movement and psychological disturbance without compromising patient safety. Management may include analgesic agents via different routes of administration, concurrent sedation or general anaesthesia and nonpharmacological methods. The choice of technique will depend on the age and previous experience of the child, the type of procedure, the expected intensity and duration of pain, the treatment environment and available resources (Murat 2003 **GL**; Atkinson 2009 **NR**). Sedation alone must not be seen as an alternative to appropriate analgesia, particularly when pain is expected after completion of the procedure. Further information is available from evidence based guidelines produced by various anaesthetic, paediatric and

emergency physician associations (RACP 2005 **GL**; Cote 2008 **GL**; Mace 2008 **GL**; Green 2011 **GL**; Godwin 2014 **GL**).

9.7.1 Procedural pain in the neonate

9.7.1.1 Blood sampling, skin puncture and intravenous cannulation

Neonates in NICUs require frequent blood sampling, cannulation and skin punctures for other reasons. Multiple interventions have been assessed to alleviate the pain experienced.

Different techniques of blood sampling

Venipuncture is less painful than heel lance (SMD -0.76; 95%CI -1.00 to -0.52) (4 RCTs, n=254), including when a sweet solution is administered (SMD -0.38; 95%CI -0.69 to -0.07), with less pain behaviour exhibited during and after the procedure and fewer attempts required (SMD 0.34; 95 CI -0.43 to -0.25) (Shah 2011b **Level I** [Cochrane], 6 RCTs, n=478). Spring-loaded automated devices for heel lance reduced the pain behaviour exhibited compared with manual lance (Shah 2003 **Level II**, n=80, JS 5).

Topical local anaesthesia

Topical local anaesthesia reduced the physiological and behavioural response to venipuncture (Taddio 1998 **Level I**, 1 RCT [venipuncture], n=60).

Breastfeeding, supplemental breast milk and sweet solutions

For skin puncture, breastfeeding reduces pain scores and results in reduced heart rate response and crying when compared to positioning (swaddling and placement in a crib), holding by the mother, no intervention, placebo, pacifier use and oral sucrose or both (Shah 2012 **Level I** [Cochrane], 10 RCTs [breastfeeding], n=1,076).

Administration of supplemental breast milk has mixed effects (Shah 2012 **Level III-1 SR** [Cochrane], 10 studies [supplemental breast milk], n=1,002). It is inferior to sucrose, glycine, pacifier use, and rocking (1 study each), superior (3 studies) but also equivalent to placebo (2 studies), and inferior to no intervention (1 study).

Sweet solutions via dropper, syringe or pacifier (sucrose 12–50% 0.05–2mL, glucose 20–50% 0.2–2mL, and artificial sweetener, fructose, glycine, honey and maltitol) reduce pain scores and responses to skin puncture (cry, grimace, sucking intensity, heart rate) in premature and term neonates (Stevens 2013 **Level I** [Cochrane], 44 RCTs [skin puncture], n=4,120; Bueno 2013 **Level I** [PRISMA], 38 RCTs [35 glucose; 5 other solutions; 36 skin puncture], total n=3,785).

Sucrose reduces pain scores post heel lance at 30 s (WMD -1.76/16 [PIPP]; 95%CI -2.54 to 0.97) (4 RCTs, n=264) and 60 s (WMD -2.05/16 [PIPP]; 95%CI -3.08 to -1.02) (3 RCTs, n=195) (Stevens 2013 **Level I** [Cochrane], 57 RCTs, n=4,730). Sucrose reduces total duration of time spent crying (WMD -39 sec; 95%CI -44 to -34) (2 RCTs, n=88) but not duration of first cry during heel lance (WMD -9 sec; 95%CI -20 to 2) (3 RCTs, n=192). Sucrose 24% also reduced crying during and after arterial puncture (Milazzo 2011 **Level II**, n=47, JS 5).

Glucose 10–50% 0.2–2 mL compared with water or no intervention in response to heel lancing reduces pain scores (6 RCTs, n≈322) and PIPP (WMD −3.6/16; 95%CI -4.6 to -2.6) (2 RCTs, n=124) (Bueno 2013 **Level I** [PRISMA], 38 RCTs, n=3,758). Glucose 25–50% 1–2 mL compared with 10% glucose, water, no intervention or EMLA® cream for venipuncture reduces pain scores (11 RCTs, n≈1,311) and cry response (RR 0.80; 95%CI 0.66 to 0.96) (3 RCTs, n=130).

Although the efficacy of sweet solutions is demonstrated, studies vary 10-fold in dosing and in their use of non-nutritive sucking (NSS) (of syringe or pacifier) vs administration by dropper. Thus, the optimal doses of sucrose and glucose remain undetermined, as does the safety of repeated doses.

Opioids

Background morphine infusions in ventilated neonates had limited efficacy for acute procedural interventions in intensive care (Bellu 2008 **Level I** [Cochrane], 2 RCTs [procedures], n=965).

Combination intervention in neonates: pharmacological

In preterm neonates, topical local anaesthesia EMLA® combined with oral sucrose 30% was more effective than sucrose alone in reducing venipuncture-related pain (Biran 2011 **Level II**, n=76, JS 3). In term neonates, the addition of liposomal lidocaine for venipuncture to sucrose did not confer additional benefit (Taddio 2011 **Level II**, n=330, JS 5).-

For peripherally inserted central catheter (PICC) placement, morphine bolus IV with topical amethocaine provided more effective analgesia than morphine or amethocaine alone in preterm neonates (Taddio 2006 **Level II**, n=132, JS 5). In ventilated term and preterm neonates pretreated with EMLA®, a glucose 30% pacifier combination was inferior to sevoflurane (Bueno 2013 **Level I** [PRISMA], 1RCT [sevoflurane], n=59).

Nonpharmacological intervention alone and in combination

"Kangaroo" care of neonates (involving ventral skin to skin contact with an adult), during heel lance (15 RCTs, n≈794) or other skin puncture (4 RCTs, n≈800) compared with no intervention reduces pain scores but does not have an impact on heart rate response (11 RCTs, n=637) (Johnston 2014 **Level I** [Cochrane], 19 RCTs, n=1,594). In five RCTs (n=268), PIPP is reduced most at 30 s (MD -3.21/16; 95%CI -3.94 to -2.48) with less impact at 60 and 90 s, and no difference at 120 s. No difference is seen between mothers and alternative providers (2 RCTs, n=80). Single trials in this review comparing kangaroo care with other active interventions demonstrate similar efficacy to breastfeeding but superiority to dextrose and glucose. Kangaroo care combined with breastfeeding is superior to no treatment, and combined with dextrose is superior to dextrose alone. In a separate RCT, kangaroo care combined with breastfeeding was superior to kangaroo care with sucrose and compared to either kangaroo care or sucrose alone for heel lance in term neonates (Marin Gabriel 2013 **Level II**, n=136, JS 3).

Facilitated tucking (swaddling) compared with standard positioning reduces pain-related distress reactivity to heel lance in term (1 RCT, n=42) and preterm neonates (2 RCTs, n=45), and to endotracheal tube suctioning in preterm neonates (1 RCT, n=20) (Pillai Riddell 2011 **Level I** [Cochrane], 51 RCTs, n=3,396). In preterm neonates having repeated heel lancing, sucrose 20% was superior to facilitated tucking, and adding facilitated tucking to sucrose did not confer additional benefit to sucrose alone (Cignacco 2012 **Level II**, n=71, JS 5).

For neonatal vaccination, providing external warming was superior to sucrose 25% or pacifier use, with shorter duration or no cry or grimace during vaccination (Gray 2012 **Level II**, n=47, JS 3).

NNS is beneficial in combination with sucrose, for SC injection (1 RCT, n=33) and for heel lance (4 RCTs, n=264) (Stevens 2013 **Level I** [Cochrane], 57 RCTs, n=4,730), including when combined with facilitated tucking (Liaw 2013 **Level II,** n=110, JS 3). For vaccination, NNS alone is inferior to sucrose alone but is superior to routine care (Liaw 2011 **Level II**, n=165, JS 3).

Applying mechanical vibration to the foot prior to heel lance, in addition to use of a pacifier with sucrose, did not impact upon pain scores compared with pacifier and sucrose alone (Baba 2010 **Level II,** n=20, JS 3).

For heel lance, passive music therapy (playing a lullaby) was superior to no music for preterm neonates and, combined with NNS, was superior compared with either alone, with lower pain and stress scores in both pre and term neonates (Wright 2013 **Level I,** 2 RCTs [heel lance], n=87).

9.7.1.2 Lumbar puncture

For infant lumbar puncture, surveyed clinicians (n=156) working in paediatric EDs at five USA centres reported frequent use of NNS (67%), with low use of other interventions (<30% of sucrose, topical and injectable lignocaine) (Hoyle 2011 **Level IV**). A further USA centre audited local anaesthetic use for lumbar puncture in children aged 0–24 mth (n=223) with 0% use in neonates, 54% in infants but 99% in toddlers (Gorchynski 2011 **Level IV**). A Canadian ED survey revealed minimal use of sucrose in infants, and low use of topical local anaesthetic, across the paediatric age range (Ali 2014 **Level IV**). The poor translation of evidence into practice is disappointing with the data known regarding the consequences of poor analgesia (Kennedy

2008 **NR**) and the suggested positive association of local anaesthetic use with increased first pass success and atraumatic taps (Kennedy 2014 **NR**).

EMLA® reduced the physiological and behavioural response with needle insertion for lumbar puncture in preterm and term neonates (Kaur 2003 **Level II**, n=60, JS 5).

9.7.1.3 Urine sampling

EMLA® reduced pain scores in neonates and young infants undergoing suprapubic aspiration (Nahum 2007 **Level II,** n=52, JS 5). Transurethral catheterisation was less painful after urethral application of lignocaine 2% than suprapubic aspiration after skin application of EMLA® (Kozer 2006 **Level II,** n=58, JS 5), and also in preterm neonates, where no topical local anaesthetic was used (El-Naggar 2010 **Level II,** n=48, JS 4). Sucrose vs water reduced cry incidence (29 vs 78%) and pain scores during transurethral catheterisation in neonates (Stevens 2013 **Level II** [Cochrane], 1 RCT [catheterisation], n=80).

9.7.1.4 Ocular examination for retinopathy of prematurity

Screening for retinopathy of prematurity (ROP) causes pain in neonates (Belda 2004 **Level IV**). Topical local anaesthetic reduces pain scores (Dempsey 2011 **Level I** [Cochrane], 2 RCTs, n=168). The benefit of treating with sucrose alone vs water, vs in combination with topical local anaesthetic and/or nonpharmacological interventions (such as swaddling and NNS) is unclear (Stevens 2013 **Level I** [Cochrane], 6 RCTs [ROP], n=195; Dilli 2014 **Level II**, n=64, JS 5). Sucrose pre eye examination does not affect cry (2 RCTs) or heart rate (2 RCTs), with mixed effects on pain scores (Stevens 2013 **Level I** [Cochrane], 5 RCTs [ROP], n=174). Two of four RCTs (n=62) report short-lived reduction in oxygen saturation in sucrose-treated infants, during but not persisting following eye examination (WMD -2.6%; 95%CI -4.9 to -0.2).

Inhaled N_2O administration did not confer additional benefit to topical local anaesthetic/oral sucrose combination in swaddled infants (Mandel 2012 **Level II**, n=40, JS 5).

9.7.1.5 Nasogastric tube insertion

Sucrose, alone and with NNS, improves pain scores compared with water for neonatal nasogastric tube insertion (Stevens 2013 **Level I** [Cochrane], 2 RCTs [nasogastric], n=44).

9.7.2 Procedural pain in infants and older children

9.7.2.1 Venipuncture and intravenous cannulation

Venipuncture causes significant distress in many children (Kennedy 2008 **NR**). Both pharmacological and nonpharmacological interventions have evidence support.

Topical local anaesthesia

Topical local anaesthesia (via cream/gel, patch, iontophoresis, and needleless compression device delivery) reduces pain associated with venipuncture and IV cannulation in all age groups (Zempsky 2008 **Level I**, 52 RCTs, n unspecified).

Amethocaine (tetracaine) gel is more effective than EMLA®cream (RR 0.78; 95%CI 0.62 to 0.98) with more rapid onset (Lander 2006 **Level I** [Cochrane], 6 RCTs, n=634). A heated lignocaine/amethocaine patch was superior to placebo (2 RCTs, n=109) and EMLA® (1 RCT, n=200) (Croxtall 2010 **Level I**, 3 RCTs [paediatric], n=309).

Iontophoresis of lignocaine 1–4% is superior to placebo (4 RCTs, n=420) and is equivalent to or superior to EMLA® (2 RCTs, n=144) with a time to onset of 10 min (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). Liposomal lignocaine 4% cream was similar with only 15 min application to placebo (Brenner 2013 **Level II**, n=120, JS 5) and after 30 min was both similar to amethocaine 4% (Poonai 2012 **Level II**, n=60, JS 5) and superior to placebo (1 RCT, n=142) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). It had a more rapid onset and was as effective as EMLA® (3 RCTs, n=240) and was as effective as buffered lignocaine (1 RCT, n=69) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified). Sonophoresis prior to application of liposomal lignocaine accelerated the onset time from 30 to 5 min (1 RCT, n=60) and sonophoresis/liposomal lignocaine was superior to sonophoresis/placebo cream (1 RCT, n=77).

Intradermal delivery of powdered lignocaine (0.5–1 mg) under high pressure (20 bar) via a needleless device (CO_2 driven) was effective within 3 min and produced more effective skin anaesthesia than EMLA® cream (Jimenez 2006 **Level II**, n=116, JS 3). It was also more effective than lower dose intradermal delivery (0.25 mg) (1 RCT, n=307) and placebo (2 RCTs, n=452) (Zempsky 2008 **Level I**, 52 RCTs, n unspecified).

Nitrous oxide

N_2O at 20–75% reduced pain and anxiety associated with venipuncture/IV cannulation and, in one study, shorter time to achieve access with fewer attempts (Tobias 2013 **Level IV SR**, 5 studies [venipuncture/cannulation], n unspecified). N_2O 70% for 3 and 5 min reduced pain scores by >50% (Furuya 2009 **Level II,** n=73, JS 5). The combination of N_2O 40–50% and topical EMLA® for IV cannulation was more effective in reducing pain scores and increased satisfaction when compared with either method alone (Pedersen 2013 **Level I** [PRISMA], 3 RCTs [IV cannulation], n=233). This systematic review also included five large case series of N_2O use in mixed minor procedures, supporting the safety of N_2O 50–70% administration in children (Pedersen 2013 **Level IV SR** [PRISMA], 5 studies, n=54,127).

Combination pharmacological intervention

The combination of EMLA® and N_2O 50% reduced procedure duration with more successful IV placements than EMLA®/low-dose oral midazolam (0.3 mg/kg [maximum 15mg]) 40 min prior (Ekbom 2011 **Level II,** n=90, JS 4). Notably, the usual oral midazolam dose is 0.5 mg/kg and, at 40 min, offset of effect is relevant.

Sweet-tasting solutions in older children

Sweetened chewing gum or sweet solution did not reduce pain scores for blood sampling in school-aged children (Harrison 2011 **Level I** [Cochrane]**,** 1 RCT [venipuncture], n=99).

Nonpharmacological intervention

Vapocoolant sprays have variable effects; ethyl chloride is either ineffective (Zempsky 2008 **Level I,** 2 RCTs [ethyl chloride], n=349), reduced pain associated with IV cannulation (Farion 2008 **Level II**, n=80, JS 3) or was as effective as topical amethocaine in children undergoing venipuncture (Zempsky 2008 **Level I,** 1 RCT [vs topical amethocaine], n=144). Ice application (0° C) for 3 min improved pain-related behaviours in children aged 6–12 y (Movahedi 2006 **Level III-2**). Vapocoolant spray (5-fluoropropane/4-fluoroethane: Painease®) applied 10 sec prior to IV cannulation was similarly effective to 3 min application of ice in older children (9–18 y) (Waterhouse 2013 **Level II**, n=95, JS 4). A device with metal applicator (Coolsense®) requiring refrigeration (to -2°C) and around 10-s application time reduced the pain of finger prick blood sampling in adults (Wainstein 2013 **Level II,** n=177, JS 4). This device awaits assessment in children.

A Buzzy® device (stimulating cold and vibration A-beta fibres) placed proximally throughout venipuncture in children (4–18 y) compared to vapocoolant spray reduced patient (MD 2/10; 95%CI -4 to 0) and parental (MD -2/10; 95%CI -4 to -2) pain scores, with greater venipuncture success on first attempt (OR 3; 95%CI 1 to 9) (Baxter 2011 **Level II**, n=81, JS 3). Use of Buzzy® device compared with no intervention in children (6–12 y) achieved lower self-reported pain (2.8/10 ±1.9 vs 6.6/10 ±1.7) and anxiety (1.6/10 ±1 vs 3.4/10 ±1) scores, with no difference in the success of blood specimen collection (93 vs 88%) (Inal 2012 **Level II**, n=120, JS 3).

9.7.2.2 Lumbar puncture and bone marrow aspiration

Numerous techniques are used to alleviate the pain and distress occurring in children undergoing lumbar puncture (alone or combined with bone marrow aspiration) in ED and oncology settings (Kennedy 2014 **NR**). Interventions have usually been assessed in isolation. Despite positive benefits, use of analgesic intervention in EDs has penetrated poorly (Ali 2014 **Level IV**). Combining techniques is recommended best practice: topical local anaesthesia, local anaesthesia infiltration by slow injection, and sucrose with NSS in infants; and, for older children, adding distraction (see Section 9.4.5) and anxiolysis with midazolam and/or further analgesia with N_2O (Kennedy 2014 **NR**). Deeper sedation techniques and general anaesthesia

are also used. The choice of intervention is best determined by the setting, the local resources and skills, and assessment of the individual child.

Topical local anaesthesia and nitrous oxide (alone or in combination)

Topical local anaesthesia with EMLA® cream was effective for lumbar puncture (Juarez Gimenez 1996 **Level III-1**). Needle-free jet injection of lignocaine compared with saline resulted in slightly lower pain scores (mean 4.1/10 ±1.3 vs 4.8/10 ±0.5) and slightly reduced cry duration (by 10 s) in infants <3 mth of age (Ferayorni 2012 **Level II,** n=55, JS 5).

Several case series have reported utility of N_2O 50–70% for these procedures, focussing on report of adverse effects (Pedersen 2013 **Level IV SR** [PRISMA], 5 studies, n=46,565 [lumbar punctures n=5,947, bone marrow aspirations n=2,799]; Babl 2010 **Level IV**; Kanagasundaram 2001 **Level IV**). Some studies specify N_2O was used as sole agent; one specified routine simultaneous use of distraction. In two studies, coadministration of local anaesthesia and sedative/anxiolytic was specified: respectively 18% and 8.2% (Onody 2006 **Level IV**, n=3,964) vs 98.7% and 64.5% (Annequin 2000 **Level IV**, lumbar punctures n=286, bone marrow aspirations n=231). The latter study described low pain scores during lumbar puncture and bone marrow aspiration (respective procedure scores: patient median 5 and 12.5/100; nurse median 0 and 2/10) with a low need overall for restraint, initially (18.2%) and during (6%) the procedure.

Fentanyl alone

Oral transmucosal fentanyl is not licensed for paediatric use but 10–15 mcg/kg reduced pain scores vs placebo dosette for lumbar puncture/bone marrow aspiration (Schechter 1995 **Level II**, n=48, JS 4). As yet, IN use is unreported for this procedural indication.

Single or double agent sedation vs general anaesthesia

For oncology lumbar puncture/bone marrow aspiration, general anaesthesia is considered by some to be best practice (eg with propofol/fentanyl) (Ghasemi 2013 **Level IV**), while volatile-based general anaesthesia (sevoflurane/N_2O) was preferred to sedation, with less distress and pain for children requiring multiple procedures (Crock 2003 **Level III-3**). Propofol has been used by an ED physician-led sedation team for these procedures (Lamond 2010 **Level IV SR,** 1 study [ED physician], n=87 [291 procedures]). In two small cross-over trials of children with leukaemia undergoing lumbar punctures/bone marrow aspirations, adding fentanyl 1 mcg/kg IV to propofol sedation improved satisfaction, recovery time by 10 min (Cechvala 2008 **Level II,** n=22, JS 5) and analgesia (Nagel 2008 **Level II**, n=25, JS 5). The addition of fentanyl 0.5–1 mcg/kg was propofol sparing with less movement during the procedure and shorter recovery times but no difference in post lumbar puncture/bone marrow aspiration pain scores (Anghelescu 2013 **Level II**, n=162, JS 5).

Oral or IV ketamine was associated with less distress during lumbar puncture and/or bone marrow aspiration in children with cancer (Tobias 1992b **Level III-3**; Evans 2005 **Level IV**). In the ED setting, ketamine 1 mg/kg IV alone vs with midazolam 0.1 mg/kg IV was similarly effective (Dilli 2008 **Level II**, n=99, JS 3). Adding ketamine 0.5 mg/kg to propofol (administered by nonanaesthetists) vs propofol alone was propofol sparing, resulted in better observer scored intraprocedural pain scores and reduced recovery time (Chiaretti 2011 **Level II**, n=121, J S3).

Nonpharmacological intervention

See Section 9.4.5.

Reduction of postdural puncture headache incidence

Following diagnostic lumbar puncture in children (n=414), less PDPH resulted with use of 27-gauge pencil point needle (0.4%) compared with a 26-gauge cutting point needle (4.5%) (Apiliogullari 2010 **Level III-2**). In children having intraspinal chemotherapy, the incidence of PDPH with a 22- vs 25-gauge cutting needle was similar (7.2%; 95%CI 3.8 to 12.2 vs 4.6%; 95%CI 2 to 8.9) (Crock 2014 **Level II**, n=93 [341 procedures], JS 5), and for 22-gauge cutting vs 25-gauge pencil point needles (11 vs 7%; p=0.7) (Lowery 2008 **Level III-2**). With guideline change from 22-gauge spinal needles to 25-gauge for diagnostic lumbar punctures/chemotherapy administration and 27-gauge for spinal anaesthesia, epidural blood patch rates decreased

from 0.8% (5-y data) to 0.2–0.3% (10-y data) (Kokki 2012b **Level III-3**). Injected mean blood volumes of 0.27 mL/kg (range 0.16–0.53 mL/kg) achieved complete persistent resolution in 83% of 42 patients (see also Section 8.6.5).

9.7.2.3 Botulinum toxin (intramuscular) or steroid (intra-articular) injection

Botulinum toxin is injected IM to treat spasticity and this is painful. Use of N_2O 70% in isolation reduced patient, parent and nurse FLACC scores compared to midazolam 0.35–0.5 mg/kg rectally (Zier 2008 **Level II**, n=50, JS 4). Using topical EMLA® and N_2O 50% in children reduced pain in only 50% of the 51 procedures (n=39) with the remainder experiencing severe pain (≥9/13 CHEOPS) (Brochard 2009 **Level IV**). US guidance may help localise muscles more accurately (Py 2009 **Level IV**). N_2O 50%/oxygen treatment for botox or joint injections was superior to inhaled nitrogen 50%/oxygen mix, with lower pain scores (by 50%; $p<0.003$) and fewer patients requiring rescue with propofol or sevoflurane (18 vs 55%) (Reinoso-Barbero 2011 **Level II**, n=100, JS 4). Use of N_2O 50–70% in a small series of children having joint injection achieved adequate analgesia in most (49 of n=55) children (Cleary 2002 **Level IV**).

General anaesthesia should be considered especially when injecting multiple muscles or joints.

9.7.2.4 Urethral catheterisation and micturating (voiding) cystourethrogram

Local anaesthesia – topical and installation

Local anaesthetic lubricant reduced the pain of urethral catheterisation when administered 10 min (Gerard 2003 **Level II**, n=20, JS 5) but not 2–3 min prior (Vaughan 2005 **Level II,** n=115, JS 5). Topical lignocaine and then intraurethral lignocaine reduced crying during catheterisation in children aged 2–24 mth vs those who received topical lubricant only or topical and intraurethral lubricant combined (Mularoni 2009 **Level II**, n=43, JS 4). In children aged 2 mth–8 y, delaying intraurethral installation of lignocaine gel to 5 min after topical application made no difference to FLACC scores during catheterisation compared to installation immediately post topical application (Boots 2010 **Level II,** n=200, JS 4).

Nitrous oxide

N_2O use is associated with low pain and distress scores in children undergoing urethral catheterisation and/or micturating cystourethrogram (Pedersen 2013 **Level IV SR** [PRISMA], 2 studies [catheterisation], n≈5,000).

Intranasal fentanyl alone

Fentanyl 2 mcg/kg IN, administered slowly by dropper 10 min prior to catheterisation for micturating cystourethrogram, with no distraction used, resulted in similarly low pain scores compared to water (Chung 2010 **Level II**, n=69, JS 5). Nasal irritation was reported by 6 and 14% respectively.

Nonpharmacological intervention

Preparing the child for the micturating cystourethrogram using a story booklet alone or with play preparation reduced distress (Phillips 1998 **Level III-2**). Hypnosis was superior to play preparation, with reduced distress and procedure duration (Butler 2005 **Level II,** n=44, JS 3).

9.7.2.5 Chest drain removal

Morphine IV, topical anaesthesia with EMLA® and N_2O reduced pain but did not provide adequate analgesia for chest drain removal in children (Bruce 2006a **Level III-2**; Bruce 2006b **SR Level IV**, 3 studies, n=519). The distress associated with chest drain and pacing wire removal in cardiac patients was reduced with introduction of an assessment tool and intervention protocol involving play therapist, topical local anaesthetic, and additional targeted pharmacological intervention based on the tool's estimate of risk (Craske 2013 **Level III-3**). Ketamine 0.5 mg/kg IN combined with sufentanil 0.5 **mcg**/kg IN has been used in children for drain removal (Nielsen 2014 **Level IV**).

9.7.2.6 Nasogastric tube insertion

Nasogastric tube insertion causes pain and distress particularly in children (Juhl 2005 **Level IV**).

Topical local anaesthesia

In adults, topical gel and/or nebulised anaesthesia of the nose and pharynx reduces pain associated with NGT insertion (OR 0.42; 95%CI 0.20 to 0.88) (Kuo 2010 **Level I**, 5 RCTs, n=212; Uri 2011 **Level II,** n=62, JS 5) and reduced NGT insertion time (Chan 2010 **Level II**, n=206, JS 5). An RCT in children aged 1–5 y of nebulised lignocaine was terminated early due to the distress associated with nebulisation and so a benefit of nebulised lignocaine was not confirmed (Babl 2009 **Level II**, n=36, JS 5).

Ketamine

In adults, ketamine 50 mg IN reduced pain scores vs placebo for NGT insertion (Nejati 2010 **Level II,** n=72, JS 5). In mostly preschool aged children having NGT insertion (for repeat gastric aspirates), ketamine 2 mg/kg and midazolam 0.5 mg/kg (maximum 10 mg) IN vs placebo achieved sedation for 71 min (95%CI 64 to 80 min) and reduced pain scores and the need for physical restraint (4 vs 100%), with low postprocedure agitation rates (11% of procedures) (Buonsenso 2014 **Level II**, n=36 [108 procedures], JS 5).

9.7.2.7 Burns dressings

Children who have sustained burn injuries often require repeated, painful and distressing dressing changes (see also Section 8.3). Considerable interindividual variation occurs and analgesia needs to be titrated to effect as requirements differ according to the surface area involved, the location, the stage of healing and need for grafts, and the child's previous experiences (Palmer 2014 **NR**). It is important to consider significant coexistent post-traumatic stress symptoms or disorder (Stoddard 2006 **Level IV**; Stoddard 2011 **Level III-1**) and anxiety and depression, which can persist for months (van Baar 2011 **Level III-2**). Long-term post-traumatic stress symptoms may be reduced by adequate early opioid administration (Sheridan 2014b **Level IV**). In the early phases, general anaesthesia may be preferred for dressing changes, stepping down to procedural interventions on the ward and then as outpatients (Palmer 2014 **NR**).

Burn dressing types

Numerous dressings for superficial and partial thickness burns have been assessed and the optimal choice is unclear (Wasiak 2013 **Level I** [Cochrane], 6 RCTs [paediatric], n=364). In paediatric patients, biosynthetic dressings are superior to silver sulphadiazine reducing daily opioid requirements (1 RCT, n=20), the time to healing, number of dressing changes and hospital stay (2 RCTs, n=109) but were similar to hydrocolloid dressing (Duoderm®) in terms of pain scores and time to healing (1 RCT, n=72).

Opioids

Opioids are frequently required and prescribed for burns dressing changes, with little published data. Compared to placebo, oral transmucosal fentanyl (≈10 mcg/kg) compared favourably with oral morphine (Robert 2003 **Level II,** n=8, JS 4), oral hydromorphone 60 mcg/kg (Sharar 1998 **Level II,** n=14, JS 4) and oral oxycodone 0.2 mg/kg in reduction of pain associated with dressing changes (Sharar 2002 **Level III-2**). Fentanyl 1.4 mcg/kg IN reduced pain scores similarly with similar recovery time compared to oral morphine 1 mg/kg in paediatric burns dressing change (Borland 2005 **Level II,** n=28, JS 4).

Ketamine

Ketamine (0.8–2 mg/kg) with propofol (0.8–2.5 mg/kg) or dexmedetomidine (0.4–1.2 mcg/kg) IV has been used for short duration (10 min) dressing change (Canpolat 2012 **Level III-1**). Ketamine 0.5 **mg**/kg IN combined with sufentanil 0.5 **mcg**/kg IN has been used in children (n=7) for burn dressing change (Nielsen 2014 **Level IV**). Ketamine administration by nonanaesthetists was audited (n=347), where doses of 6–800 mg were given to children weighing 3–111 kg for procedures of 1–105 min duration (Owens 2006 **Level IV**). Ten

events occurred that required intervention (2.9% incidence); eight were airway related and responded to repositioning, supplemental oxygen or bag-mask ventilation and two hypotensive events responded to fluid administration.

Oral ketamine 5 mg/kg with midazolam 0.5 mg/kg compared to combination oral midazolam 0.5 mg/kg, paracetamol 10 mg/kg and codeine 1 mg/kg may provide superior analgesia (mean pain score 7.4/13 CHEOPS; 95%CI 4 to 12 vs 8.9/13; 95%CI 4 to 13) for burns dressing changes in children aged 1–5 y (Norambuena 2013 **Level II**, n=60, JS 4).

Dexmedetomidine

Dexmedetomidine 2 mcg/kg IN has been used as premedication prior to burns reconstructive surgery (Talon 2009 **Level II**, n=50, JS 3) and 0.5 mcg/kg combined with ketamine for procedural sedation for short duration burns surgery (Canpolat 2012 **Level III-1**) but no conclusion can be drawn as to the impact upon pain outcome.

Nonpharmacological intervention for burns dressings

Nonpharmacological strategies such as distraction, preparation, parental presence and hypnosis may be effective (see Section 9.7.5). Pain scores associated with burn dressing changes reduced with immersive VR games (computer-generated environment with immersive head gear) (Das 2005 **Level II,** n=7, JS 3), music ("active alternate engagement") (Fratianne 2001 **Level II,** n=24, JS 3**;** Klassen 2008 **Level III-2 SR,** 1 RCT [paediatric burn dressing change], n=14) and massage therapy (Hernandez-Reif 2001 **Level IV**; O'Flaherty 2012 **Level IV**). Twice weekly massage for 15–20 min for 5 wk lowered heart and respiratory rate, with positive response (becoming relaxed or falling asleep in 93%, verbally requesting more in 20%) (O'Flaherty 2012 **Level IV**) and decreased pain and anxiety by 58% ($p<0.01$) compared with no change in patients receiving standard care (Parlak Gurol 2010 **Level III-1**).

Augmented reality gaming (screen with 3D animation of chosen figurine) achieved lower patient pain scores vs basic cognitive therapy intervention (2.9/10; SD 0.9 vs 5.4/10; SD 0.6) (Mott 2008 **Level III-1**). Immersive VR game use compared with standard distraction reduced nurse observer pain scores (mean 2.9/10; SD 2.4 vs 4.7/10; SD 2.5) and rescue use of N_2O (15 vs 43%) (Kipping 2012 **Level II**, n=41, JS 3). Multimodal procedural preparation (video shown on screen device: "Bobby got a burn") and multimodal distraction (same screen device using games ("touch and find" stories with multisensory visual, auditory, and vibratory feedback; Ditto™) lowered pain scores (child by 20–27%, parent by 29–37% and nursing staff by 16–34%) compared with a hand-held video game device or standard distraction (varied use of TV, video games, stories, toys, nursing staff soothing and care giver support) (Miller 2010 **Level II**, n=80, JS 3). Across three procedures, multimodal distraction use reduced pain scores, while multimodal procedural preparation, video or standard distraction did not. Ditto™ vs standard distraction (in addition to varying pharmacological agents) did not impact significantly on pain or anxiety ratings during the first three dressing changes (Brown 2014 **Level II**, n=117, JS 3).

Nonpharmacological interventions for physiotherapy in burns rehabilitation

In adult and paediatric burn patients having physiotherapy, immersive VR SnowWorld® reduced mean worst pain intensity by 20% (54/100 ±3 vs 44/100 ±4), pain unpleasantness by 26% (41/100 ±4 vs 30/100 ±3), and time spent thinking about pain by 37% (47/100 ±4 vs 30/100 ±3) (Sharar 2007 **Level II**, n=88 [66 children], JS 3). Repeated use of SnowWorld® in addition to pharmacotherapy by children with burns having physiotherapy reduced cognitive, sensory and affective pain scores (by 44, 27 and 32%; $p<0.05$) with patients experiencing three-fold more fun ($p<0.001$) than when no immersive VR was used, although there was no difference in the maximum range of motion achieved (Schmitt 2011 **Level II,** n=54, JS 3).

Distraction through purposeful activity with play and games compared with "exercise by rote" modulated the pain experience and improved range of motion achieved during physiotherapy for hand burns in children (Omar 2012 **Level II**, n=30, JS 2).

9.7.3 Immunisation pain in infants and children

There is supportive evidence for various interventions in immunisation pain. Translation to practice is slow but can be improved with a (telephone-based) educational outreach program (Schechter 2010 **Level IV**), assessment of lay and medical perceptions and practice (Harrison 2014 **Level IV**) and then use of novel techniques to effect change eg social media (Center for Pediatric Pain Research).

9.7.3.1 Procedural modifications

Procedural modifications to reduce pain during immunisation include rapid IM needle insertion/injection without aspiration (1 RCT, n=113), stroking the skin close to the injection site before and during injection (1 RCT, n=105), the vaccine formulation (5 RCTs, n=1,104) (Taddio 2009a **Level III-1 SR,** 19 studies, n=2,814) and using a longer (25 vs 16 mm) and wider needle (23- vs 25-gauge) (Schechter 2007 **Level I,** 2 RCTs, n unspecified; Bharti 2010 **Level II**, n=155, JS 5). Applying pressure has positive effect in adults and may be of use in children (Schechter 2007 **Level I**, 1 negative RCT, 2 positive unpublished RCTs, n unspecified).

9.7.3.2 Topical local anaesthesia

Topical local anaesthesia effectively reduces child-reported (2 RCTs, n=276) and observed infant pain scores (4 RCTs, n=527) for SC and IM vaccination (Shah 2009 **Level I SR**, 10 RCTs, n=1,156; Gupta 2013 **Level II**, n=90, JS 5). Selective use of topical local anaesthesia has been recommended in older children (Schechter 2007 **GL**).

9.7.3.3 Sweet solutions

In infants aged 1–12 mth having immunisation, oral sucrose 12–75% and glucose 30–40% 1–2 mL compared to water, saline or no treatment reduced incidence of cry and crying duration (MD -13.5; 95%CI -16.8 to -10.2) (Kassab 2012 **Level I** [Cochrane], 14 RCTs, n=1,551). In infants aged 2–6 mth, high-dose sucrose (2 mL 50–75%) was equivalent to water in terms of FLACC scores and crying time (Curry 2012 **Level II**, n=113, JS 5). In older children, two RCTs conflicted in their conclusions regarding efficacy of low-dose sucrose 12% in toddlers aged 13–48 mth (n=116); while, in school-aged children (n=115), sweetened chewing gum did not affect pain scores (Harrison 2011 **Level I** [Cochrane], 3 RCTs [immunisation], n=231).

9.7.3.4 Nonpharmacological intervention for immunisation

Physical interventions

The benefit of vapocoolant spray for immunisation is uncertain. Studies suggest equivalency with EMLA®, equivalency to placebo, and inferiority to standard care with sucrose and comforting or distraction (Schechter 2007 **Level III-1 SR**, 4 studies, n unspecified; Shah 2009 **Level III-1 SR**, 4 studies, n=247) (overlap by 2 studies).

Compared with the supine position, parental holding of the infant or sitting upright for older children reduces cry duration in three of four studies (Taddio 2009a **Level I**, 4 RCTs, n=281). Physical intervention post immunisation by nursing staff using the 5S's (swaddling, side position, shushing, swinging and sucking) was superior to parent-led comforting of infants (Harrington 2012 **Level II**, n=230, JS 5). Parent-led tactile stimulation (of the thigh distal to the injection site) did not add benefit to the combination of sucrose, upright position, parental holding with soothing and injection without aspiration in terms of cry and parent or researcher pain scores (Hogan 2014 **Level II**, n=120, JS 5).

Psychological interventions

Parental responses during injection such as excessive reassurance, criticism or apology increase distress, whereas humour and distraction tend to decrease distress (Schechter 2007 **Level IV SR**, 4 studies, n unspecified). Psychological interventions, including breathing exercises, child or nurse-directed distraction and combined cognitive-behavioural interventions reduce pain and parent and observer rated distress during immunisation of children aged 1 mth–11 y (Chambers 2009 **Level I**, 20 RCTs, n=1,380). A subsequent Cochrane review is positive for

distraction overall and overlaps by 5 RCTs in immunisation; it has a further positive RCT of adolescents, where distraction with both headphones and loudspeaker music is superior to standard nurse-led distraction (1 RCT, n=118) (Uman 2013 **Level I** [Cochrane], 6 RCTs [immunisation], n=490).

Combination intervention

Combining sucrose, oral tactile stimulation and parental holding reduced the duration of crying in infants receiving multiple immunisations (Reis 2003 **Level II**, n=116, JS 5). Combinations of two or more analgesic interventions, such as breastfeeding, use of topical local anaesthesia and sweet-tasting solutions, are more effective than individual interventions alone for reducing injection pain in young infants (Shah 2009 **Level III-1 SR**, 6 studies [combinations], n=592). In older children aged 4–12 y, the combination of topical EMLA®, preparation, parental presence and distraction reduced pain scores during immunisation (SMD -0.5/10; 95%CI -0.73 to -0.3) (4 RCTs, n=350). EMLA® use alone or in combination with breastfeeding prolongs the latency to cry slightly (Gupta 2013 **Level II**, n=90, JS 5). EMLA® combined with N_2O 50% was superior to either alone for observed pain in infants and toddlers during and post immunisation (Carbajal 2008 **Level II**, n=55, JS 5).

9.7.4 Procedural pain management in the emergency department

Clinical guidelines from various bodies have been developed for procedural pain management in the ED. The American College of Emergency Physicians has published guidelines specifically for ketamine use in children (Green 2011 **GL**) and, for both adults and children, evidence-based recommendations for the use of ketamine, propofol, short-acting opioids, etomidate and dexmedetomidine in this setting (Godwin 2014 **GL**).

9.7.4.1 Laceration repair

All oral agents as specified in Sections 9.4.1 to 9.4.5 have been used in children having laceration repair, usually to supplement topical or injected local anaesthetic. Fentanyl IN use is not yet specifically reported for laceration repair.

Topical local anaesthesia

Topical local anaesthetic application for wound closure can avoid the distress caused by intradermal injection; importantly cocaine-containing preparations are no longer recommended (Eidelman 2011 **Level I** [Cochrane], 20 RCTs [children], n=3,128). Numerous topical local anaesthetic agents have been assessed. Only a descriptive analysis is possible as trials have high risk of bias, involve only single comparisons and only 13 of 20 RCTs report pain scores. The most widely used topical agent applied to paediatric wounds is currently lignocaine-adrenaline-amethocaine (tetracaine) preparation (abbreviated to ALA in Australia and LAT or LET in the USA). This combination is as effective as tetracaine-adrenaline-cocaine (3 RCTs, n=341), buffered lignocaine-adrenaline infiltration (1 RCT, n≈66 adults and children) and as a gel or solution with no other comparator (1 RCT, n=194) (Eidelman 2011 **Level I** [Cochrane], 5 RCTs, n≈601). Topical ALA solution applied to wounds at triage reduced treatment time by 31 min vs controls (Priestley 2003 **Level II,** n=161, JS 4) and pain associated with subsequent intradermal injection of lignocaine (Singer 2000 **Level II**, n=43, JS 5).

Alternatives to suturing: tissue adhesives and hair apposition

Tissue adhesives are as effective as suturing for simple lacerations (6 RCTs, n=570), produce less pain (WMD -13.4/100; 95%CI -20 to -6.9) with shorter procedure time (WMD -5.6 min; 95%CI 8.2 to -3.1) and may be more acceptable to children (Farion 2002 **Level I** [Cochrane], 11 RCTs [children], n=1,327). No studies reported on ease of use. The risk of dehiscence is increased slightly with tissue adhesive vs standard wound care (NNH 25; 95%CI 14 to 100) but it is offered to parents as a preferred initial intervention. Hair apposition was as effective as suturing for simple scalp lacerations (Hock 2002 **Level II**, n=189, JS 3).

Children who received topical anaesthetic (ALA) prior to tissue adhesive application were more likely to have a pain-free procedure vs placebo by self or observer report (RR 0.54; 95%CI 0.37 to 0.80) (Harman 2013 **Level II**, n=221, JS 5).

Improved efficacy is established, in mainly adult trials, of warming (to 37–43°C) (Hogan 2011 **Level I** [PRISMA], 1 RCT [paediatric], n=44) and buffering (increasing the pH of lignocaine to ≥7.35) by sodium bicarbonate addition (Cepeda 2010 **Level I** [Cochrane], 2 RCTs [mixed age], n=165 and 1 RCT [paediatric], n=7) (see also Section 4.4.2).

Midazolam

Midazolam is a useful adjunct in the procedural sedation pharmacotherapy armamentarium for laceration repair in younger or noncooperative children. IN administration stings and the oral route is generally preferred, although efficacy may be more variable (influenced by first-pass metabolism and duration of fasting). Compared to oral route or aerosolised buccal delivery prior to laceration repair in young children (0.5–7 y), aerosolised delivery IN had faster onset and achieved adequate sedation, at the expense of nasal irritation and being less readily accepted than the oral route (Klein 2011 **Level II**, n=169, JS 5).

Nitrous oxide and ketamine alone or in comparison

Inhaled N_2O 50–70% (with oxygen) is commonly used for laceration repair and minor surgery in children and reduces pain and anxiety, with large case series affirming the utility and safety of the technique for this and other indications (Tobias 2013 **Level I,** 1 RCT [laceration], n=30; Pedersen 2013 **Level IV** [PRISMA], 1 RCT [laceration], n=204 and multiple studies [laceration], n unspecified; Babl 2010 **Level IV**, n=504). Ketamine is also commonly used as dissociative sedation and analgesia for laceration repair. Common doses used as sole agent in the ED are 0.5–1 mg/kg IV and 3–5 mg/kg IM; coadministration of atropine or benzodiazepine is no longer recommended (Green 2011 **GL**). Oral and IN routes are also used (see below).

N_2O 50–70% and ketamine 2 mg/kg IV had similar analgesic efficacy, with deeper sedation and longer median duration by 13.5 min in those ketamine treated (Lee 2012 **Level II**, n=32, JS 3). The addition of oral ketamine 5 mg/kg to oral midazolam 0.5 mg/kg vs midazolam alone for laceration repair, resulted in similar pain scores during local anaesthetic injection (parent and researcher: 4/10), with increased sedation and time to discharge for the combination group (MD 65 min; 95%CI 22 to 107) (Barkan 2014 **Level II**, n=60, JS 5). Ketamine 3–9 mg/kg IN was used for laceration repair in young children (Tsze 2012 **Level IV**).

The safety of ketamine has been documented in a large paediatric ED series (n=8,282) with low rates of emergence reactions (clinically important 1.4% vs "any" 7.6%), vomiting 8.4% and respiratory events 3.9% (Green 2009c **Level IV**). Variables independently associated with increased risk of respiratory effects included age <2 y (OR 2.00; 95%CI 1.47 to 2.72) and ≥13 y (OR 2.72; 95%CI 1.97 to 3.75), high IV dosing (initial dose ≥2.5 mg/kg or total dose ≥5.0 mg/kg) (OR 2.18; 95%CI 1.59 to 2.99) and coadministered anticholinergic (OR 1.82; 95%CI 1.36 to 2.42) or benzodiazepine (OR 1.39; 95%CI 1.08 to 1.78). Oropharyngeal procedures, ASA class ≥3 and use of IV vs IM route were not associated with increased risk.

9.7.4.2 Fracture pain and reduction

For children with suspected fractures presenting to the ED, fast-tracking is occurring to facilitate rapid analgesic administration and direct referral for X-ray from triage. To avoid the distress associated with IV access or IM injection, alternative administration routes for analgesics are being increasingly used in this setting.

Fracture pain

Opioids, tramadol and NSAIDs

Following limb fracture, fentanyl IN 1–2 mcg/kg effectively reduces pain in the ED (Hansen 2012 **Level IV SR** [PRISMA], 3 RCTs [paediatric] and 5 studies [fracture], n=575). It is equivalent to IV (1 RCT, n=65) and IM morphine with more rapid onset (1 RCT, n=45) and is effective in usual concentration 50 mcg/mL compared with high concentration 300 mcg/mL (lower volumes required) (1 RCT, n=189). Fentanyl IN was also effective in reducing pain when administered in the prehospital setting in 90% of paediatric trauma patients who received it as a single agent (n=231), including when given in combination with morphine and/or methoxyflurane (n=143) (Bendall 2011 **Level III-2**).

Introduction of an IN fentanyl protocol for paediatric fracture in a mixed ED led to reduced time to opioid analgesia compared to IV morphine (median 32 min; IQR 17 to 96 vs 59 min; 25 to 121) (Holdgate 2010 **Level III-3**). Results were similar for a paediatric ED series (n=617) over a 2-y assessment: 31.2 (SD 2.6) for IN fentanyl vs 55.6 min (SD 2.4) for IV morphine, and 1 y later 23.7 (SD 2.8) vs 53.1 min (SD 3.1) (Borland 2008 **Level III-3**).

Transmucosal (transbuccal) fentanyl 10–15 mcg/kg was equiefficacious when compared with morphine 0.1 mg/kg IV over 15–75 min (Mahar 2007 **Level II**, n=95, JS 3). Nebulised fentanyl 3–4 mcg/kg was similarly effective when compared with fentanyl 1.5 mcg/kg IV (Miner 2007 **Level II**, n=41, JS 3) and morphine 0.1 mg/kg IV (Furyk 2009 **Level II**, n=77, JS 4).

Diamorphine 0.1 mg/kg IN drops and spray also provide rapid effective analgesia for fracture pain (Kendall 2015 **Level IV,** n=226; Regan 2013 **Level III-3,** n=297) with similar efficacy but more rapid onset compared with morphine 0.2 mg/kg IM (Kendall 2001 **Level II**, n=404, JS 3). A pharmacokinetic study has been done of IV vs IN diamorphine in children with fractures (n=24) (Kidd 2009 **PK**).

Morphine 0.5 mg/kg oral alone and combined with midazolam 0.2 mg/kg SL in displaced long bone fractures reduced pain scores similarly, at the expense of increased sedation for 59% patients with combination treatment vs 23% with morphine alone (Wille-Ledon 2011 **Level II,** n=58, JS 5).

Oral oxycodone was more effective and produced less itching than codeine but early administration at triage was required as having X-rays, rather than examination or casting, was identified as the most painful period (Charney 2008 **Level II**, n=107, JS 5). For children with fracture pain, oral codeine 1 mg/kg added to ibuprofen 10 mg/kg did not further improve analgesia (Le May 2013 **Level II,** n=81, JS 5) and combined with paracetamol 10 mg/kg was similarly effective to ibuprofen (Friday 2009 **Level II**, n=68, JS 3). Children treated with parent-directed prn dosing of ibuprofen 10mg/kg had better functional outcomes and less nausea, vomiting and sedation compared to combination paracetamol 24 mg/kg and codeine 1mg/kg over 72 h (Drendel 2009 **Level II**, n=336, JS 4). With strict dosing of oral ibuprofen 10 mg/kg every 8 h or paracetamol 15 mg/kg every 6 h, no differences in pain scores were seen over 48 h (Shepherd 2009 **Level II**, n=94, JS 3).

SL ketorolac 0.5 mg/kg was compared to SL tramadol 2 mg/kg for moderate to severe fracture pain. Although both agents were effective, the lack of comparison with other analgesics limits the usefulness of this study (Neri 2013 **Level II**, n=131, JS 5).

See Sections 9.4.2 and 4.3.1 on NSAIDs, including effects on bone healing.

Ketamine

Ketamine has been used prehospital and in the ED for suspected fracture. Doses of 0.25–1 mg/kg have been used in children via IV and IN routes and higher doses 5 mg/kg IM (Bredmose 2009a **Level IV**; Svenson 2007 **Level IV**; Reid 2011 **CR**; Yeaman 2013 **Level IV**). S-ketamine IN 0.45 to 1.25 mg/kg has also been used prehospital for fracture pain in six children aged 7–17 y (Johansson 2013 **Level IV**).

Methoxyflurane

Although no longer used as an anaesthetic (Brown 2012 **NR**), methoxyflurane is available as a self-administered Penthrox® inhaler which dispenses 0.2–0.4% methoxyflurane (Medical Developments International 2001). In adolescents who presented with minor trauma and moderate pain to the ED, methoxyflurane was effective vs placebo (Coffey 2014 **Level II**, n=300 [90 adolescents], JS 5). Methoxyflurane use by children with trauma as the sole agent in the prehospital setting was effective (reduced NRS pain score by ≥30%) for 78% (n=2,093), compared with 90% of IN fentanyl treated (n=306) and 88% of IV morphine treated (n=306) (Bendall 2011 **Level III-2)**. An additional 586 patients received it in combination with opioids. In smaller series, methoxyflurane reduced pain scores associated with extremity injuries by 2.5–4.7/10 with high satisfaction but did not provide analgesia for subsequent fracture manipulation (Grindlay 2009 **Level IV SR**, 6 studies, n=293) (see also Section 4.5.2).

Closed fracture reduction

Closed fracture reduction is a major procedure, which may be performed in EDs with a variety of analgesic techniques including N_2O (Pedersen 2013 **Level IV SR** [PRISMA], 4 studies, total n=45,120; Babl 2010 **Level IV**), ketamine IV or IM (Babl 2010 **Level IV**), opioids (morphine IV, fentanyl IN or IV and alfentanil IV), propofol or combinations of these agents (Migita 2006 **Level I**, 5 RCTs, n=526; Schofield 2013 **Level IV**; Godwin 2014 **GL**). The majority of studies assess procedural pain scores and not postprocedural impact. Additional paediatric guidelines for procedural sedation, as opposed to analgesia, have been produced by the American Academy of Pediatrics and of Pediatric Dentistry (AAP 2006 **GL**) and American College of Emergency Physicians (Godwin 2014 **GL**) and the Scottish Intercollegiate Guidelines Network (SIGN 2004 **GL**).

Bier's block (or IV regional anaesthesia/block [IVRA/IVRB]) is also used in Australian, New Zealand and North American EDs (Schofield 2013 **NR**; Constantine 2007 **Level IV**). Local anaesthetic IVRB is highly effective (Migita 2006 **Level I**, 3 RCTs [IVRB], n=560; Murat 2003 **Level III-3 SR**, 5 studies, n=1,178) but complications may arise with faulty equipment, inappropriate local anaesthetic use, or inadequate monitoring and training of staff.

For fracture reduction (with oral oxycodone 0.2 mg per kg pretreatment), N_2O 50% and haematoma block (2.5 mg/kg 1% buffered lignocaine) compared with ketamine 1 mg/kg with midazolam 0.1 mg/kg had similar parental and child pain scores, with earlier readiness for discharge (mean 16 vs 83 min) (Luhmann 2006 **Level II**, n=102, JS 3). Ketamine/midazolam compared with etomidate/fentanyl in a small trial achieved lower observer pain scores, similar amnesia and greater parental satisfaction, despite longer recovery time (Lee-Jayaram 2010 **Level II**, n=23, JS 5)

Following ED intervention for fracture reduction, laceration repair and other painful procedures (where procedural pain scores were not assessed), ketamine mostly as a single agent (or combined with midazolam) compared with fentanyl/midazolam had similar vomiting rates (20 vs 14%), low incidence of emergence reaction (1 vs 0%) and lower incidence of posthospital behavioural disturbance (McQueen 2009 **Level III-3,** n=294 fracture reductions of total 554 sedations).

Dexmedetomidine is not yet reported as used for this indication (McMorrow 2012 **NR**).

Opioid/propofol and ketamine/propofol combinations

Opioid/propofol or ketamine/propofol (ketofol) combinations for deeper procedural sedation are increasingly used in paediatric EDs. In various paediatric procedural sedation settings, adverse effects of propofol use (of 0.5–2mg/kg and higher) have been reported at rates of: cardiovascular (hypotension 15.4% and bradycardia 0.1%); respiratory (desaturation 9.3%, apnoea 1.9%, assisted ventilation 1.4%, unplanned intubation 0.02%, laryngospasm 0.1%); and postprocedure vomiting (0.14%) (Lamond 2010 **Level IV SR,** 60 studies, n=17,066). Of the seven included ED studies, six were for fracture reduction (2 RCTs, n=204; 4 case series, n≈610) with coadministration of opioid (morphine or fentanyl) and supplemental oxygen. Desaturation rates varied from 5–31%, with lower rates of airway intervention (such as jaw manoeuvres and bag-mask assistance) and no intubations. Ketofol has been compared to propofol only (with and without opioid pretreatment) for fracture reduction with focus upon satisfaction with procedural sedation (and no pain score outcomes) and respiratory (9–28% depending how defined) and other adverse effects (Shah 2011a **Level II**, n=140, JS 5; David 2011 **Level II**, n=220, JS 5). Pharmacokinetic modelling has been done for ketofol with dosing recommendations for longer duration procedures (Coulter 2014 **PK**).

9.7.4.3 Psychological interventions

In addition to pharmacological interventions, procedural planning for children in the ED should include age-appropriate psychological interventions, such as distraction techniques (see Section 9.7.5).

9.7.5 Nonpharmacological strategies in children and adolescents

A Cochrane review of nonpharmacological strategies in children and adolescents summarises interventions for various needle procedures (Uman 2013 **Level I** [Cochrane], 39 RCTs, n=3,394). The procedures include: venipuncture (13 RCTs), IV insertion (7 RCTs) and both (1 RCT); immunisation (6 RCTs); lumbar puncture (5 RCT), bone marrow aspirations (2 RCTs) and both (1 RCT); and injections for IM immunisation (1 RCT), local anaesthetic (dental: 1 RCT), allergy testing (1 RCT) and laceration repair (1 RCT). Distraction can be as simple as being read a book or listening to music. Distraction reduces self-reported needle-related pain (SMD -0.61/10; 95%CI -0.91 to -0.32) (19 RCTs, n=1,759) but not distress (3 RCTs, n=286). Hypnosis requires the skills of a trained health professional and time for the child to learn the technique. Hypnosis reduces reported pain (SMD -1.4/10; 95%CI -2.32 to -0.48) and both distress scores (-2.53/10; 95%CI -3.93 to -1.12) (5 RCTs, n=176) and behavioural measures of distress (SMD -1.15; 95%CI 1.76 to -0.53) (6 RCTs, n=193). The combination of directed hypnosis with EMLA® was superior to "attention" and EMLA® vs EMLA® alone with reduced pain, anxiety and distress associated with venipuncture (Liossi 2009 **Level II**, n=45, JS 5). The positive effect was maintained with self-directed hypnosis for a subsequent venipuncture procedure. Benefits were confirmed in children undergoing cancer-related procedures (5 RCTs overlap) where hypnosis is an effective pain-control technique (Tome-Pires 2012 **Level I**, 10 RCTs [cancer procedural pain], n=394).

The evidence is not currently supportive for other nonpharmacological techniques such as combined cognitive-behavioural therapy (4 RCTs, n=305), parent coaching plus child distraction (3 RCTs, n=612), suggestion only (3 RCTs, n=218), preparation and information (2 RCTs, n=154), VR (2 RCTs n=50), memory alteration (1 RCT, n=15), blowing out air (1 RCT, n=50), distraction plus suggestion (1 RCT, n=160) and parental positioning plus child distraction (1 RCT, n=20) (Uman 2013 **Level I** [Cochrane], 39 RCTs, n=3,394). An RCT not included in this review supports the child being positioned vertically and being held by a parent, with reduced distress during IV cannulation (Sparks 2007 **Level II**, n=118, JS 4).

Further reviews are available assessing studies of specific techniques with lower levels of evidence. The first, overlapping with the Cochrane review by one RCT only, assesses distraction use in a range of procedures (venipuncture, cannulation, lumbar puncture), including immersive (4 studies, n=188) and nonimmersive VR (7 studies, n=270), breathing (4 studies, n=249), guided imagery (8 studies, n=242) and distraction (eg simple passive such as music, TV and active self or nurse directed) (14 studies, n=626) (Koller 2012 **Level III-2 SR,** 37 studies, n=1,575). The second review (overlapping by 2 studies) is of ED interventions in various procedures (venipuncture, cannulation, laceration repair, musculoskeletal trauma and lumbar puncture) and is positive for the use of distraction with books, kaleidoscope, music and distraction boxes (containing items for various ages) (Wente 2013 **Level III-2 SR,** 10 studies [distraction], n=1,164). The third, assessing techniques for needle, lumbar puncture or bone marrow aspiration procedures in paediatric oncology patients, overlaps by 10 RCTs with the Cochrane review (Landier 2010 **Level III-2 SR,** 26 studies, n=1,675). It draws similar positive conclusion for distraction (guided imagery, relaxation, play or music) (18 studies), hypnosis (11 studies) and states cognitive-behavioural therapy shows promise (3 studies). The fourth review summarises music therapy studies (in addition to those studies referenced in Section 9.7.2). Music therapy involves either passive listening to recorded or played music or active participation with the patient playing instruments. In children aged 1 mth–20 y of age, music therapy has a positive impact on pain (8 RCTs, n=882), anxiety (6 RCTs, n=324) or both (5 RCTs, n=279) with various procedures (venipuncture/IV cannulation, bone marrow aspiration, dental/oral and other surgery) (Klassen 2008 **Level I,** 19 RCTs [5 active, 14 passive], n=1,513). Music therapy reduces pain (SMD -0.39; 95%CI -0.66 to -0.11) (5 RCTs, n=465) and anxiety (SMD -0.39; 95%CI -0.76 to 0.03) (5 RCTs, n=284).

A further RCT in IV cannulation in the ED showed the addition of passive music therapy to standard care (topical local anaesthetic, nurse explanation and reassurance) achieved lower pain and anxiety scores vs standard care alone (Hartling 2013 **Level II**, n=42, JS 3).

Inviting parental presence for procedures (with and without sedation) is increasingly common practice in paediatric care. During venipuncture, fearful parental expression and being

reassured uninformatively (told "don't worry") increased children's fear, while informative reassurance and distraction use decreased it (McMurtry 2010 **Level IV**). Preprocedural preparation of the parent and child in a developmentally appropriate way is considered best practice and is being incorporated within hospital and national guidelines (Duff 2012 **GL**), as is staff and parent training in the use of nonprocedural talk (RACP 2005 **GL**) and use of child-friendly language for preparation/explanation (Stock 2012 **GL**).

Nurse or play therapist coaches or hospital employed "child life interventionists" are also being employed to educate, distract and plan procedural intervention strategies for children and their parents informally and formally (LeBlanc 2014 **NR**).

Key messages

1. Sweet-tasting solutions (sucrose, glucose and other) reduce pain scores and behavioural response for skin-breaking procedures in neonates (**S**) (**Level I** [Cochrane Review]).
2. Breastfeeding reduces infant heart rate response and crying compared to positioning, holding by mother, placebo, pacifier use, no intervention and/or oral sucrose for skin-breaking procedures in neonates (**S**) (**Level I** [Cochrane Review]).
3. Supplemental breast milk reduces heart rate response and crying when compared to placebo but not when compared to sucrose, glycine, pacifier use, rocking or no intervention for skin-breaking procedures in neonates (**N**) (**Level I** [Cochrane Review]).
4. Sweet-tasting solutions preimmunisation reduce incidence and duration of crying in infants (1–12 months) (**N**) (**Level I** [Cochrane Review]) but not in children older than 12 months (**N**) (**Level II**).
5. Providing physical comfort measures, including kangaroo care (maternal or alternate provider), facilitated tucking (swaddling) or non-nutritive sucking (alone or combined with sweet-tasting solutions) reduces pain experienced by term and preterm neonates having skin-breaking procedures (**N**) (**Level I** [Cochrane Review]).
6. EMLA® is an effective topical anaesthetic for children but amethocaine is superior for reducing needle-insertion pain (**U**) (**Level I** [Cochrane Review]).
7. Topical local anaesthetic application (**S**) (**Level I** [Cochrane Review]), inhalation of nitrous oxide (50%) or the combination of both provides effective and safe analgesia for minor procedures in children (**S**) (**Level I** [PRISMA]).
8. Distraction reduces pain (**Q**) (**Level I** [Cochrane Review]) and hypnosis reduces both pain and distress associated with needle-related procedures in children and adolescents (**S**) (**Level I** [Cochrane Review]).
9. Active and passive music therapy reduces pain and anxiety associated with needle-related procedures in children (**N**) (**Level I**).
10. Combinations of hypnotic and analgesic agents are effective for procedures with moderate pain severity in children (**U**) (**Level II**).
11. Prior application of nonpharmacological physical interventions (cold and vibration) reduced the pain of venipuncture in children (**N**) (**Level II**).
12. Intranasal fentanyl is equivalent to intravenous or intramuscular morphine in reducing pain associated with paediatric fracture presenting to the emergency department (**N**) (**Level II**) and incorporated into a triage protocol achieves earlier onset opioid analgesia compared to intravenous morphine intervention (**N**) (**Level III-2**).
13. In paediatric trauma, prehospital administration of intranasal fentanyl and inhaled subanaesthetic doses of methoxyflurane provides equivalent analgesia to intravenous morphine (**N**) (**Level III-2**).
14. Ketamine is an effective analgesic for children in the prehospital and emergency department settings and is safe and effective for paediatric procedural pain management (**N**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Inadequate monitoring of the child, lack of adequate resuscitation skills and equipment, and the use of multiple medicine combinations has been associated with major adverse outcomes during procedural analgesia and sedation (**U**).

☑ Hypnosis requires teaching by a trained professional but distraction can be readily provided by staff or parents and should be routinely offered in the paediatric setting (**N**).

9.8 Acute pain in children with cancer

Pain is a common symptom in children with cancer (Friedrichsdorf 2014 **NR**) and is associated with significant fear and distress (Ljungman 1999 **Level IV**). Compared with adults, the pattern and sources of acute pain differ significantly in children with cancer. The WHO guideline written in 1999 entitled *Cancer Pain Relief and Palliative Care in Children* was updated in 2012 to *Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses* (WHO 2012 **GL**). This addresses pain in cancer and other medical conditions (such as HIV/AIDS, sickle cell disease, burns, trauma and phantom limb pain) and recommends a two-step analgesic management approach, abolishing the middle step that previously contained codeine. The 2012 guideline states the evidence base where available, and proposes a research agenda for the treatment of pain in this patient group.

9.8.1 Cancer-related pain

9.8.1.1 Tumour-related pain

Pain due to tumour is present at diagnosis in the majority of children (Miser 1987 **Level IV**) and usually resolves with initial chemotherapy treatment. Breakthrough cancer pain in children is usually of sudden onset, severe and of short duration (Friedrichsdorf 2014 **NR**; WHO 2012 **GL**). For incident and breakthrough pain treatment, IR opioids are recommended at 10–15% of total daily dose. Commonly oral or IV morphine is used but all other opioids have been administered including novel routes eg fentanyl and diamorphine IN or transmucosally (translated from adult practice) with no trial support. "End of dose" pain is managed with escalation of background dosing, as in adults.

Neuropathic pain in children is often treatment related (see below); cancer-related neuropathic pain usually occurs with invasion or compression of nerves, plexus or spinal cord (by sarcomas) or following limb-sparing surgery (Collins 1995 **NR**). It requires multimodal and adjuvant therapy (alpha-2-delta ligands, antidepressants and opioids; see respective sections in Section 4) including nonpharmacological approaches (see Section 9.7.5) with physiotherapy and psychology (Friedrichsdorf 2014 **NR**; Anghelescu 2014 **Level IV**). Methadone has been used in the acute setting for new-onset neuropathic pain, to assist weaning and postoperatively (Anghelescu 2011a **Level IV**).

9.8.1.2 Pain in the terminal stages

Pain and opioid requirements may escalate in terminal stages of cancer. Benefit has been reported with the use of PCA opioids to allow rapid dose titration (Schiessl 2008 **Level IV**), with the addition of ketamine (Finkel 2007 **Level IV**; Taylor 2014 **Level IV**) and intervention with nerve block catheters (Anghelescu 2010 **Level IV**) (see Section 9.7). Methadone has been used in a small series of children/young adults with cancer for terminal care and chronic pain unresponsive to escalation of other opioids (Anghelescu 2011a **Level IV**; Davies 2008 **Level IV**).

9.8.2 Procedure-related pain

Children, their parents, physicians and nurses all rate pain due to procedural interventions and treatment as a significant source of pain (Ljungman 1996 **Level IV**; Ljungman 1999 **Level IV**). Multiple diagnostic and therapeutic interventions are required during the course of treatment, and require treatment matched to the procedure type and needs of the child.

9.8.2.1 Lumbar punctures, bone marrow aspirations, blood sampling

See Section 9.7.2 for pharmacological intervention and Section 9.7.5 for nonpharmacological intervention used in paediatric oncology care.

9.8.2.2 Central venous port access

For pain relief during central venous port access in children with cancer, EMLA® was evaluated as superior to placebo (Miser 1994 **Level II**, n=47, JS 5). When added to topical anaesthesia with EMLA® for port access, neither oral morphine 0.25 mg/kg (Heden 2011 **Level II,** n=50, JS 5) nor oral paracetamol 40 mg/kg (maximum 2 g) (Heden 2014 **Level II**, n=51, JS 5) impacted upon pain, fear and distress VAS scores, which were equally low in placebo-treated patients. Outcomes for second and subsequent procedures were improved if adequate analgesia was provided for the first procedure (Weisman 1998 **Level III-2**).

9.8.3 Treatment-related pain

Pain related to adverse effects of chemotherapy and radiotherapy is a source of high distress to children with cancer (Ljungman 2000 **Level IV**; Collins 2000 **Level IV**).

9.8.3.1 Mucositis

Mucositis is a common adverse effect of many chemotherapeutic regimens (Cella 2003 **Level IV**). It can be difficult to assess (Tomlinson 2008 **NR**), and is a frequent indication for IV opioid therapy. Opioid requirements are often high and escalate with the severity of mucositis (Dunbar 1995 **Level IV**; Coda 1997 **Level II**, n=119, JS 5). A systematic review (1 RCT of adolescent patients and 2 adult RCTs) concludes that morphine by PCA or continuous infusion provides similar analgesia (no difference in pain scores), and PCA use results in reduced hourly and overall morphine intake and duration of pain by 1.9 d (95%CI 0.25 to 3.5) with a stated concern of bias due to drop out rates in these studies is a stated concern (Clarkson 2010 **Level I** [Cochrane], 3 RCTs, n=184). Morphine and pethidine PCA (Oudot 2011 **Level II**, n=29, JS 5) and PCA morphine and hydromorphone had similar efficacy (Collins 1996 **Level II**, n=10, JS 4) but PCA sufentanil was less effective than PCA morphine or hydromorphone (Coda 1997 **Level II**, n=199, JS 5). Prolonged administration is often required (6–74 d) (Dunbar 1995 **Level IV**). If excessive or dose-limiting adverse effects occur, rotation to another opioid (morphine to fentanyl or fentanyl to hydromorphone) can produce improvement in the majority of patients, without loss of pain control (Drake 2004 **Level IV**).

Ketamine improved pain scores when added to morphine PCA/NCA as 20–40 mcg/kg/mL (James 2010 **Level IV**) and also decreased morphine consumption when patients were requiring ≈1mg/kg of morphine per day (White 2011 **Level III-3**). In a small case series of children with mucositis, topical morphine (0.025–0.4 mg/kg) was used in a dose-response study and reduced pain scores by ≥36% in six of seven children (Nielsen 2012 **Level IV**). Plasma levels were low, suggesting minimal systemic absorption.

There is limited evidence in children that low-level laser treatment reduces the severity of the mucositis (1 RCT, n=21), that topical compared to ingested vitamin E improves mucositis (1 RCT, n=40) and debridement in addition to standard care reduces severity and days to resolution (1 RCT, n=80) (Clarkson 2010 **Level I** [Cochrane], 32 RCTs, n=1,505).

9.8.3.2 Neuropathic pain

Neuropathic pain can occur acutely secondary to chemotherapy for childhood leukaemia (and is the reason for dose limiting of vincristine therapy). Gabapentin (15–70 mg/kg/d) has been used (Anghelescu 2011b **Level IV**), as have multimodal interventions including nonpharmacological therapy (Anghelescu 2014 **Level IV**).

9.8.3.3 Postoperative pain

Postoperative pain related to surgical procedures for diagnostic biopsies, insertion of long-term IV access devices and tumour resection is also a frequent source of treatment-related pain. Analgesic intervention using all modalities including preoperative gabapentin and

postoperative wound and CPNB catheter local anaesthetic infusions have been described for limb salvage surgery (n=150) (Anghelescu 2010 **Level IV**) and for upper limb forequarter amputation (n=4) (Kaddoum 2013 **Level IV**). In children with cancer requiring morphine infusions, the highest rate of breakthrough pain was found in postoperative cases, of which 92% had solid tumours (Flogegard 2003 **Level IV**). In children with thoracic, abdominal or lower limb cancer, supplemental IV opioid boluses (either nurse-administered or via PCA) were safely combined with epidural bupivacaine and fentanyl infusion to control postoperative pain. Of 117 patients, 1 developed respiratory depression (due to a dosing error) but patients were closely monitored and had pre-existing tolerance to opioids (Anghelescu 2008 **Level IV**).

For further reading, see Section 8.7 (management of acute cancer pain) and Section 8.6.7 (management of acute mucositis pain).

Key messages

1. Patient-controlled analgesia and continuous opioid infusions are equally effective in the treatment of pain in mucositis in children but opioid consumption and duration of pain is less with patient-controlled analgesia (**S**) (**Level I** [Cochrane Review]).
2. There is very limited evidence that low-level laser treatment, topical Vitamin E and debridement reduces the severity of the mucositis in children (**N**) (**Level I** [Cochrane Review]).
3. Patient-controlled morphine and hydromorphone are equally effective for the control of pain associated with oral mucositis in children (**U**) (**Level II**).
4. Topical local anaesthetic application for children having central venous port access is effective and analgesia is not further improved by oral analgesics (morphine or paracetamol) (**N**) (**Level II**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ In paediatric cancer pain management, the same therapeutic approaches as in adults are used, although evidence is limited (**N**).

☑ The World Health Organization has removed codeine from the management approach to paediatric cancer pain reducing the number of tiers from three to two: with tier one including nonopioid analgesics and adjuvants and tier two including strong opioids (**N**).

9.9 Paediatric migraine

Paediatric headache is an infrequent diagnostic presentation to EDs (1%). Of ED presentations, primary headache makes up 40%, of which migraine accounts for three-quarters (Sheridan 2014a **NR**). Migraine headaches are common in children (7.7% over all age ranges; more prevalent in girls 9.7% vs boys 6.0%). Frequency increases from 3% (age 3–7 y) to 8–23% in adolescence (11–16 y) (Jacobs 2012 **GL**; Gelfand 2012 **GL**). The general principles are the same as for adult migraine management (see Section 8.6), and environmental modification and nonpharmacological/psychological intervention should be considered (see Section 9.9.3).

Guidelines for the treatment of migraine in children and adolescents acknowledge the lack of large paediatric efficacy and safety studies, summarise the same trials and make similar recommendations (Gelfand 2012 **GL**; NICE 2012 **GL**; Sheridan 2014a **GL**). Triptan trials in adolescents have resulted in licensing changes for use in this age group (Gelfand 2012 **GL**).

The challenges in assessing efficacy of the various agents include the high placebo response rate (eg 28–58% for pain free at 2 h) and the use of different outcomes: headache "relief" vs pain free at 1, 2, 4, or 24 h vs recurrence within 24–48 h, or relief of other migraine symptoms (Barnes 2011 **Level IV SR**, 22 SRs, RCTs and studies, n unspecified) (see also Section 8.6.5).

9.9.1 Single pharmacological therapies

The one cross-over RCT of paracetamol 15 mg/kg, limited by high withdrawal rates (17%), suggests equivalence to placebo (Barnes 2011 **Level I,** 1 RCT [paracetamol], n=106). Ibuprofen 7.5–10 mg/ kg is more effective than placebo in low-quality RCTs, with more patients with relief (NNT 2.4) and pain free at 2 h (NNT 4.9) (Silver 2008 **Level I,** 2 RCTs [ibuprofen], n=242). This overlaps with a more recent meta-analysis with one further RCT (Barnes 2011 **Level I,** 3 RCTs [ibuprofen], n=306). Di-hydroergotamine was not more effective than placebo in a small cross-over trial (Barnes 2011 **Level I,** 1 RCT [ergotamine], n=12).

For adolescents (>12 y of age), triptan studies have response rates that are equivalent to or ≈10% better when compared to placebo, depending upon the outcome being measured. Sumatriptan IN is effective vs placebo for headache relief at 2 h (NNT 7.4) (RR 1.26; 95%CI 1.13 to 1.41) and for proportion pain free (NNT 6.9) (RR 1.56; 95%CI 1.26 to 1.93) with disturbed taste in up to 33 vs 2–3% in placebo-treated patients (NNTs from Silver 2008 **Level I,** 4 RCTs [sumatriptan], n=1,447; RRs from Barnes 2011 **Level I,** 5 RCTs [sumatriptan], n=963; overlap 4 RCTs). The evidence is conflicting for oral rizatriptan (Sheridan 2014a **Level I**, 2 positive RCTs [rizatriptan], n=1176; Barnes **Level I**, 1 negative RCT [rizatriptan], n=360), positive for oral almotriptan with reduction in headache severity but no difference in nausea, photophobia and phonophobia (Barnes 2011 **Level I,** 1 RCT [almotriptan], n=866), and negative for oral eletriptan (Barnes 2011 **Level I**, 1 RCT [eletriptan], n=348) and zolmitriptan (Barnes 2011 **Level I,** 2 RCTs [zolmitriptan], n=882; Sun 2013 **Level I,** 1 nonoverlapping RCT [zolmitriptan], n=696). Another systematic review supports the aforementioned findings and overlaps by five RCTs with the other reviews but additionally summarises the triptans' pharmacokinetic properties (Sun 2013 **Level I,** 7 RCTs, n=3,732).

A systematic review of "ED migraine treatments" for children identified the "at home/abortive intervention" RCTs (paracetamol, ibuprofen and triptan) quoted above and does not provide additional information (Bailey 2008 **Level I**, 14 RCTs, n unspecified). One single additional RCT was actually performed in the ED setting; after failing at-home treatments, prochlorperazine IV was superior to ketorolac IV with complete resolution within 1 h in 85 vs 55% of patients (SMD 30%; 95%CI 8 to 52%) (Brousseau 2004 **Level II**, n=62, JS 5).

Dopamine antagonists and acute interventions with antileptic agents have not been studied in paediatric migraine (Sheridan 2014a **Level I**, 0 RCTs, n=0).

9.9.2 Combination pharmacological therapies

Three dose combinations of oral sumitriptan/naproxen (10/60, 30/180 and 85/500 mg) were effective with the percentage of patients pain free at 2 h of 29, 27 and 24% respectively vs 10% of placebo-treated (Derosier 2012 **Level II**, n=589, JS 5). Repeated use (>12 mth) in recurrent migraine of the higher combination dose was effective [12,957 exposures in adolescents n=622), with 42% pain free at 2 h after an acute episode (McDonald **Level IV**).

In acute childhood migraine, a standardised IV regimen including 20 mL/kg normal saline hydration (maximum 1 L), ketorolac (0.5 mg/kg, maximum 30 mg), prochlorperazine or metoclopramide (0.15 mg/kg, maximum 10 mg) or diphenhydramine (1 mg/kg, maximum 50 mg) vs a combination of various other regimens reduced pain scores by 6.9 vs 5.3/10 (SMD -1.6/10; 95%CI -2.2 to -0.8), length of ED stay 4.4 vs 5.3 h (SMD 0.9 h; 95%CI 0.2 to 1.6) and hospital admission rate (3 vs 32%; p <0.001) without changes in ED return rate (2 vs 7%; p=0.148) (Leung 2013 **Level III-3**).

9.9.3 Nonpharmacological therapies

Psychological interventions are effective as a preventive strategy and should be considered as acute pain management interventions (Trautmann 2006 **Level I,** 23 RCTs [10 migraine/12 migraine and tension type/1 tension type only], n=999). Individual and group relaxation training, including progressive muscle relaxation (16 RCTs with 4 including stress/pain management strategies), biofeedback (7 RCTs) and cognitive-behavioural therapy (10 RCTs) reduce the intensity of headache by ≥50% in 70% of adolescents vs 30% of waitlist controls. Treatment success is maintained for at least 1 y, although comparative efficacy with pharmacological treatments has not been investigated.

Key messages

1. In children and adolescents, effective migraine treatments include ibuprofen and intranasal sumatriptan, however there is a significant placebo response rate in this setting (**N**) (**Level I**).
2. Nonpharmacological preventive therapies including relaxation training, biofeedback and cognitive-behavioural therapy reduce the intensity of headache in adolescents for 1 year (**N**) (**Level I**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Guidelines for the treatment of migraine in children and adolescents recommend environment modification, paracetamol, ibuprofen, naproxen (or other nonselective NSAIDs), dopamine antagonists (if nausea prominent), fluid therapy and intranasal (and oral) triptans. Nonpharmacological interventions should also be considered based on their efficacy as preventive strategies (**N**).

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10. OTHER SPECIFIC PATIENT GROUPS

10.1 The pregnant patient

10.1.1 Management of acute pain during pregnancy

Pregnant women with pain that is severe enough to warrant pharmacological treatment (self-administered or prescribed by attendants) represent a challenging group as medicines given to them almost always cross the placenta. While most medicines are safe, there are particular times of concern, notably the period of organogenesis (wk 4–10) and just before birth. Where possible, nonpharmacological treatment options should be considered before analgesic medications are used. Ongoing analgesic use requires close liaison between the health professional managing the pregnancy and the health professional managing the pain.

10.1.1.1 Medicines used in pregnancy

Medicine use during pregnancy is common and the data on which to make clear statements of fetal risk is limited (Daw 2011 **SR**; Lupattelli 2014 **Level IV**). Medicines that may be prescribed during pregnancy have been categorised according to fetal risk by the TGA (TGA 2015a). The categories used are listed in Table 10.1. It is important to note that the system is not hierarchical and that medicines in Category B are not necessarily safer than those in Category C. The classification of some of the medicines that might be used in pain management is summarised in Table 10.2. A list of these medicines, including regular updates, is maintained by the TGA (TGA 2015b).

Paracetamol

Paracetamol is a Category A medicine and is regarded as the analgesic of choice during pregnancy (2012 **NR**) as no increased prevalence of congenital anomalies has been reported with its use (Rebordosa 2008 **Level III-3**; Scialli 2010 **NR**). There was also no association of paracetamol with an increased risk of spontaneous abortion (OR 1.2; 95%CI 0.8 to 1.8) (Li 2003 **Level III-2**). However, it has been suggested that its potential influence on prostaglandin synthesis may have adverse effects in women at high risk of pre-eclampsia (Zelop 2008 **Level IV**). A large Danish cohort study (n=98,140) suggested an increased risk of preterm birth following paracetamol exposure in early pregnancy in mothers with pre-eclampsia (OR = 1.55; 95%CI 1.16 to 2.07) but not in women without pre-eclampsia (OR 1.08; 95%CI 0.97 to 1.20) (Rebordosa 2009 **Level III-3**).

Exposure to paracetamol during the first two trimesters was associated with an increased rate of cryptorchidism (OR 1.33; 95%CI 1.00 to 1.77) (Jensen 2010 **Level III-3**). Specifically, exposure for more than 4 wk within the postulated time-window of programming testicular descent (gestational wk 8–14) was associated with an OR of 1.38 (95%CI 1.05 to 1.83) for cryptorchidism.

A review of epidemiological studies shows an association between paracetamol use during pregnancy and the incidence of later development of childhood asthma (Henderson 2013 **NR**). However, concern exists that the observed increased risk of asthma may be due to unmeasured confounders (eg duration of breastfeeding, socioeconomic status, later childhood use of paracetamol) or by the influence of factors such as self-reporting and recall bias. This uncertainty can only be resolved by a prospective RCT. A large cohort study (n=197,060; exposed to paracetamol n=976) found an adjusted incidence ratio of 1.35 (95%CI 1.17 to 1.57) (Andersen 2012 **Level III-2**). Another study (n=1,505; exposed to paracetamol n=1,035) found no association between maternal paracetamol use and risk of childhood asthma (adjusted OR 0.76; 95%CI 0.53 to 1.0); it found a reduction of risk of asthma with use in the first or third trimester (adjusted OR 0.59; 95%CI 0.36 to 0.98) (Kang 2009 **Level III-2**). The use of paracetamol in late (20–32 wk) but not early pregnancy was associated with an increase in childhood wheezing (OR 2.10; 95%CI 1.30 to 3.41) (n=9,400) (Shaheen 2002 **Level III-2**). Two systematic reviews support an association between paracetamol use in pregnancy and subsequent childhood wheezing (OR 1.5; 95%CI 1.1 to 2.1) (5 studies) and asthma (OR 1.28; 95%CI 1.13 to 1.39) (4 studies) (Etminan 2009 **Level III-3 SR**, 19 studies, n unspecified) (OR 1.21; 95% CI 1.02 to 1.44)

(Eyers 2011 **Level III-3 SR**, 6 studies, n=28,038), with no overlap of included studies and different methodology used in each.

Another observational study (n=64,322) found an association between paracetamol use during pregnancy and the incidence of childhood hyperkinetic disorders (including ADHD) (OR 1.37; 95%CI 1.19 to 1.59) (Liew 2014 **Level III-3**).

Non-steroidal anti-inflammatory drugs

Nonselective NSAIDs are Category C medicines. Intrauterine exposure to NSAIDs was not associated with increased risk for major congenital malformations (n=110,783; exposed to NSAIDs n=5,267) (Daniel 2012 **Level III-2**), confirmed in another smaller study (Van Marter 2013 **Level III-3**) and four older cohort studies (Bloor 2013 **NR**).

Use of nsNSAIDs during pregnancy was associated with increased risk of miscarriage (adjusted OR 1.8; 95%CI 1.0 to 3.2) (n=1,055; exposed to nsNSAIDs n=53) (Li 2003 **Level III-2**), and (OR 2.43; 95%CI 2.12 to 2.79) (n=4,725; exposed to nsNSAIDs n=352) (Nakhai-Pour 2011 **Level III-2**); in particular if exposed in the last 12 wk before miscarriage (n=1,599; exposed to NSAIDs n=45) (Nielsen 2004 **Level III-2**). These findings were not confirmed in subsequent studies with more women exposed to NSAIDs (OR 1.01, 95%CI 0.82 to 1.24) (n=2,780; exposed to NSAIDs n=1,185) (Edwards 2012 **Level III-2**) and nsNSAIDs (adjusted OR 1.10; 95%CI 0.99 to 1.22) and coxibs (adjusted OR 1.43; 95%CI 0.79 to 2.59), except for indomethacin (adjusted OR 2.8; 95%CI 1.70 to 4.69) (n=65,457; exposed to NSAIDs n=4,495) (Daniel 2014 **Level III-2**). There is a potential modification by race reported (Velez Edwards 2014 **Level III-2**).

While relatively safe in early and mid pregnancy, NSAIDs can precipitate fetal cardiac and renal complications in late pregnancy, as well as interfere with fetal brain development and the production of amniotic fluid; they should be discontinued in gestational wk 32 (Bloor 2013 **NR**). Fetal exposure to nsNSAIDs has been associated with persistent pulmonary hypertension in the newborn in one study (Alano 2001 **Level III-2**) but not another (Van Marter 2013 **Level III-3**). There is also an increased risk of premature closure of the ductus arteriosus (OR 15.04; 95%CI 3.29 to 68.68) (Koren 2006 **Level I** [Cochrane], 8 RCTs, n=438). In the third trimester, associations between NSAID use and renal injury, oligohydramnios, necrotising enterocolitis and intracranial hemorrhage have also been reported (Bloor 2013 **NR**); the incidence may be increasing with exposure occurring closer to delivery.

One observational study showed an increased association between maternal aspirin use during pregnancy and the development of psychotic symptoms during adolescence (Gunawardana 2011 **Level III-3**).

Opioids

Most opioids are Category C medicines. Much of the information about the effects of opioids on newborns comes from pregnant patients who abuse opioids or who are on maintenance programs for drug dependence. Maternal opioid use was thought to have significant developmental effects in the fetus, although social and environmental factors (eg other drugs, smoking) may also have an impact (Farid 2008 **NR**; Winklbaur 2008 **NR**). Behavioural effects on the newborn are likely (Fodor 2014 **NR**). A pilot study (n=16) suggested that on MRI scans brain volumes of opioid-exposed babies may be smaller than controls, in particular in specific regions such as basal ganglia (Yuan 2014 **Level IV**). However, a systematic review found no significant impairments for cognitive, psychomotor or observed behavioural outcomes after chronic intrauterine opioid exposure in infants (4 studies, n=423) and preschool children (3 studies, n=455) compared to non-exposed controls (Baldacchino 2014 **Level III-2 SR** [PRISMA], 5 studies, n unspecified). It is of note that there was a trend to poor outcomes in all domains in both groups with small effect sizes and there were significant limitations of this systematic review (small number of studies analysed, heterogeneous populations, small numbers within the individual studies).

NAS requiring treatment occurs in 60–90% of infants exposed to opioids *in utero* (Farid 2008 **NR**; Kocherlakota 2014 **NR**); there is no clear relationship between maternal dose and the likelihood or duration of NAS (Bakstad 2009 **Level III-2**). Issues in this area are the lack of appropriate tools for its assessment and the lack of early recognition of NAS symptoms

resulting in possible underreporting and, as a consequence, inappropriate and too early neonatal discharge from hospital (Wolff 2014 **NR**). Guidelines for the management of NAS have been published (Wiles 2014 **GL**).

A small study suggested that neonatal outcome was better in mothers receiving opioids for chronic pain rather than addiction, although differences in dose and other environmental factors may contribute (Sharpe 2004 **Level III-2**). Overall, the short-term use of opioids to treat pain in pregnancy appears safe (Wunsch 2003 **NR**) but minimising the use of opioid therapy for chronic pain during pregnancy has been recommended (Chou 2009 **GL**). The use of tramadol in pregnancy has been reviewed specifically (Bloor 2012 **NR**).

For management of acute pain in pregnant patients with an addiction see Section 10.7.1.

Alpha-2-delta ligands

Data on gabapentin use in pregnancy suggest its safety so far, although the number of documented exposures is small (Guttuso 2014 **Level IV SR**, 6 studies, n>555). The rate of congenital malformations was not different from the general population (n=294). There were also roughly equivalent rates of premature birth, birth weight after correction for gestational age at birth, and maternal hypertension/eclampsia with gabapentin use compared to the general population (n=261). Gabapentin and pregabalin were confirmed to have comparable malformation rates to an unexposed control population (Veiby 2014 **Level III-2**). However, in another cohort study (n=223), while there was no increased rate of malformations, there was a higher rate of preterm births (p=0.019) and birth weight <2,500 g (p=0.033) in the gabapentin group (Fujii 2013 **Level III-2**).

10.1.2 Pain syndromes in pregnancy

10.1.2.1 Musculoskeletal pain syndromes

Low-back pain and/or pelvic-girdle pain are common during pregnancy (Gutke 2008 **Level III-2**; Bhardwaj 2014 **NR**) and although low-back pain may persist, pelvic-girdle pain tends to resolve following the birth (Elden 2008 **Level II**, n=386, JS 3; Vleeming 2008 **GL**; Robinson 2014 **Level IV**). Nevertheless, low-back and/or pelvic-girdle pain that had not resolved at 3 mth was persistent in 80.6% of these patients at 14 mth (Bergstrom 2014 **Level IV**). Pelvic-girdle pain occurred more often after Caesarean delivery than after vaginal birth (33 vs 8.3%; n=284) (Mukkannavar 2013 **Level IV**). Self-administered tests and questionnaires have been used for classification of women with suspected pelvic-girdle pain (Fagevik Olsen 2014 **Level IV**). A clinical pathway for treatment of pelvic-girdle pain has been published (Verstraete 2013 **GL**).

An exercise program, compared to standard care in pregnancy, reduced low-back pain (SMD -0.80; 95%CI -1.07 to -0.53) (6 RCTs, n=543) and associated disability (SMD -0.56; 95%CI -0.89 to -0.23) (2 RCTs, n=146) in low-quality trials (Pennick 2013 **Level I** [Cochrane], 26 RCTs, n=4,093). Water-based exercise significantly reduces low back pain related sick leave (RR 0.40; 95%CI 0.17 to 0.92) (1 RCT, n=241). Similarly, an 8–20-wk exercise program reduces the risk of lumbopelvic pain (RR 0.85; 95%CI 0.73 to 1.00) (4 RCTs, n=1,344) and lumbopelvic pain related sick leave (RR 0.76; 95%CI 0.62 to 0.94) (2 RCTs, n=1,062). Acupuncture reduces evening pelvic-girdle pain better than exercise and both better than usual care. Benefits of other approaches were only found in single trials of low quality and are not reported here.

Despite this evidence, only 14.6% of Norwegian pregnant women (n=3,482) were found to follow recommended exercise practice (3 times/wk >20 min); these women were less likely to report pelvic-girdle pain (adjusted OR 0.76; 95%CI 0.61 to 0.96), while those exercising 1–2 times/wk were less likely to report low-back pain (adjusted OR 0.80; 95%CI 0.66 to 0.97) (Gjestland 2013 **Level IV**).

Pregnancy-specific back support garments reduced movement pain and analgesic use (Kalus 2008 **Level III-2**) and were superior (nonrigid lumbopelvic belt), at least in the short term, to pelvic stabilising exercises, as long as accompanied by information (Kordi 2013 **Level II**, n=105, JS 3). Yoga was superior to posture-orientated information (Martins 2014 **Level II**, n=60, JS 3). Chiropractic care is associated with improved outcomes in pregnancy-related low-back pain (Stuber 2008 **Level IV SR**, 6 studies, n unspecified).

Oral magnesium therapy did not reduce the frequency or severity of painful leg cramps during pregnancy (Nygaard 2008 **Level II**, n=45, JS 2).

10.1.2.2 Meralgia paraesthetica

This variable condition comprising some or all of the sensations of pain, tingling and numbness in the lateral thigh affects pregnant women more than a nonpregnant population (OR 12.0; 95%CI 1.2 to 118.0) (van Slobbe 2004 **Level III-2**). Multiple therapies have been reported but have not been fully evaluated or compared, including ice packs, local infiltration with steroid and local anaesthetic, topical lignocaine or capsaicin, TENS, pharmacological therapy (TCAs, antiepileptics) and surgical intervention (Van Diver 1995 **NR**; Harney 2007 **NR**). Other compressive neuropathies, such as carpal tunnel syndrome and Bell's palsy also occur more commonly during pregnancy (Sax 2006 **NR**).

10.1.2.3 Symphysial diastasis

This occasionally disabling disorder (sometimes called osteitis pubis), involving separation of the symphysis pubis during pregnancy or immediately after giving birth, has a quoted incidence of 1:600 (Taylor 1986 **Level IV**) and can produce persistent pain but there are limited data to inform management (Aslan 2007 **NR**).

Key messages

Use of analgesics in pregnancy

1. Short-term use of NSAIDs in late pregnancy is associated with a significant increase in the risk of premature closure of the ductus arteriosus (**N**) (**Level I** [Cochrane Review]).
2. No significant impairments for cognitive, psychomotor or observed behavioural outcomes are observed in children after chronic intrauterine opioid exposure (**N**) (**Level III-2 SR**).
3. Use of NSAIDs during pregnancy may be associated with an increased risk of miscarriage, however study results are contradictory (**W**) (**Level III-2**).
4. Epidemiological data show an association between paracetamol use during pregnancy and subsequent development of childhood wheezing and asthma but causation has not been proven (**N**) (**Level III-3 SR**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ For pain management in pregnancy nonpharmacological treatment options should be considered where possible before analgesic medications are used (**U**).

☑ Use of medications for pain in pregnancy should be guided by published recommendations; ongoing analgesic use requires close liaison between the health professional managing the pregnancy and the health professional managing the pain (**U**).

☑ Nonselective NSAIDs and Coxibs should be used with caution in the last trimester of pregnancy and should be avoided after the 32nd week (**U**).

Painful conditions in pregnancy

1. Exercises or acupuncture reduce low-back and pelvic-girdle pain during pregnancy (**N**) (**Level I** [Cochrane Review]).
2. Chiropractic care reduces low-back pain during pregnancy (**N**) (**Level IV SR**).

Table 10.1 TGA medicine categorisation according to fetal risk

A	Medicines which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
B2	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
B3	Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Medicines which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Notes: *For medicines in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does NOT imply greater safety than the C category. Medicines in category D are not absolutely contraindicated in pregnancy (eg anticonvulsants). Moreover, in some cases the 'D' category has been assigned on the basis of "suspicion".*

Due to legal considerations in Australia, sponsoring companies have, in some cases, applied a more restrictive category than can be justified on the basis of the available data.

In some cases there may be discrepancies between the published product information and the information in this table due to the process of ongoing document revision.

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Table 10.2 Categorisation of medicines used in pain management

Medicine	Cat	Comments
Opioids		
alfentanil, buprenorphine, dextromoramide, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, phenoperidine, remifentanil, tramadol	C	Opioid analgesics may cause respiratory depression in the newborn. Withdrawal symptoms in newborns have been reported with prolonged use of this class of medicines including tramadol
codeine, dihydrocodeine	A	Prolonged high-dose use of codeine prior to birth may produce codeine withdrawal symptoms in the newborn
Paracetamol	A	

Medicine	Cat	Comments
Aspirin	C	Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the fetal ductus arteriosus, delay labour and birth. Aspirin increases the bleeding time both in the newborn and in the mother because of its antiplatelet effects. Products containing aspirin should be avoided in the last trimester. Low-dose aspirin (100 mg/d) does not affect bleeding time.
Other nsNSAIDs		
diclofenac, diflunisal, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, nabumetone, naproxen, phenylbutazone, piroxicam, sodium salicylate, sulindac, tenoxicam, tiaprofenic acid	C	These agents inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation and delayed labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.
Coxibs		
celecoxib	B3	
parecoxib	C	
Local anaesthetics		
bupivacaine, cinchocaine, lignocaine (lidocaine),	A	
mepivacaine, prilocaine	B1	
etidocaine, ropivacaine	B2	
procaine hydrochloride	B3	
levobupivacaine		
Antidepressants		
SSRIs:	C	SSRIs have had limited use in pregnancy without a reported increase in birth defects. The use of SSRIs in the third trimester may result in a withdrawal state in the newborn.
citalopram, fluoxetine, fluvoxamine, sertraline		
paroxetine	D	Category changed Sept 2005
Tricyclic antidepressants:		
amitriptyline, clomipramine, desipramine, dothiepin (dosulepin), doxepin, imipramine, nortriptyline, protriptyline, trimipramin	C	Withdrawal symptoms in newborn infants have been reported with prolonged maternal use of this class of medicines.
Other antidepressants:		
mirtazapine, moclobemide, nefazodone, duloxetine	B3	
venlafaxine, desvenlafaxine	B2	

Medicine	Cat	Comments
Anticonvulsants		
carbamazepine	D	Spina bifida occurs in about 1% of pregnancies in which carbamazepine is used as monotherapy. Carbamazepine taken during pregnancy also has been associated with minor craniofacial defects, fingernail hypoplasia and developmental disability. Carbamazepine also can cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn, which may be preventable by the prophylactic administration of vitamin K to the mother prior to the birth.
phenytoin sodium	D	This medicine taken during pregnancy has been associated with craniofacial defects, fingernail hypoplasia, developmental disability, growth retardation and, less frequently, oral clefts and cardiac anomalies. This clinical pattern is sometimes called the "fetal hydantoin syndrome". Phenytoin can also cause coagulation defects with consequent risk of haemorrhage in the fetus and the newborn, which may be preventable by the prophylactic administration of vitamin K to the mother prior to the birth.
sodium valproate	D	If taken in the first trimester of pregnancy, sodium valproate (valproic acid) is associated with a 1–2% risk of neural tube defects (especially spina bifida) in the exposed fetus. Women taking sodium valproate (valproic acid) who become pregnant should be encouraged to consider detailed midtrimester morphology US for prenatal diagnosis of such abnormalities.
lamotrigine	D	Category changed June 2006
clonazepam	C	Clonazepam is a benzodiazepine. These medicines may cause hypotonia, respiratory depression and hypothermia in the newborn if used in high doses during labour. Withdrawal symptoms in newborns have been reported with this class of medicines.
gabapentin,	B1	Used for neuropathic pain
tiagabine, topiramate, pregabalin	B3	
Lamotrigine	D	Anticonvulsants for partial complex seizures, possibly mood stabilising and antineuropathic
Levetiracetam	B3	
Antiemetics, antinauseants		
Phenothiazines:		
prochlorperazine, promethazine, thiethylperazine	C	When given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the infant.
Others:		
dimenhydrinate, diphenhydramine, metoclopramide	A	
dolasetron, granisetron, ondansetron	B1	
domperidone, hyoscine, hyoscine hydrobromide	B2	
tropisetron	B3	

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10.1.3 Management of acute pain during labour and birth

Pain during labour and birth represents a complex interaction of multiple physiological and psychological factors involved in parturition. Women's desires for and expectations of pain relief during labour and delivery vary widely. High-quality pain relief does not necessarily equate with a high level of satisfaction; while epidural analgesia seems to provide the best pain relief overall, there is no difference in maternal satisfaction compared to other options (Anim-Somuah 2011 **Level I** [Cochrane], 38 RCTs, n=9,658). Severe pain during labour is one of several factors associated with post-traumatic stress symptoms following birth (Slade 2006 **Level IV**). Personality traits, anxiety and analgesic expectations partially predict labour pain, epidural analgesic consumption and satisfaction (Carvalho 2014 **Level IV**).

An overview of systematic reviews of methods for pain control in labour has the following overall conclusions (Jones 2012c **Level I** [Cochrane], 15 Cochrane reviews [255 RCTs] and 3 non-Cochrane reviews [55 RCTs], n unspecified).

- There is good evidence for the efficacy of epidural, combined spinal-epidural and inhalational analgesia but these techniques may be associated with increased adverse effects.
- There is some evidence that immersion in water, relaxation, acupuncture, massage, local anaesthetic nerve blocks and nonopioid medicines may improve analgesia but evidence is often based on single studies, compared with placebo or standard of care. These forms of analgesia were associated with a low incidence of reported adverse effects; relaxation was associated with fewer assisted vaginal births and acupuncture was associated with fewer assisted vaginal births and Caesarean deliveries.
- There is insufficient evidence based on limited studies that hypnosis, biofeedback, sterile water injection, aromatherapy, TENS and parenteral opioids are more effective than placebo or other interventions for pain management in labour.

10.1.3.1 Systemic analgesia in labour pain

Nonopioids

A variety of nonopioids (NSAIDs, paracetamol, antispasmodics, sedatives and antihistamines) have been investigated with regard to their effect in labour pain (Othman 2012 **Level I** [Cochrane], 19 RCTs, n=2,863). Most of these studies are very old (>30 y) and show very limited efficacy compared to placebo and inferior efficacy compared to opioids. Sedatives may have a limited benefit compared to placebo with regard to analgesia and satisfaction. Overall, there is insufficient evidence for the use of nonopioids to manage pain during labour.

Opioids

Systemic opioids continue to be used in labour although practice varies and use in Australia is declining (to 21.8% at 2011) (Li 2011 **Level IV**).

The following conclusions are for healthy women with an uncomplicated pregnancy giving birth at or near term when opioids were compared to placebo or another opioid (Ullman 2010 **Level I** [Cochrane], 54 RCTs, n>7,000):

- parenteral opioids provide moderate pain relief in labour but two thirds of women report severe or moderate pain and poor pain relief following opioid use;
- opioids cause sedation, nausea and vomiting;
- opioids cause short-term neonatal respiratory and neurobehavioural depression but there is no clear evidence of long-term adverse effects;
- there is insufficient evidence to support the choice of one opioid over another; and
- when systemic opioid analgesia is compared with TENS, there is no difference in pain relief achieved.

In comparison with epidural analgesia, systemic opioids provide less effective analgesia and increase the need for additional pain relief methods, although with no measurable difference

in maternal satisfaction (Anim-Somuah 2011 **Level I** [Cochrane], 33 RCTs [vs opioids], n unspecified). Administration of the opioid was by IV PCA (12 RCTs), intermittent IV bolus (10 RCTs) and IM (5 RCTs). Most common opioids used were pethidine (17 RCTs), fentanyl (5 RCTs) and remifentanil (4 RCTs).

Remifentanil intravenous PCA

In comparison to other opioids, remifentanil offers advantages due to its rapid metabolism. Therefore, remifentanil is being increasingly used for labour analgesia as an alternative to both epidural analgesia and other systemic opioids (Devabhakthuni 2013 **NR**). In the UK, 49% of obstetric wards use IV PCA with remifentanil as the most common agent followed by morphine and fentanyl. In Belgium, 36% of obstetric wards use IV PCA, with remifentanil being the most commonly used opioid (77%).

However, remifentanil IV PCA provides inferior analgesia (Liu 2014, **Level I**, 5 RCTs, n=884) and is not equivalent to epidural analgesia with respect to maternal satisfaction (Freeman 2015 **Level II**, n=1,414, JS 3; Stocki 2014 **Level II**, n=39, JS 3). Pain scores were higher at 1 h (MD 1.9/10; 95%CI 0.5 to 3.3) and 2 h (MD 3.0/10; 95%CI 0.7 to 5.2) after initiation of analgesia (Liu 2014, **Level I**, 5 RCTs, n=884). With regard to adverse effects, the incidence of nausea, vomiting, pruritus and pathological umbilical artery pH values is not different but with wide 95% confidence intervals. These findings are consistent with a preceding meta-analysis comparing remifentanil IV PCA to several other modalities for labour analgesia (Schnabel 2012 **Level I** [PRISMA], 12 RCTs, n=541). Remifentanil IV PCA provides inferior analgesia to epidural techniques (3 RCTs, n=102) but is superior to IM or IV pethidine; reducing pain scores at 1 h (MD -2.17/10, 95%CI 2.7 to 1.64), with higher patient satisfaction and comparable adverse effects (8 RCTs, n=417). Comparisons to other techniques in this meta-analysis were limited to single RCTs and showed better analgesia than N_2O (1 RCT, n=15 [crossover]) and better efficacy than IV PCA fentanyl at 1 h (MD -1.4/10; 95%CI -2.33 to -0.47) (1 RCT, n=106).

Remifentanil IV PCA analgesia during labour has no effect on Apgar scores at 1 and 5 min or neonatal admission rate (Liu 2014 **Level I**, 5 RCTs, n=884; Freeman 2015 **Level II,** n=1,414, JS 3) or on oxygen saturation, heart rate and blood pressure in newborns (n=44) in the first 24 h after birth (Konefal 2013 **Level III-2**).

However, remifentanil is a potent opioid and carries the risk of severe respiratory depression (Muchatuta 2013 **NR**). Hypoxaemia is more likely than with epidural analgesia and approximately one-quarter of women experience apnoeic events (Van de Velde 2008 **NR**; Stocki 2014 **Level II**, n=39, JS 3). Furthermore, a number of respiratory (Bonner 2012 **CR**; Pruefer 2012 **CR**) and even cardiorespiratory arrests (Marr 2013 **CR**) have been reported with its use. Therefore, use of remifentanil IV PCA is only recommended if there is one-on-one continuous presence of a midwife, with both continuous oxygen saturation and cardiotocograph (CTG) monitoring (as an indirect method of detecting global hypoxaemia) (Goudra 2013 **NR**; Muchatuta 2013 **NR**). In view of these risks and the monitoring required, remifentanil IV PCA should not be regarded as an alternative to epidural analgesia based purely on economic considerations or convenience (Kranke 2013 **NR**).

10.1.3.2 Inhalational analgesia

A meta-analysis of inhaled analgesia for pain management in labour compared various volatile agents (flurane derivatives) and N_2O to each other, placebo or no analgesia (Klomp 2012 **Level I** [Cochrane], 26 RCTs, n=2,959). Flurane derivatives (multiple volatiles studied, most recently sevoflurane) provide better pain relief than N_2O in first stage of labour; they result in lower pain intensity (MD 14.4/100; 95%CI 4.4 to 24.4) (3 RCTs, n=70) and higher pain relief scores (MD -16.3/100; 95%CI -26.9 to -5.8) (2 RCTs, n=70) but cause more drowsiness. N_2O causes more nausea compared with flurane derivatives (RR 6.60; 95%CI 1.85 to 23.52) (2 RCTs, n=98). However, trial design was often poor including lack of blinding for volatile agents.

Subgroup analysis of N_2O shows minimal difference in analgesic effect compared to placebo (RR 0.06; 95%CI 0.01 to 0.34) (MD -3.5/100; 95%CI -3.75 to -3.25) (Klomp 2012 **Level I** [Cochrane], 3 RCTs [N_2O], n=819). A subsequent systematic review confirms some analgesic efficacy in labour (Likis 2014, **Level IV SR**, 58 studies, n=20,266) but only two studies were of

good quality. N_2O provides less pain relief than epidural analgesia but more than pethidine, bathing, showering or acupuncture. Maternal satisfaction with analgesia during their birth experience is heterogeneous and difficult to assess. Most women using N_2O report a positive experience but far fewer than those having epidural analgesia (Likis 2014, **Level IV SR**, 58 studies, n=20,266). The maternal adverse effects of N_2O are nausea (RR 43.1; 95%CI 2.6 to 707) (1 RCT, n=509), vomiting (RR 9.1; 95%CI 1.2 to 69) (2 RCTs, n=619), dizziness (RR 114; 95%CI 7.1 to 1834) (1 RCT, n=509) and drowsiness (RR 77.6; 95%CI 4.8 to 1255) (1 RCT, n=509) (Klomp 2012 **Level I** [Cochrane], 3 RCTs [N_2O], n=819); the wide confidence interval in the latter two outcomes suggests significant uncertainty in the estimate. Apgar scores are not different for N_2O when compared with no analgesia.

10.1.3.3 Neuraxial and regional analgesia in labour pain

Epidural analgesia

Epidural analgesia provides better pain relief than all other forms of labour analgesia studied (MD -3.36/10; 95%CI -5.41 to -1.31) (3 RCTs, n=1,166); it also reduces the need for additional pain relief (RR 0.05; 95%CI 0.02 to 0.17) (15 RCTs, n=6,019) but does not increase maternal satisfaction with pain relief (RR 1.31; 95%CI 0.84 to 2.05) (7 RCTs, n=2,929) (Anim-Somuah 2011 **Level I** [Cochrane], 38 RCTs, n=9,658), except compared with remifentanil IV PCA (Freeman 2015 **Level II**, n=1,414, JS 3; Stocki 2014 **Level II**, n=39, JS 3).

Epidural analgesia reduces the risk of fetal acidosis (RR 0.80; 95%CI 0.68 to 0.94) (7 RCTs, n=3,643) and the need for naloxone administration (RR 0.15; 95%CI 0.10 to 0.23) (10 RCTs, n=2,645) (Anim-Somuah 2011 **Level I** [Cochrane], 38 RCTs, n=9,658).

Use of epidural analgesia does not increase the rate of Caesarean delivery overall (RR 1.10, 95%CI 0.97 to 1.25) (27 RCTs, n=8,417) but increases the rate of Caesarean delivery for fetal distress (RR 1.43; 95%CI 1.03 to 1.97) (11 RCTs, n=4,816). It also increases the duration of second stage of labour (MD 13.66 min; 95%CI 6.67 to 21) (13 RCTs, n=4,233) and the rate of assisted vaginal birth (RR 1.42; 95%CI 1.28 to 1.57) (23 RCTs, n=7,935) (Anim-Somuah 2011 **Level I** [Cochrane], 38 RCTs, n=9,658).

The most common complications caused by epidural analgesia are maternal hypotension (RR 18.23; 95%CI 5.09 to 65) (8 RCTs, n=2,789), motor block (RR 31.67; 95%CI 4.33 to 232) (3 RCTs, n=322), urinary retention (RR 17.05; 95%CI 4.82 to 60) (3 RCTs, n=283) and maternal fever (RR 3.34; 95%CI 2.63 to 4.23) (6 RCTs, n=2,741) (Anim-Somuah 2011 **Level I** [Cochrane], 38 RCTs, n=9,658).

Epidural analgesia does not result in more Apgar scores <7 at 5 min compared with various opioids via intermittent administration or PCA alone or in combination with antihistamines (RR 0.80; 95%CI 0.54 to 1.20) (18 RCTs, n=6,898) (Anim-Somuah 2011 **Level I** [Cochrane], 38 RCTs, n=9,658).

Epidural analgesia does not lead to long-term backache (RR 0.96; 95%CI 0.86 to 1.07) (3 RCTs, n=1,806) nor headache or migraine (Orlikowski 2006 **Level II**, n=992, JS 2).

These results are influenced by substantial heterogeneity for pain relief, maternal satisfaction, need for additional means of pain relief, length of second stage of labour and oxytocin augmentation. This heterogeneity did not seem to relate to subgroup or sensitivity confounders, where data could be analysed. None of these studies reported on the rare, serious adverse effects of epidural analgesia (see Sections 5.6.5.1 to 5.6.5.3). However, in a case series of women before childbirth (n=509), 39% expressed concerns about neuraxial analgesia and 46% of 129 women deciding against epidural analgesia did so because of concerns about the technique (Toledo 2013 **Level IV**).

Timing of epidural

A meta-analysis assessed outcomes of early vs late initiation of epidural analgesia for labour, showing no clinically significant differences dependent on timing of epidural analgesia (Sng 2014 **Level I** [Cochrane], 9 RCTs, n=15,752); specifically there are no differences in rate of instrumental birth (RR 0.93; 95%CI 0.86 to 1.01) (8 RCTs, n=15,379), duration of second stage of labour (MD -3.22 min; 95%CI -6.71 to 0.27) (8 RCTs, n=14,982) or adverse fetal outcomes.

Different concentrations of and different local anaesthetics for epidural analgesia

A meta-analysis favours lower (≤0.1%) bupivacaine (8 RCTs, n=852) or ropivacaine (≤0.17%) concentrations (3 RCTs, n=293) over higher concentrations for epidural analgesia in labour (Sultan 2013 **Level I**, 11 RCTs, n=1,145). Low concentrations are associated with fewer assisted vaginal births (OR 0.70; 95%CI 0.56 to 0.86), a shorter second stage of labour (WMD -14.03 min; 95%CI -27.52 to -0.55), less motor block (OR 3.9; 95%CI 1.59 to 9.55), greater ambulation (OR 2.8; 95%CI 1.1 to 7.14), less urinary retention (OR 0.42; 95%CI 0.23 to 0.73) but no difference in Caesarean delivery rate (OR 1.05; 95%CI 0.82 to 1.33).

However, lower concentrations are associated with increased pruritus (OR 3.36; 95%CI 1.00 to 11.31) and a higher rate of Apgar scores <7 at 1 min (OR 1.53; 95%CI 1.07 to 2.21), not persisting at 5 min. No differences are apparent for pain, nausea and vomiting, hypotension, fetal heart rate abnormalities or need for neonatal resuscitation (Sultan 2013 **Level I**, 11 RCTs, n=1,145).

Use of bupivacaine vs ropivacaine for epidural analgesia shows no difference with regard to mode of birth, maternal satisfaction or neonatal outcomes (Halpern 2003 **Level I**, 23 RCTs, n=2,074). There may be differences in motor block but this issue remains unresolved.

Patient-controlled epidural analgesia for labour pain

PCEA can provide effective analgesia but the optimal settings are not clear (Leo 2008 **Level IV**; Loubert 2011 **NR**). A meta-analysis of PCEA in labour concluded that dilute concentrations of bupivacaine (0.125%) or ropivacaine (≤ 0.16%), with and without background infusion, (6 RCTs, n=789; comparing the 2 agents 11 RCTs, n=2,083) provide acceptable analgesia and that use of large bolus doses (6 RCTs, n=588) and background infusions (7 RCTs, n=573) with PCEA may improve analgesia and result in reduction of unscheduled clinician interventions, compared with other interventions (Halpern 2009 **Level I**, 30 RCTs, n=4,033).

A meta-analysis comparing PCEA with and without a background infusion shows that continuous background infusion was associated with increased instrumental vaginal birth (RR 1.66, 95%CI 1.08 to 2.56), prolonged second stage of labour (WMD 12.3 min, 95%CI 5.1 to 19.5), reduced requirement for physician-administered boluses (RR 0.35, 95%CI 0.25 to 0.47), with no difference in Caesarean delivery rate (RR 0.83, 95%CI 0.61 to 1.13) (Heesen 2015 **Level I** [PRISMA], 7 RCTs, n=891). Programmed intermittent boluses (PIEB) with PCEA provided similar analgesia with lower doses of local anaesthetics and higher patient satisfaction compared with continuous infusion with PCEA (Wong 2006 **Level II**, n=158, JS 5). Increasing the bolus dose and interval time for PIEB from 2.5 mL every 15 min to 10 mL every 60 min reduced local anaesthetic doses required further without any other effects on outcome (Wong 2011 **Level II**, n=190, JS 5). In another study, PIEB with PCEA reduced motor block and medicine consumption compared with background continuous infusion (Capogna 2011 **Level II**, n=145, JS 5).

Combined spinal-epidural analgesia for labour pain

Combined spinal-epidural (CSE) analgesia provides slightly more rapid pain relief than epidural techniques alone (Simmons 2012 **Level I** [Cochrane], 37 RCTs, n=3,274). In comparison to traditional epidural techniques (local anaesthetic concentration ≥0.25% bupivacaine), the time to onset is shorter (MD -2.87 min; 95%CI -5.07 to -0.67) (2 RCTs, n=129), with reduced need for rescue analgesia (RR 0.31; 95%CI 0.14 to 0.70) (1 RCT, n=42) and lower rates of urinary retention (RR 0.86; 95%CI 0.79 to 0.95) (1 RCT, n=704) and instrumental birth (RR 0.81; 95%CI 0.67 to 0.97) (6 RCTs, n=1,015).

However, a comparison of CSE with low-dose epidurals (local anaesthetic concentration equivalent to bupivacaine <0.25%; reflecting current practice) shows a faster onset of effect (MD -5.42 min; 95%CI -7.26 to -3.59) (5 RCTs, n=461) but no difference in maternal satisfaction (RR 1.01; 95%CI 0.98 to 1.05) (7 RCTs, n=520) and an increased rate of mild pruritus (RR 1.80; 95%CI 1.22 to 2.65) (11 RCTs, n=959) (Simmons 2012 **Level I** [Cochrane], 37 RCTs, n=3,274).

Fetal heart rate abnormalities have been reported with similar frequency following both epidural and CSE analgesia (Patel 2014 **Level II**, n=113, JS 5). Maternal pain scores and maternal age were predictors of fetal bradycardia, independent of the technique used (Nicolet 2008 **Level III-2,** n=223). Abnormalities were more frequent with CSE and predicted by the presence

of uterine hypertonus, the speed of onset of analgesia (Abrao 2009 **Level II**, n=91, JS 5), high sensory block, high maternal pain scores or a larger decrease in pain score (Nicolet 2008 **Level III-2**; Cheng 2013 **Level III-2,** n=29).

Intrathecal analgesia for labour pain

Single-injection intrathecal opioids

Single-injection IT opioids are as effective as epidural local anaesthetics for the management of pain in early labour and they do not affect nausea or mode of delivery (Bucklin 2002 **Level I**, 7 RCTs, n=332). IT opioids increase the risk of fetal bradycardia (NNH 28) and maternal pruritus (NNH 1.7) in comparison with non-IT opioid analgesia (Mardirosoff 2002 **Level I**, 24 RCTs, n=3,513).

Respiratory depression related to epidural or IT opioids during labour is rare (Carvalho 2008 **NR**).

Intrathecal catheters for labour analgesia

IT microcatheters (24- to 28-gauge) are used infrequently for labour analgesia but may be useful in some specific cases, such as those patients who are morbidly obese, have significant cardiac disease or previous spinal surgery (Palmer 2010 **NR**). Continuous IT medicine infusion improved early analgesia, with no differences in neonatal or obstetric outcomes but more technical difficulties, when compared with epidural administration (Arkoosh 2008 **Level II**, n=429, JS 3); this trial used 28-gauge catheters and there were no safety concerns. Subsequent case series have used larger catheters: one has used 23-gauge successfully (n=7) (Tao 2011 **Level IV**), while another described a high failure rate (20%) with 22- and 24-gauge catheters (n=92) and a high incidence of PDPH (29%), requiring a blood patch in 18% of these patients (Alonso 2009 **Level IV**). The authors concluded the risks outweigh the benefits of this technique as a primary method for labour analgesia.

Placement of an epidural catheter (20–22-gauge) in women who have experienced an unintentional dural puncture is widely practised. A study comparing IT placement with epidural placement of an epidural catheter after unintentional dural puncture (n=97) reported a similar PDPH incidence (72 vs 62%) but easier establishment of neuraxial analgesia with the IT method (Russell 2012 **Level III-1**). Another study (n=128) found a lower rate of PDPH (42% for IT placement vs 62% for epidural placement; OR 2.3; 95%CI 1.04 to 4.86) (Verstraete 2014 **Level III-2**).

10.1.3.4 Other regional techniques in labour pain

Paracervical block and pudendal nerve block are the most commonly performed local anaesthetic PNBs, with a long history of use for pain management in labour.

Local anaesthetic nerve blocks (11 paracervical; 1 pudendal), using various agents, are effective (8 RCTs), and superior to placebo (1 RCT, n=200), opioid (2 RCTs, n=129) and nonopioid analgesia (1 RCT, n=100) (Novikova 2012 **Level I** [Cochrane], 12 RCTs, n=1,549); however it is noted that these findings are based on RCTs of unclear quality and limited numbers. Adverse effects are more common in comparison with placebo (1 RCT, n=200). There is no difference in quality of analgesia and satisfaction with analgesia between different local anaesthetics (4 RCTs, n=789). Specifically in comparison to placebo, paracervical blocks with lignocaine 2% are associated with higher patient satisfaction (RR 32.3; 95%CI 11 to 99) but more adverse effects (RR 29.0; 95%CI 1.8 to 480) (Novikova 2012 **Level II** [Cochrane], 1 RCT [vs placebo], n=200). In comparison with opioids (IM pethidine or fentanyl IV PCA), nerve blocks provide better pain relief (RR 2.52; 95%CI 1.65 to 3.83) without an increase in the rate of assisted vaginal birth (RR 1.02; 95%CI 0.56 to 1.87) or of Caesarean delivery (RR 0.23; 95%CI 0.03 to 1.87) (Novikova 2012 **Level I** [Cochrane], 2 RCTs [vs opioids], n=129).

Paracervical block was equally efficacious but required supplementation more frequently than epidural analgesia (Manninen 2000 **Level II**, n=44, JS 3) and was less effective than single-injection IT analgesia (Junttila 2009 **Level III-2**). Serious fetal complications may occur (Shnider 1970 **NR**), so this technique should be limited to hospitals without other obstetric anaesthesia

services (Levy 1999 **Level III-2**) or for patients with contraindications to neuraxial techniques (Junttila 2009 **Level III-2**).

10.1.3.5 Complementary and other methods of pain relief in labour

Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, rate of instrumental and operative birth and dissatisfaction, especially if the support person is not a member of the hospital staff, was present from early labour, or if an epidural analgesia service was not available (Hodnett 2013 **Level I** [Cochrane], 22 RCTs, n=15,288).

For some nonpharmacological or complementary therapies there is some, but no strong, evidence of effectiveness compared to standard care (Jones 2012c **Level I** [Cochrane], 15 Cochrane reviews [255 RCTs] and 3 non-Cochrane reviews [55 RCTs], n unspecified; Chaillet 2014 **Level I**, 57 RCTs, n=34,300).

The following interventions are supported by some evidence for effectiveness.

- Immersion in water reduces the requirements for regional and neuraxial analgesia, in particular when used in the first stage of labour (OR 0.82; 95%CI 0.70 to 0.98) (6 RCTs) without an increase in adverse effects on mother or newborn (Cluett 2009 **Level I** [Cochrane], 11 RCTs, n=3,146).
- Relaxation by use of instructions and yoga, but not by music or "audioanalgesia", may reduce pain intensity and increases patient satisfaction (Smith 2011c **Level I** [Cochrane], 11 RCTs, n=1,374).
- Acupuncture reduces pain compared with no intervention (SMD -1.00; 95%CI -1.33 to 0.67) (1 RCT, n=163), as does acupressure compared with placebo (SMD -0.55; 95%CI -0.92 to -0.19) (1 RCT, n=120) and a combined control (SMD -0.42; 95%CI -0.65 to -0.18) (2 RCTs, n=322) (Smith 2011b **Level I** [Cochrane], 13 RCTs, n=1,986). Acupuncture reduces use of pharmacological pain relief compared with placebo (RR 0.72; 95%CI 0.58 to 0.88) (1 RCT, n=136) and with standard care (RR 0.68; 95%CI 0.56 to 0.83) (3 RCTs, n=704) with fewer instrumental births compared with standard care (RR 0.67; 95%CI 0.46 to 0.98) (3 RCTs, n=704), and increases satisfaction with pain management vs placebo (RR 2.38; 95%CI 1.78 to 3.19) (1 RCT, n=150) (Smith 2011b **Level I** [Cochrane], 13 RCTs, n=1,986). However, a critical review of this and another meta-analysis in this field (Cho 2010 **Level I**, [PRISMA], 10 RCTs, n=2,038) suggests that these meta-analyses compare very different approaches in very different settings, in particular by comparing trials of efficacy with trials of effectiveness (Levett 2014 **NR**). Two subsequent RCTs confirmed that women who had electroacupuncture had shorter labour duration and were less likely to have epidurals (Mucuk 2013 **Level II**, n=120, JS 1; Vixner 2014 **Level II**, n=303, JS 3); in the latter RCT electroacupuncture was better than manual acupuncture and standard care (see also Section 7.3).
- Massage reduces pain during first stage of labour (SMD -0.82; 95%CI -1.17 to -0.47) (4 RCTs, n=225), reduces anxiety (MD -16.27; 95%CI -27.03 to -5.51) (1 RCT, n=60) and improves emotional wellbeing (1 RCT, n=28) (Smith 2012 **Level I** [Cochrane], 5 RCTs, n=326).

For the following interventions, the evidence is not supportive.

- Hypnosis has no effect on use of pharmacological pain relief, rate of spontaneous vaginal birth or satisfaction with pain relief (Madden 2012 **Level I** [Cochrane], 7 RCTs, n=1,213).
- Biofeedback does not affect the use of pharmacological pain relief or the rates of assisted vaginal birth or Caesarean delivery (Barragan Loayza 2011 **Level I** [Cochrane], 4 RCTs, n=186).
- Sterile water injections intra or subcutaneously do not reduce low-back pain vs saline injection during the first stage of labour, or mode of birth or other maternal or fetal outcomes (Derry 2012 **Level I** [Cochrane], 7 RCTs, n=766).
- Aromatherapy has no effect on any primary or secondary outcomes in labour (Smith 2011a **Level I** [Cochrane], 2 RCTs, n=535).
- In labour, TENS has no effect on pain, interventions or outcomes compared with sham TENS (10 RCTs) or routine care (7 RCTs), when applied to the back (13 RCTs, n=1,150) or cranium (2 RCTs, n=140), with the exception of a reduction of reports of severe pain when

applied to acupuncture points (2 RCTs, n=190) (Dowswell 2009 **Level I** [Cochrane], 17 RCTs, n=1,466). The findings of no analgesic effect were confirmed by two subsequent meta-analyses overlapping by 14 RCTs (Bedwell 2011 **Level I**, 14 RCTs, n=1,456) and 3 RCTs (Mello 2011 **Level I**, 9 RCTs, n=1,076) (see also Section 7.2).

10.1.3.6 Analgesia for forceps delivery

Rates of assisted vaginal birth vary throughout the world (10–15% in high-resource settings). Neuraxial analgesia is commonly used for forceps delivery in these settings but local infiltration and pudendal nerve block are also used, while the rate of general anaesthesia is very low (Osterman 2011 **Level IV**). Studies in this setting are limited and old (Nikpoor 2013 **Level I** [Cochrane], 4 RCTs, n=388). Three of these RCTs compared diazepam to other agents for provision of general anaesthesia, without finding clinically relevant differences. In one trial IT analgesia, compared to pudendal nerve block, resulted in more women regarding their analgesia as adequate (RR 3.36; 95%CI 2.46 to 4.60) with fewer reporting severe pain (RR 0.02; 95%CI 0.00 to 0.27) (Nikpoor 2013 **Level I** [Cochrane], 1 RCT [IT], n=183). The authors conclude that there is a lack of evidence to guide practice.

10.1.3.7 Pain after Caesarean delivery

Pain after Caesarean delivery has been treated by multiple analgesic modalities and multimodal analgesia is recommended (Lavoie 2013 **NR**). Pain on d 1 may be higher than that from many other types of major surgery (Gerbershagen 2013 **Level III-2**, n=456 [Caesarean delivery] of total n=70,764).

When asked to rate their pain after Caesarean delivery, patients using pain scores had increased pain reporting and a worse experience during the postoperative period than the comfort score reporting group (Chooi 2013 **Level II**, n=300, JS 4).

Systemic analgesia

Oral analgesia

A meta-analysis of oral analgesia (opioids, tramadol, paracetamol, NSAIDs, coxibs, gabapentin) for pain after Caesarean delivery identified mainly small trials with contradictory results, not permitting definitive conclusions regarding the most effective or safest approach (Mkontwana 2015 **Level I** [Cochrane], 8 RCTS, n=962). Opioids and nonopioids showed little effect in comparison to placebo and each other with significant heterogeneity except for ketoprofen 100 mg (RR 0.55; 95%CI 0.39 to 0.79) (1 RCT, n=72). The systematic review states that gabapentin reduces the need for additional analgesia vs placebo. However, the results given for gabapentin (300 mg [RR 0.25; 95%CI 0.13 to 0.49] and 600 mg [RR 0.44; 95%CI 0.27 to 0.71] [1 RCT, n=126]) are based on incorrect calculations and do not reflect the results of the underlying published trial, which did not find any significant improvement with gabapentin in either dose (Short 2012 **Level II**, n=132, JS 5). Oral oxycodone was as effective as IV PCA piritramide in this setting but there was no placebo comparator (Dieterich 2012 **Level II**, n=239, JS 3). Oral naproxen or tramadol were similarly effective, with fewer adverse effects with naproxen (Sammour 2011 **Level II**, n=120, JS 3). A study comparing oral oxycodone with IT morphine on top of background oral nonopioid analgesia found comparable analgesia and less pruritus but lower maternal satisfaction (McDonnell 2010 **Level II**, n=111, JS 5).

Parenteral analgesia

The data on parenteral analgesia after Caesarean delivery are similarly inadequate. In addition to spinal morphine, a single IV dose of diclofenac 75 mg improved pain relief scores but not pain scores nor opioid requirements at 24 h postoperatively (Thienthong 2012 **Level II**, n=30, JS 5). Use of coxibs (parecoxib, then celecoxib) or paracetamol or the combination did not reduce epidural PCA pethidine requirements after Caesarean delivery (Paech 2014 **Level II**, n=111, JS 5). In combination with IV PCA morphine, parecoxib and ketorolac had similar efficacy, but without a placebo control (Wong 2010 **Level II**, n=66, JS 2).

As mentioned above, IV PCA piritramide was as effective as oral oxycodone but with no placebo comparator (Dieterich 2012 **Level II**, n=239, JS 3). A continuous IV infusion of tramadol

compared to IV PCA tramadol resulted in higher tramadol consumption but lower patient satisfaction (Demirel 2014 **Level II**, n=40, JS 1).

Dexmedetomidine had an opioid-sparing effect when combined with sufentanil PCA (Nie 2014 **Level II**, n=120, JS 5); more pronounced when dexmedetomidine was continued in the PCA after an initial bolus than if an initial bolus only was administered. Dexamethasone 10 mg IV reduced nausea and vomiting following Caesarean delivery under bupivacaine/morphine spinal anaesthesia, with fewer complaints of pain at rest and on movement in the first 24 h compared to saline control (Cardoso 2013 **Level II**, n=70, JS 5).

Low-dose ketamine bolus and subsequent low-dose infusion for 12 h resulted in an opioid-sparing effect for 24 h without any further benefits or improved long-term outcome (Suppa 2012 **Level II**, n=56, JS 4). However, three different intraoperative IV bolus doses of ketamine (0.25, 0.5, and 1 mg/kg) had no effect on postoperative pain, opioid requirements or long-term outcomes after Caesarean delivery (Bilgen 2012 **Level II**, n=140, JS 4). Similarly, there were no obvious benefits when 10 mg IV ketamine was added to IT morphine and IV ketorolac (Bauchat 2011 **Level II**, n=188, JS 5). In contrast, ketamine 0.15 mg/kg IV given in addition to a bupivacaine spinal anaesthetic resulted in a longer duration and better quality of early postoperative analgesia (Menkiti 2012 **Level II**, n=60, JS 4).

Epidural analgesia

After Caesarean delivery, single-dose epidural morphine (1–8 mg) increases the time until rescue analgesic is required and decreases pain and postoperative morphine requirements for 24 h compared to systemic opioid analgesia (Bonnet 2010 **Level I** [QUOROM], 10 RCTs, n=431); however there is an increased incidence of pruritus (RR 2.7; 95%CI 2.1 to 3.6) and nausea (RR 2.0; 95%CI 1.2 to 3.3). The requirement for rescue IV opioid reduces as the morphine dose increases from 1.25–3.75 mg, with no apparent benefit from 5 mg (Palmer 2000 **Level II**, n=60, JS 5). Epidural morphine 1.5 mg was noninferior to 3 mg and caused fewer adverse effects (Singh 2013b **Level II**, n=90, JS 5). EREM 10 mg decreased supplemental opioid use and improved functional ability scores for 48 h compared with 5 mg of conventional epidural morphine (Carvalho 2005 **Level II**, n=79, JS 3). Bupivacaine/morphine/ magnesium for epidural administration was superior to bupivacaine/morphine or bupivacaine/magnesium with regard to pain relief, time to rescue analgesia and patient satisfaction (Sun 2012 **Level II**, n=200, JS 5) but the neurotoxicity of neuraxial magnesium has not been adequately investigated (Albrecht 2013 **Level I** [PRISMA], 25 RCTs [IV magnesium], n=1,461).

PCEA with 0.2% ropivacaine compared to epidural morphine 2 mg every 12 h provided equivalent analgesia (Chen 2011 **Level II**, n=120, JS 5); although it resulted in more motor weakness, this did not impair ambulation. Other adverse effects (pruritus, nausea, vomiting and urinary retention) occurred more often after epidural morphine, resulting in improved satisfaction scores with PCEA ropivacaine. No differences were found between PCEA with 0.1% levobupivacaine vs 0.06% combined with fentanyl 2 mcg/mL (Chen 2014 **Level II**, n=80, JS 4).

Intrathecal analgesia

IT morphine and other opioids effectively reduce pain and analgesic requirements post Caesarean delivery (Dahl 1999 **Level I**, 15 RCTs, n=535). IT fentanyl was inferior to IT morphine 0.1 mg with regard to analgesia and its duration as well as patient satisfaction, despite fewer adverse effects (pruritus, nausea and vomiting) (Sawi 2013 **Level II**, n=60, JS 4). Doses of IT morphine from 50–400 mcg are effective (Girgin 2008 **Level II**, n=100, JS 5), with 100–200 mcg providing similar analgesia to epidural morphine 3 mg (Sarvela 2002 **Level II**, n=150, JS 3). IT morphine 200 mcg compared with 100 mcg provided better analgesia and more sparing of additional opioids but also caused more nausea requiring treatment and more pruritus (n=241) (Wong 2013 **Level III-2**). IT hydromorphone 40 mcg produced similar outcomes to IT morphine 100 mcg (n=114) (Beatty 2013 **Level III-2**) and IT diamorphine 250 mcg similar outcomes to IT morphine 100 mcg (Barkshire 2001 **Level II**, n=60, JS 4).

The addition of clonidine to IT hyperbaric bupivacaine improved early analgesia after Caesarean delivery, with reduced morphine consumption during the first 24 h but increased intraoperative sedation (Paech 2004 **Level II**, n=232, JS 5; van Tuijl 2006 **Level II**, n=106, JS 5).

IT tramadol 10 mg compared to IT fentanyl 10 mcg added to spinal anaesthesia with bupivacaine increased the duration of analgesia and reduced postoperative shivering (Subedi 2013 **Level II**, n=80, JS 5). IT midazolam gave short duration postoperative analgesia (Prakash 2006 **Level II**, n=60, JS 3). The safety of both these medicines with respect to neurotoxicity is not established.

Other regional techniques

Local anaesthetic techniques in general (wound infiltration, bupivacaine-soaked gelatin sponge placement or catheter infusions, ilioinguinal/ iliohypogastric block, TAP block) reduce opioid consumption following Caesarean delivery performed under general or regional anaesthesia compared to placebo (Bamigboye 2009 **Level I** [Cochrane], 20 RCTs, n=1,150). The reduction in opioid consumption is most beneficial where abdominal nerve blocks are used to supplement regional anaesthesia (MD -25.80 mg; 95%CI -50.4 to -5.4) (4 RCTs, n=175).

Wound infiltration or infusion

There is benefit from adding diclofenac (Lavand'homme 2007 **Level II**, n=92, JS 3) or low-dose ketorolac, but not hydromorphone, to a 48-h continuous bupivacaine wound infusion (Carvalho 2013 **Level II**, n=60, JS 5). Ketorolac reduced pain scores and need for analgesia and also inflammatory cytokines (IL-6 and IL-10) in the wound exudate. Adding tramadol (1.5 mg/kg) to levobupivacaine wound infiltration reduced pain scores early in the postoperative period but there was no systemic control group (Demiraran 2013 **Level II**, n=90, JS 4). SC pethidine or tramadol improved analgesia and were opioid sparing compared with infiltration of bupivacaine 0.25% or placebo (Jabalameli 2012 **Level II**, n=120, JS 3). Placing a multiorifice catheter for wound infiltration with ropivacaine/ketoprofen below the superficial abdominal fascia resulted in improved analgesic efficacy vs placement above (Rackelboom 2010 **Level II**, n=56, JS 5).

Subsequent RCTs have confirmed these results. Continuous wound infiltration with ropivacaine was superior to epidural morphine with regard to pain relief, adverse effects, need for nursing care and length of stay (O'Neill 2012 **Level II**, n=58, JS 3). A comparison of infiltration of equivalent doses of ropivacaine 0.5%, ropivacaine 0.2% and a placebo control, found opioid sparing with either local anaesthetic and similar analgesia but a small reduction in opioid use with a high concentration/low volume vs low concentration/high volume (Larsen 2015 **Level II**, n=90, JS 5). Combining a pre with a postincisional wound infiltration with lignocaine 1% had superior efficacy to a pre or postincisional infiltration alone (Fouladi 2013 **Level II**, n=281, JS 4). Results from trials of preincisional infiltration with lignocaine alone are contradictory: either no benefits over placebo (Kessous 2012 **Level II**, n=153, JS 4) or reduced pain and opioid requirements (Sekhavat 2011 **Level II**, n=104, JS 4). Continuous wound infusion with ropivacaine or saline for 48 h is less effective than IT morphine with no difference between the local anaesthetic and placebo groups (Kainu 2012 **Level II**, n=66, JS 4).

Ilioinguinal-iliohypogastric block

Bilateral ilioinguinal-iliohypogastric blocks (local anaesthetic vs saline placebo) used in addition to IT morphine improved analgesia, lowered analgesic requirements and increased satisfaction (Wolfson 2012 **Level** II, n=34, JS 5). However in another study, US-guided ilioinguinal-iliohypogastric blocks with bupivacaine, combined with IT morphine (variable dosing), conferred no further benefit (Vallejo 2012 **Level II**, n=50, JS 4)

Transversus abdominis plane block

Following Caesarean delivery, local anaesthetic TAP block reduces postoperative opioid requirements for 24 h and pain scores for 12 h but only when IT morphine is not used (Mishriky 2012 **Level I** [PRISMA], 9 RCTs, n=524; Abdallah 2012 **Level I** [PRISMA], 5 RCTs, n=312 [overlapping by 5 RCTs]); IT morphine provides better analgesia than TAP blocks but with an increased rate of adverse effects.

Subsequent RCTs with small patient numbers of TAP blocks used in combination with IT morphine have shown no (McKeen 2014 **Level II**, n=83, JS 5) vs early 0–24 h analgesic benefit (Lee 2013a **Level II**, n=51, JS 5; Onishi 2013 **Level III-2**; Singh 2013a **Level II**, n=60, JS 5). The latter study

compared high-dose (3 mg/kg) with low-dose ropivacaine (1.5 mg/kg) and found only high-dose ropivacaine produced benefits for up to 12 h.

Single-dose US-guided TAP blocks and continuous wound infusions were compared in women having Caesarean delivery under spinal anaesthesia without morphine (Chandon 2014 **Level II**, n=65, JS 3). The trial was abandoned after a generalised seizure in the TAP group; however there were no differences between the groups with regard to analgesia and pain at 1 mth. In a similar study, there was also no difference in morphine use or pain when TAP blocks and SC wound infiltration with bupivacaine 0.25% and adrenaline were compared (Telnes 2015 **Level II**, n=60, JS 5).

With regard to duration of effect, TAP blocks performed by a posterior approach (4 RCTs) reduce opioid consumption and rest and dynamic pain scores over 48 h vs controls; longer than that from a lateral approach where rest pain scores only were lower than controls at 12 h (8 RCTs) (Abdallah 2013 **Level I** [PRISMA], 12 RCTs [8 Caesarean], n=641). Subanalysis of the varying agents and dose equivalents administered was not performed.

TAP blocks are associated with high peak plasma levels of local anaesthetic after 30 min (Torup 2012 **PK**) and mild toxicity is reported after total doses of ropivacaine of ≥2.5 mg/kg (Griffiths 2013 **Level IV**) and convulsions after 150 mg of levobupivacaine (Weiss 2014 **CR**).

Risk of chronic pain following Caesarean delivery

Persistent postsurgical pain has been reported in 1–18% of women following Caesarean delivery (Landau 2013 **NR**). In two studies with detailed follow-up, the incidence of persistent pain was 14.6% at 2 mth, reducing to 4.2% at 12 mth (n=426) (Liu 2013 **Level IV**) and 11% at 8 wk, reducing to 0.6% at 12 mth (n=381) (Ortner 2014 **Level III-2**). For repeat Caesarean delivery, preoperative scar hyperalgesia (seen in 41% of patients) is a risk factor for postoperative pain (Ortner 2013 **Level III-2**). Patients with chronic postsurgical pain had higher rates of general vs spinal anaesthesia (37% general vs 17% in the no-pain group; p=0.02); in this study the incidence of significant pain at 10 mth postoperatively was 5.9 % (Nikolajsen 2004 **Level III-2**).

Prior Caesarean delivery is also a risk factor for chronic pelvic pain (Latthe 2006 **Level III-3 SR**, 63 studies, n=64,286). See also Section 1.4.

Key messages

Neuraxial and regional analgesia

1. Epidural and combined spinal-epidural analgesia provide superior pain relief for labour and childbirth compared with all other analgesic techniques (**S**), however with no difference in maternal satisfaction (**N**) (**Level I** [Cochrane Review]) except in comparison with remifentanil IV PCA (**N**) (**Level II**).
2. Epidural analgesia reduces the risk of fetal acidosis (**N**), increases the duration of the second stage of labour slightly (**Q**) and the rate of instrumental birth (**U**) but does not increase the rate of Caesarean delivery (**U**) or long-term backache (**U**) (**Level I** [Cochrane Review]).
3. Early versus late initiation of epidural analgesia leads to no clinically significant differences in outcome (**N**) (**Level I** [Cochrane Review]).
4. Lower concentrations of local anaesthetics for epidural analgesia in labour result in a shorter duration of second stage of labour, fewer assisted vaginal births, greater ambulation and less urinary retention than higher concentrations (**N**) (**Level I** [Cochrane Review]).
5. In comparison with epidural analgesia, combined spinal-epidural analgesia reduces time to effective analgesia (**U**), does not increase maternal satisfaction (**U**) and increases the incidence of mild pruritus (compared to low-dose epidurals) (**Q**) (**Level I** [Cochrane Review]).

6. Local anaesthetic nerve blocks (in particular paracervical blocks) provide better analgesia than placebo, nonopioids and opioids for labour pain but with an increased rate of adverse effects (**N**) (**Level I** [Cochrane Review]).
7. Patient-controlled epidural analgesia provides effective analgesia for labour (**U**) but optimal settings (**U**) (**Level I**), the need for a background infusion and the utility of programmed intermittent boluses remain unclear (**N**) (**Level I** [PRISMA]).
8. There is no significant difference between use of bupivacaine and ropivacaine for epidural analgesia in labour for any outcome (**U**) (**Level I**).
9. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics, with increased pruritus but no difference in nausea (**U**) (**Level I**).

Systemic analgesia

10. Analgesic concentrations of inhaled volatile anaesthetics provide superior analgesia in labour but more drowsiness, compared to nitrous oxide (**N**) (**Level I** [Cochrane Review]).
11. Nitrous oxide has some analgesic efficacy in labour pain (**S**), increases maternal adverse effects (nausea, vomiting, dizziness) (**N**) but has no adverse effects on the newborn (**S**) (**Level I** [Cochrane Review]); pain relief is comparable to pethidine but inferior to epidural analgesia (**N**) (**Level IV SR**).
12. Use of nonopioid analgesics alone for labour analgesia is not supported by current evidence (**N**) (**Level I** [Cochrane Review]).
13. Parenteral opioids provide moderate analgesic effects in labour pain (**N**), are inferior to epidural analgesia (**N**) and cause increased adverse maternal effects (sedation, nausea, vomiting) (**N**) and adverse short-term effects on the newborn, although long-term effects remain unclear (**W**) (**Level I** [Cochrane Review]).
14. Remifentanil intravenous PCA provides better analgesia in labour compared to parenteral pethidine (**N**) (**Level I**) and probably nitrous oxide (**N**) (**Level II**) but is inferior to epidural analgesia (**N**) (**Level I**).

Complementary and other methods of pain relief in labour

15. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, rate of instrumental and operative birth and dissatisfaction (**S**) (**Level I** [Cochrane Review]).
16. Immersion in water during labour may reduce the requirements for regional and neuraxial analgesia, without any increase of adverse effects on mother or newborn compared to standard care (**N**) (**Level I** [Cochrane Review]).
17. Relaxation by use of instructions and yoga, but not by music or "audioanalgesia", may reduce labour pain intensity and increases maternal satisfaction compared to standard care (**N**) (**Level I** [Cochrane Review]).
18. Acupuncture and acupressure reduce labour pain, use of pharmacological pain relief, instrumental birth rates and increase satisfaction with pain management compared to standard care or placebo (**S**) (**Level I** [Cochrane Review]).
19. Massage reduces pain during the first stage of labour and improves emotional wellbeing (**N**) (**Level I** [Cochrane Review]).
20. Transcutaneous electrical nerve stimulation has no effect on pain, interventions or outcomes in labour, with the exception of reduction of reports of severe pain when applied to acupuncture points (**Q**) (**Level I** [Cochrane Review]).
21. Hypnosis (**R**), biofeedback (**N**), sterile water injections intra or subcutaneously (**N**) and aromatherapy (**N**) have no effect on labour pain or other outcomes (**Level I** [Cochrane Review]).

Pain relief after Caesarean delivery

22. Local anaesthetic wound infiltration, in particular abdominal nerve blocks, reduce opioid consumption following Caesarean delivery (**S**) (**Level I** [Cochrane Review]).
23. Local anaesthetic transversus abdominis plane blocks reduce postoperative opioid requirements and pain scores after Caesarean delivery but only when intrathecal morphine is not used (**N**) (**Level I** [PRISMA]).
24. In relation to controls only and with no direct comparison between the two approaches, local anaesthetic transversus abdominis plane blocks performed by a posterior approach provide longer duration of benefit versus the lateral approach after lower abdominal incision surgery including Caesarean delivery (N) (**Level I** [PRISMA]).
25. Epidural (**N**) (**Level I** [QUOROM]) and intrathecal morphine (**N**) (**Level I**) and patient-controlled epidural analgesia (**N**) (**Level II**) provide effective analgesia after Caesarean delivery but neuraxial morphine increases the rate of pruritus and nausea compared with systemic administration (**N**) (**Level I** [QUOROM]).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Remifentanil IV PCA for relief of labour pain carries a risk of maternal respiratory depression; use is recommended only if there is one-on-one continuous presence of a midwife, continuous oxygen saturation monitoring and continuous cardiotocograph monitoring (as an indirect method of detecting global hypoxaemia) (**N**).

☑ Transversus abdominis plane blocks after Caesarean delivery may result in high plasma concentrations of local anaesthetic and potential toxicity; minimum effective doses should be used (**N**).

10.1.4 Pain management during lactation

A number of general principles apply when administering analgesic and antiemetic medicines for pain management during lactation:

- the choice of medicines should be based on knowledge of their potential impact on breastfeeding and on the breastfed infant secondary to transfer in human milk; and
- the lowest possible effective maternal dose of analgesic is recommended, breastfeeding is best avoided at times of peak medicine concentration in milk and the infant should be observed for effects of medication transferred in breast milk.

The effects of many analgesic and antiemetic medicines during lactation have not been adequately investigated, leaving clinical decisions to be made on evidence derived from pharmacokinetic or observational studies, case reports and anecdotes. For most medicines, information on infant outcome is inadequate (based on single-dose or short-term administration or on case reports) or absent, so maternal consent is advisable and caution is warranted.

The principles of passage of medicines in human milk (Ito 2000 **NR**; Ito 2000 **NR**; Ilett 2005 **NR**; Berlin 2005 **NR**) including medicines relevant to pain management (Rathmell 1997 **NR**; Spigset 2000 **NR**; Bar-Oz 2003 **NR**) have been reviewed. The maternal plasma concentration, which is influenced by the dose and the ability of the mother to metabolise the medicine, is an important determinant of medicine levels in breast milk. High lipid solubility, low molecular weight, low protein binding and the unionised state favour secretion into breast milk. Most medicines have a milk-to-plasma ratio of ≤1 (Ito 2000 **NR**). Infant exposure is often 0.5–4% of the maternal dose but infant medicine metabolism may be impaired and much of the data is from single maternal dose studies rather than chronic therapy (Berlin 2005 **NR**). A safe level of infant exposure to a medicine has been arbitrarily defined as no more than 10% of the therapeutic dose for infants (or the adult dose standardised by weight if the infant dose is not known) (Ito 2000 **NR**). Until about d 3–4 postpartum only very small amounts of colostrum are secreted, so early breastfeeding is unlikely to pose a hazard, even from medicines administered in the peripartum period.

Guidelines and reviews relevant to anaesthesia and analgesia for the breastfeeding mother have been published (Sachs 2013 **NR**; Montgomery 2012 **GL**; Chu 2013 **NR**). Furthermore, the National Library of Medicine maintains a database on medication and breastfeeding (LactMed Database 2015); among the data included are maternal and infant levels of medicines, possible effects on breastfed infants and on lactation and alternate medicines to consider.

10.1.4.1 Nonopioids

Paracetamol

The weight-adjusted maternal dose of paracetamol transferred to the newborn was 1.85% of a 1 g dose (Notarianni 1987 **Level IV PK**). Although glucuronide conjugation may be deficient in the newborn, the medicine is considered safe as there have been no reports of adverse effects and levels in breast milk are a fraction of the recommended neonatal doses.

NSAIDs

Short-term maternal NSAID use during lactation, with the exception of aspirin >150 mg/d, appears safe for the healthy term infant (Bloor 2013 **NR**). Despite similar proportional transfer to paracetamol, salicylates are eliminated slowly by the newborn, cause platelet dysfunction and have been associated with Reye's syndrome; aspirin in analgesic doses cannot be recommended as safe (Bar-Oz 2003 **NR**).

NSAIDs must be considered individually but in general levels in breast milk are low because they are weak acids and extensively plasma protein bound. In particular, ibuprofen has very low transfer (<1% weight-adjusted maternal dose), is short acting, free of active metabolites and has the best documented safety (Ito 2000 **NR**). Ibuprofen is therefore considered the ideal agent in this group (Montgomery 2012 **GL**).

Diclofenac and ketorolac are minimally transported into breast milk and short-term or occasional use is compatible with breastfeeding (Rathmell 1997 **NR**). The safety of naproxen is less clear but it is also considered compatible. Indomethacin has been associated with central maternal adverse effects, such as agitation and psychosis, in previously healthy postnatal women (n=32) (Clunie 2003 **Level IV**).

Following a single 200 mg dose of celecoxib, <0.5% of the weight-adjusted maternal dose was present in breast milk, suggesting that breastfeeding during routine dosing poses minimal risk (Gardiner 2006 **Level IV PK**; Hale 2004 **Level IV PK**). The relative infant dose of parecoxib and valdecoxib after a single dose of maternal parecoxib is very low (<1%) and neonatal neurobehavioural scores are within the normal range (Paech 2012 **Level IV PK**).

10.1.4.2 Opioids and tramadol

With some provisos, the short-term use of opioids is generally considered safe during lactation as most opioids are secreted into breast milk in low doses (Hendrickson 2012 **NR**).

An association between opioid exposure in breast milk and episodes of apnoea and cyanosis in infants has been described (Naumburg 1988 **Level IV**), leading some to suggest that opioids should be avoided if the newborn experiences such events during the first week of life. Cases of infant toxicity due to human milk exposure are reported (Madadi 2007 **CR**), mostly involving codeine in infants <2 mth of age, therefore infants should be monitored for drowsiness (Hendrickson 2012 **NR**) (see also Sections 1.7.3 and 4.1.1).

Morphine has been recommended as the opioid of choice if potent analgesia is required in breastfeeding mothers (Ito 2000 **NR**). About 6% of the weight-adjusted maternal dose of morphine is transferred in breast milk (Feilberg 1989 **Level IV PK**) but the oral bioavailability in the infant is low (about 25%), so smaller amounts reach the infant's plasma. In mothers treated with IV PCA morphine for 48 h following Caesarean delivery, levels of morphine and M6G were low in breast milk, suggesting minimal medicine would be transferred to the newborn (Baka 2002 **Level IV PK**). Compared with IV PCA pethidine (meperidine), there is significantly less neurobehavioural depression than with morphine (Wittels 1990 **Level III-2**).

Pharmacokinetic studies suggest the more lipophilic opioids such as fentanyl and alfentanil are unlikely to cause problems. Following a single dose of IV fentanyl, the weight-adjusted maternal dose received by the newborn was 3%, levels in colostrum became undetectable within several hours and the nursing infant appeared unaffected (Steer 1992 **Level IV PK**; Nitsun 2006 **Level IV PK**).

Breastfed infants whose mothers received IV PCA pethidine were less alert and oriented to auditory cues after Caesarean delivery than infants of mothers receiving morphine (Wittels 1997 **Level III-2**, n=47). As norpethidine (normeperidine) accumulates in breast milk with repeated use and has a very slow neonatal elimination; pethidine use during breastfeeding is not recommended (Ito 2000 **NR**).

However, pethidine PCEA, which results in much lower plasma levels, is associated with a low combined relative infant dose of pethidine and norpethidine (1.8%) (Al-Tamimi 2011 **Level IV PK**) and appears a low-risk method during very early lactation (Sakalidis 2013 **Level III-2**).

Codeine has a milk-to-plasma ratio of slightly more than 1 and is suggested to be generally safe with short-term use but should be used with caution when dosing is repeated (Meny 1993 **PK**; Hendrickson 2012 **NR**). A case-control study that included a newborn who died while breastfed by a mother taking codeine, has highlighted that breastfed infants of mothers who are extensive or ultrarapid metabolisers (20–40% of the population, depending on ethnicity, with duplications of CYP2D6 gene) are at increased risk of life-threatening CNS depression (Madadi 2009 **Level III-2**). A number of similar cases have been reported and healthcare workers and breastfeeding mothers should be aware of this risk (Madadi 2008 **Level IV**). A relationship between infant CNS symptoms (decreased alertness, lethargy, poor feeding) and maternal symptoms, codeine dose and, in some cases CYP2D6 phenotype, has been identified (Madadi 2009 **Level III-3**). Pharmacokinetic simulation suggests potentially toxic morphine concentrations can be reached in the newborn within 4 d of repeated maternal codeine administration (Willmann 2009 **PK**).

Oxycodone shows a low relative infant dose of 1.5–3% but has high oral bioavailability and is concentrated in human breast milk, so breastfed infants may receive >10% of a therapeutic dose. Also, poor CYP2D6 metabolisers may have decreased clearance of oxycodone and ultrarapid metabolisers higher concentrations of the more potent metabolite oxymorphone, leading to sedation (Samer 2010 **Level II PK**, n=10 [5-arm crossover], JS 5). The safety with repeated maternal dosing has been questioned (Ito 2000 **NR**; Lam 2012 **Level III-2**); a case of opioid toxicity in a breastfed newborn of a mother taking oxycodone has been reported (Timm 2013 **CR**). Oxycodone use during breastfeeding resulted in increased rate of CNS depression of the newborn compared with paracetamol (20.1 vs 0.5%) (OR 46.16; 95%CI 6 to 344) but no difference to codeine (16.7%) (OR 0.79; 95%CI 0.46 to 1.38) (Lam 2012 **Level III-2,** n=533). As a component of multimodal analgesia in the first 72 h after Caesarean delivery, there may be minimal risk to breastfeeding infants as only a low volume of milk is ingested during this period. Only 1 of 44 newborns had detectable plasma levels and none were oversedated despite maternal exposure up to 90 mg/d (Seaton 2007 **Level III-3**).

Tramadol (100 mg every 6 h) on d 2–4 after Caesarean delivery was associated with a milk-to-plasma ratio of 2.2, a relative infant dose of 2.9% and no detectable behavioural effects in the infants (Ilett 2008 **Level III-2**). However, as with other medicines, these data cannot be directly extrapolated to long-term use at later postpartum stages when the volume of ingested milk is higher. The use of tramadol during pregnancy and in lactation has been reviewed (Bloor 2012 **NR**); the opinion being that during early lactation short-term use of tramadol appears unlikely to cause harm to healthy term infants.

After IN hydromorphone exposure of the mother, 0.67% of the maternal dose of hydromorphone (adjusted for body weight) is transferred into breast milk (Edwards 2003 **Level IV PK**). Hydrocodone is metabolised in small quantities to a more potent metabolite, hydromorphone, and ultrarapid metabolisers exist. The relative infant dose is 2.4% (Sauberan 2011 **Level IV PK**) and possible infant toxicity has been reported (Hendrickson 2012 **NR**).

Methadone is considered compatible with breastfeeding; even with high methadone doses, breast milk concentrations were relatively low at 2.1–3.5% (Bogen 2011 **Level IV PK**).

Plasma levels of methadone were low in infants of breastfeeding mothers on methadone-maintenance programs and no effect on infant neurobehavioural outcomes were found on d 3, 14 and 30 following birth (Jansson 2008 **Level III-3**). Breastfeeding reduced NAS in newborns of mothers on methadone substitution and is encouraged (McQueen 2011 **Level III-2**).

Buprenorphine has very low passage into breast milk and the combined relative infant dose of both buprenorphine and its active metabolite norbuprenorphine is <1% (Ilett 2012 **Level IV PK**). When used for drug substitution therapy in breastfeeding mothers, buprenorphine did not lead to adverse effects in newborns up to 4 wk postnatally (Gower 2014 **Level IV**).

10.1.4.3 Other analgesics and medications related to pain relief

After epidural administration, local anaesthetics showed acceptable milk-to-plasma ratios of 1.1 for lignocaine (lidocaine), 0.34 for bupivacaine (Ortega 1999 **PK**) and 0.25 for ropivacaine (Matsota 2009 **PK**). These are considered safe (Rathmell 1997 **NR**), including for anaesthesia and analgesia during very early lactation (Matsota 2009 **Level IV** n=25; Hirose 1996 **Level II**, n=30, JS 2). Use of epidural analgesia (local anaesthetic ± fentanyl) during labour (Chang 2005 **Level III-3**) or as PCEA after Caesarean delivery (Matsota 2009 **Level IV**) did not influence neurobehavioural scores in healthy term infants.

The possible effect of epidural analgesia on breastfeeding is complex and may not only be related to medications administered, with selection bias (lack of randomised trials), nonstandardised breastfeeding evaluations and failure to control for confounding variables making firm conclusions impossible (Szabo 2013 **NR**). In a study of more than 1,000 nulliparous women randomised to different methods of epidural analgesia in labour and matched with 351 nonepidural controls, there was no association with breastfeeding initiation (Wilson 2010 **Level III-2**). However, epidural analgesia in labour was associated with an increased risk of breastfeeding cessation at 30 d after adjusting for demographic and intrapartum factors (HR 1.26; 95%CI 1.1 to 1.44) (Dozier 2013 **Level III-2**, n=772).

The alpha-2-delta ligands are increasingly popular analgesics for acute pain after operative birth, especially among women with neuropathic pain, opioid tolerance or where opioid dose minimisation is recommended. For gabapentin, the milk-to-plasma concentration was 0.86, the relative infant dose was 2.4% and no adverse effects were noted in the infant (Ohman 2005 **Level IV PK**). While suggestive of safety during lactation, a careful individual risk-benefit analysis was suggested (Kristensen 2006 **CR PK**). There are also limited human data on pregabalin during breastfeeding. Pregabalin is a small molecule that undergoes negligible metabolism and is thus expected to be excreted in breast milk. A breastfed infant of a mother on long-term pregabalin (for epilepsy) had serum concentrations of about 8% of the maternal levels, although no adverse effects were observed (Ohman 2011 **Level IV PK**). During a much later stage of lactation, the mean milk-to-plasma ratio was 0.53–0.76; and 0.2% of the maternal daily dose was secreted into breast milk, representing 7% of the body weight normalised maternal dose (Lockwood 2014 **Level IV PK**). The medicine was well tolerated and the overall safety of anticonvulsants in breastfeeding mothers is regarded as high, with continuation of breastfeeding recommended (Reimers 2012 **NR**).

There is very little information about antiemetic use and breastfeeding and, in almost all cases, the manufacturers do not recommend their use during lactation; although in practice most antiemetics are used, with the best data for metoclopramide (Pistilli 2013 **NR**). Metoclopramide is used both for cancer chemotherapy and to increase milk production, so although it concentrates in human milk the relative infant exposure is much lower than the therapeutic dose in paediatrics (Kauppila 1983 **Level IV PK**) and authors have reported the absence of adverse effects in newborns whose mothers were exposed (Pistilli 2013 **NR**). Animal studies suggest possible CNS effects in the newborn but human anecdotal experience is favourable with medicines such as metoclopramide, domperidone and dexamethasone.

See Table 10.3 for recommendations.

Table 10.3 The breastfeeding patient and medicines used in pain management

Medicine	Comments
Opioids buprenorphine, codeine, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, tramadol	Safe to use occasional doses, but avoid codeine. Use repeated doses with caution, especially if infant is premature or <4 wk old; monitor infant for sedation and other adverse effects
Paracetamol	Safe to use
Aspirin	Avoid due to theoretical risk of Reye's syndrome
Other NSAIDs Non-selective NSAIDs (nsNSAIDs), COX-2 Selective NSAIDs (coxibs)	Safe to use, ibuprofen is preferred Limited data; appear safe
Ketamine	Limited data
Tapentadol	No data yet, avoid
SSRIs: Sertraline, citalopram, fluoxetine, escitalopram, fluvoxamine, paroxetine	SSRIs are used in postnatal depression (some consider sertraline one of the preferred antidepressants in breastfeeding); avoid fluoxetine because of its long half-life
TCAs: amitriptyline, clomipramine, dothiepin (dosulepin), doxepin, imipramine, nortriptyline, trimipramine	TCAs have been used to treat postnatal depression. Avoid doxepin if possible; a single case of neonatal respiratory depression has been reported
SNRIs Duloxetine, venlafaxine, desvenlafaxine	Low concentrations in milk: check baby for sedation and adequate weight gain. Consider using an alternative to duloxetine until more is known about it
Anticonvulsants carbamazepine	Safe to use; monitor infant for drowsiness and poor suckling
phenytoin sodium	Safe to use
sodium valproate	Should be safe to use (one report of adverse effects); consider monitoring baby for petechial rash
clonazepam	Risk of sedation in infant; contact specialised information service
tiagabine	Contact specialised information service
gabapentin, pregabalin, lamotrigine, topiramate	Pass into breast milk (see above); contact one of the pregnancy drug information centres
Antiemetics, antinauseants *Phenothiazines:* prochlorperazine	Safe to use
promethazine	Limited data but short-term use appears safe. Sedation of mother is main concern
metoclopramide	Safe to use (used to stimulate lactation)
granisetron, ondansetron, tropisetron	Contact specialised information service; no data but 1–2 doses after birth appear safe
domperidone	Used during first months of breastfeeding to stimulate lactation; mother may be less drowsy than with metoclopramide
droperidol, haloperidol	Avoid if possible, or contact one of the pregnancy medicine information centres; if used, monitor infant for sedation

Source: Modified information taken with permission from data to be published in Australian Medicines Handbook 2016.

Key messages

1. Local anaesthetics, paracetamol and several NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (**S**) (**Level IV**).
2. Morphine, fentanyl, methadone, and short-term oxycodone immediately after giving birth are considered to be safe in the lactating patient and are preferred over pethidine (**S**) (**Level IV**).
3. Repeated dosing of codeine or oxycodone in lactating patients should be avoided if possible and the infant monitored for central nervous system depression (**S**) (**Level IV**).

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Prescribing medications during lactation requires consideration of possible transfer into breast milk, uptake by the infant and potential adverse effects for the infant; it should follow available prescribing guidelines (**U**).

10.1.5 Pain in the puerperium

Pain during the puerperium is common and of multiple aetiologies, most often being perineal or uterine-cramping pain initially, and breast pain from the d 4 postpartum. In the first 6 mth postpartum, backache was reported by 44% of women and perineal pain by 21% (Brown 1998 **Level IV**). Headache has multiple aetiologies, mainly primary causes such as tension, migraine and musculoskeletal headache and, in a large observational study (n=985) was reported by 40% of women in wk 1 after giving birth (Goldszmidt 2005 **Level IV**). Severe perineal and uterine pain limited mobility during maternal-infant bonding and perineal trauma and pain was associated with delayed resumption of sexual relations after birth (Williams 2007 **Level IV**). Breast, especially nipple, pain may result in abandonment of breastfeeding (Morland-Schultz 2005 **Level III-3 SR**). Chronic postnatal pain is also a risk factor for postnatal depression (Gaudet 2013 **Level IV**).

10.1.5.1 Perineal pain

Many obstetric and surgical factors contribute to perineal trauma and episiotomy. After adjusting for parity, perineal trauma and length of labour, women with instrumented vs unassisted vaginal births reported more perineal pain (Thompson 2002 **Level IV**). Restrictive use vs routine mediolateral episiotomy reduced the rate of episiotomy from 75–28% and reduced the risk of severe perineal trauma and the requirement for suturing but did not influence the incidence or degree of perineal pain (Carroli 2009 **Level I** [Cochrane], 8 RCTs, n=5,541).

In comparison with interrupted suturing methods, continuous suturing reduced pain incidence for up to 10 d (particularly suturing of all layers) (RR 0.65; 95%CI 0.60 to 0.71) (4 RCTs, n=2,488) but not for skin only (RR 0.89; 95%CI 0.73 to 1.07) (2 RCTs, n=1,217) and reduced postpartum analgesic use (RR 0.70; 95% CI 0.58 to 0.84) (for all layers 2 RCTs and skin only 2 RCTs, n=2,973) (Kettle 2007 **Level** [Cochrane], 7 RCTs, n=3,822).

There is only limited evidence to support the effectiveness of local cooling treatments (ice packs, cold gel pads, cold/iced baths) for relieving perineal trauma pain compared to various alternatives or no interventions (East 2012 **Level I** [Cochrane], 10 RCTs, n=1,825). Ice packs provided superior analgesia compared with no treatment for 24–72 h postpartum (RR 0.61; 95%CI 0.41 to 0.91) (1 RCT, n=208).

Although improvement in perineal pain has been reported with US, there is insufficient evidence to fully evaluate efficacy (Hay-Smith 2000 **Level I** [Cochrane] 4 RCTs, n=659). Ear acupressure did not relieve perineal trauma pain in the first 48 h after birth (Kwan 2014 **Level II**, n=266, JS 5).

For women without prior vaginal birth, antenatal perineal massage (from 35 wk gestation) reduced the incidence of perineal trauma requiring suturing (NNT 15; 95%CI 10 to 36) and the requirement for episiotomy (NNT 21; 95%CI 12 to 75) (Beckmann 2013 **Level I** [Cochrane],

4 RCTs, n=2,497). Effects on acute postpartum pain have not been reported but a reduction in the incidence of perineal pain at 3 mth postpartum was found in women who used antenatal perineal massage and had previously given birth vaginally (NNT 13; 95%CI 7 to 60) (1 RCT, n=376).

Pharmacological treatments

More women with perineal pain experience pain relief from paracetamol than from placebo (RR 2.14; 95%CI 1.59 to 2.89) (Chou 2013 **Level I** [Cochrane] 11 RCTs, n=1,367); fewer women require additional analgesia (RR 0.34; 95%CI 0.21 to 0.55) (8 RCTs, n=1,132).

Suppositories of nsNSAIDs reduce perineal pain in the first 48 h postpartum more effectively than placebo (Hedayati 2003 **Level I** [Cochrane], 3 RCTs, n=249). Rectal indomethacin was as effective as rectal diclofenac (Yildizhan 2009 **Level** II, n=200, JS 3). IV dexketoprofen was as effective as IV paracetamol (Akil 2014 **Level II**, n=95, JS 5). Both oral celecoxib and diclofenac reduced perineal pain, with celecoxib showing a slight advantage with respect to pain scores at rest and the incidence of gastrointestinal symptoms (Lim 2008 **Level II**, n=329, JS 5).

Topical local anaesthetics (lignocaine, cinchocaine, pramoxine plus hydrocortisone preparations) or placebo did not improve pain relief in the 24 h postpartum (Hedayati 2005 **Level I** [Cochrane], 8 RCTs, n=976). The use of systemic analgesics was not standardised across these studies and may be a confounding factor. Following mediolateral episiotomy repair under epidural analgesia, a pudendal block with ropivacaine improved pain scores and reduced the proportion of women requiring additional analgesia (Aissaoui 2008 **Level II,** n=42, JS 4).

10.1.5.2 Breast pain

Painful breasts are a common reason for ceasing breastfeeding (Amir 2003 **NR**). Management is firstly directed toward remedying the cause, whether this is infant-related (incorrect attachment, sucking, oral abnormalities), lactation-related (breast engorgement, blocked ducts or forceful milk ejection), nipple trauma, dermatological or infective problems (candida or mastitis) or other causes. There is insufficient evidence to recommend glycerine gel dressings, breast shells with lanolin, lanolin alone or an all-purpose nipple ointment for treatment of nipple pain (Dennis 2014 **Level III-1 SR** [Cochrane], 4 studies, n=656). Irrespective of treatment, nipple pain resolves by 7–10 d postpartum for most women.

Symptomatic treatments for breast engorgement have been assessed (Mangesi 2010 **Level III-1 SR** [Cochrane], 8 studies, n=744); acupuncture (2 studies), cabbage leaves (2 studies), cold gel packs (1 study), pharmacological treatments (2 studies) and US (1 study) did not result in a faster resolution of symptoms than no treatment.

Mastitis is defined by at least two breast symptoms (pain, redness or lump) and at least one of fever or flu-like symptoms. The incidence is 17–33% of breastfeeding women, most episodes occurring in the first 4 wk postpartum (Amir 2007 **Level IV**). Infective mastitis is most commonly due to *Staphylococcus aureus* and noninfective mastitis is equally common. There is insufficient evidence to confirm the efficacy of antibiotics in relieving symptoms, with only two trials meeting the inclusion criteria for analysis (Jahanfar 2013 **Level I** [Cochrane], 2 RCTs, n≈125).

10.1.5.3 Uterine pain

Uterine pain or "after pains" often worsen with increasing parity and are experienced by most multiparous women. Uterine contraction results from the release of oxytocin from the posterior pituitary gland, especially in response to breastfeeding. Lower abdominal pain may be mild to severe, accompanied by back pain and is described as throbbing, cramping and aching. Ergot alkaloids during the third stage of labour increase the requirement for analgesia for pain after birth due to persistent uterine contraction (RR 2.53; 95%CI 1.34 to 4.78), but also decreases mean blood loss and the incidence of postpartum haemorrhage compared with no uterotonic medicines (Liabsuetrakul 2007 **Level I** [Cochrane], 6 RCTs, n=3,941).

NSAIDs are superior to placebo (3 RCTs, n=204) and paracetamol (1 RCT, n=48) for the relief of "after pains" following vaginal birth (Deussen 2011 **Level I** [Cochrane], 18 RCTs, n=1,498).

Paracetamol is no better than placebo (1 RCT, n=48). Data on opioids are contradictory and do not permit an assessment of their efficacy for this indication.

High-intensity TENS was more effective than low-intensity TENS for treating postpartum uterine pain but also produced more local discomfort (Olsen 2007 **Level III-2**).

Key messages

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I** [Cochrane Review]).
2. Continuous suturing of all layers compared with interrupted suturing for repair of episiotomy or second-degree tears reduces perineal pain and analgesic use in the postpartum period (**N**) (**Level I** [Cochrane Review]).
3. Paracetamol and NSAIDs are effective in treating perineal pain after childbirth (**S**) (**Level I** [Cochrane Review]).
4. NSAIDs, but not paracetamol, are effective in treating pain from uterine cramping after vaginal birth (**Q**) (**Level I** [Cochrane Review]).
5. There is limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**U**) (**Level I** [Cochrane Review]).
7. There is insufficient evidence to recommend any specific treatments for nipple pain and breast engorgement (**W**) (**Level I** [Cochrane Review]).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Pain after childbirth requires appropriate treatment as it coincides with new emotional, physical and learning demands and may trigger postnatal depression (**U**).

☑ Management of breast and nipple pain should target the cause (**U**).

10.2 The older patient

The need to manage acute pain in the older patients is becoming more common as the population ages. Advances in anaesthetic and surgical techniques mean that increasingly older patients, including patients >100 y old (Konttinen 2006 **Level IV**), are undergoing major surgery (Kojima 2006 **Level IV**). Medical conditions are more likely in older people and may lead to acute pain; these include acute exacerbations of arthritis, osteoporotic fractures of the spine, cancer and also pain from other acute medical conditions including ischaemic heart disease, herpes zoster and peripheral vascular disease. Furthermore, older adults are more likely to undergo potentially painful medical procedures, and experience trauma as well as surgery.

Factors that can combine to make effective control of acute pain in the older person more difficult than in younger patients include: a higher prevalence of coexistent diseases and concurrent medications, which increases the risk of drug-drug and disease-drug interactions; age-related changes in physiology, pharmacodynamics and pharmacokinetics; altered responses to pain; and difficulties with assessment of pain, including problems related to cognitive impairment. Furthermore, the elderly may fail to report pain because they think it is a normal part of ageing, or they acquiesce to family members/medical staff or have fears about intervention or the unwanted effects of analgesics, especially opioids (Fine 2012 **GL**). Sensory impairment and social isolation may further impair the effective treatment of pain.

10.2.1 Physiology and perception of pain

Several reviews summarise the age-related changes that occur in the neurophysiology of nociception and pain perception (Gibson 2004 **NR**; Gagliese 2005 **Level III-2**; Farrell 2012 **NR**; Yezierski 2012 **NR BS**). Compared with a younger person's nervous system, there are extensive changes in the older person's structure, neurochemistry and function of both peripheral and

central nervous systems, including neurochemical deterioration of the opioid and serotonergic systems. Therefore there may be changes in nociceptive processing, including impairment of pain-inhibitory systems.

10.2.1.1 Neurophysiological changes

In the peripheral nervous system there is a decrease in the function and density of both myelinated and, particularly, unmyelinated peripheral nerve fibres (Kemp 2014 **EH**). There are also increased number of fibres with damage or degeneration and conduction velocity slowing. In rats, reductions in substance P, CGRP and somatostatin levels have been reported (Yezierski 2012 **NR BS**). Similar structural and neurochemical changes have been noted in the CNS. In older humans, there are sensory neuron degenerative changes and loss of myelin in the dorsal horn of the spinal cord as well as reductions in substance P, CGRP and somatostatin levels. Age-related loss of neurons and dendritic connections is seen in the human brain, particularly in the cerebral cortex; including those areas involved in nociceptive processing. The synthesis, axonal transport and receptor binding of neurotransmitters also change. Opioid-receptor density is decreased in the brain but not in the spinal cord, and there may be decreases in endogenous opioids. However, the functional consequences of such age-related changes remain a subject of debate. Functional MRI studies show more age-related similarities than differences in the magnitude of activation in response to acute noxious mechanical stimulation (Cole 2010 **EH**; Farrell 2012 **NR**). A specific difference that has been identified was reduced activation in the middle insular cortex and primary somatosensory cortex in response to noxious heat (Tseng 2013 **EH**).

Variations in pain perception are best determined in controlled situations where the severity of the noxious stimulus is standardised, and psychopathology (such as impaired cognitive function or mood) is absent (Kunz 2009 **EH**; Radinovic 2014 **Level IV**). Assessment of variation can be done with experimental pain stimuli or, to a lesser extent, with standard medical procedures such as venipuncture and wound dressings.

Studies of the effects of experimental pain stimuli (brief noxious stimuli without tissue injury) on pain thresholds are conflicting and results depend on the type of stimulus used. Psychophysical studies using experimental pain provide limited evidence for a modest increase in pain threshold (ie a reduced sensitivity to mild pain) with advancing age, particularly for thermal pain stimuli (Gibson 2004 **NR**; Tseng 2013 **EH**) and radiant more than contact heat (Lautenbacher 2012 **Level III-2 SR EH**, 25 studies, n= 13,580). The results for electrical, mechanical and ischaemic stimuli are equivocal, with reports of no change or even decreased pain thresholds in adults of advanced age. Of note, there were racial differences similar to those found in younger patients and increased decrement in the lower extremities (Riley 2014 **Level III-3 EH**). The applicability of these experimental observations to pain occurring with tissue injury remains uncertain. These findings could indicate some deficit in the early warning function of pain with reduced capacity to identify a painful stimulus and that it might cause tissue injury (Gibson 2006 **NR**; Hadjistavropoulos 2014 **NR**). For example, in patients with an acute myocardial infarction, greater intensity of chest pain was inversely correlated with lower pain threshold (Granot 2007 **Level III-3 EH**); presentation and treatment of those patients with less pain may therefore be delayed.

Studies looking at age-related changes in pain tolerance are limited, but in general, using a variety of experimental pain stimuli, there is a reduced ability in older people to endure or tolerate intense pain (Gibson 2003 **NR EH;** Farrell 2012 **NR**). Lessened ability to tolerate pain could mean that severe pain may have a greater impact on the more vulnerable older person.

Also, in the elderly, there are significantly smaller increases in pain thresholds following prolonged noxious stimulation and a prolonged recovery from hyperalgesia (Zheng 2000 **EH**; Zheng 2009 **EH**; Gibson 2006 **EH**). Using experimental pain stimuli in the elderly, there is a lower threshold for temporal summation (Gibson 2004 **EH**; Lautenbacher 2012 **Level III-2 SR EH**, 25 studies, n= 13,580); older subjects showed temporal summation with trains of brief electrical stimuli at all stimulation frequencies, unlike younger subjects where this was not seen at the lower frequencies. Temporal summation of thermal stimuli was increased in the older compared with younger subjects. The summation was more prolonged but otherwise

temporal summation of pressure pain showed no age-related effects. After topical application of capsaicin, the magnitude and duration of primary hyperalgesia was similar on both older and younger subjects but secondary hyperalgesia (tenderness) resolved more slowly in older people. The proposed underlying mechanism for these findings is impaired descending inhibitory mechanisms and reduced capacity to down-regulate after sensitisation thereby leading to prolonged recovery in the older person (Gagliese 2005 **NR**).

10.2.1.2 Clinical implications

Several clinical reports (summarised in Gibson 2003 **NR**; Pickering 2005 **NR**; Cole 2006 **Level III-3 EH**) suggest that pain symptoms and presentation may change in the older patient; pain becomes a less frequent or a less severe symptom of a variety of acute medical conditions. Examples of differences in reports of acute pain are commonly related to abdominal pain (eg associated with infection, peptic ulcer, cholecystitis, or intestinal obstruction) or chest pain (eg myocardial ischaemia or infarction or pneumonia) and are in general agreement with the experimental finding of increased pain thresholds in the older person.

Compared with the younger adult with the same clinical condition, the older adult may report less pain or atypical pain, report it later or report no pain at all (Pickering 2005 **NR**). Examples in older patients include the absence of right upper quadrant or epigastric pain in 85% with cholecystitis, in 30% of those with peptic ulcer disease and up to 90% with pancreatitis, while in those with advanced peritonitis, pain may be a symptom in only 55%. Chest pain is absent, or pain is atypical, in up to 33% of older patients with acute myocardial infarction and 50% with unstable angina.

Pain intensity after surgery may also be less. Older patients, matched for surgical procedure, reported less pain in the postoperative period: pain intensity decreased by 10–20% each decade after 60 y of age (Thomas 1998 **Level III-2**). Older men undergoing prostatectomy reported less pain on a present pain intensity scale and MPQ (but not a VAS) in the immediate postoperative period and used less PCA opioid than younger men undergoing the same procedure (Gagliese 2003 **Level III-2**). In a study of pain following IV cannula placement (a relatively standardised pain stimulus), older patients reported significantly less pain than younger patients (WMD -15/100; 95%CI -26 to -4) (Li 2001 **Level III-2**). An observational study of patients (n=5,957) undergoing painful procedures (wound care, drain and femoral sheath removal, tracheal suctioning, turning, and central line insertion) found there was no age-related difference in pain scores (NRS) between the young and the elderly (>65 y), however the younger patients reported more pain-related distress (Stotts 2007 **Level III-2**).

10.2.2 Assessment of pain

10.2.2.1 Cognitive impairment

Even though cognitively impaired patients are just as likely as cognitively intact patients of the same age to have painful conditions and illnesses, the number of pain complaints and the reported pain intensity decreases with increasing cognitive impairment (Lukas 2012 **NR**; Hadjistavropoulos 2014 **NR**; Radinovic 2014 **Level IV**). Reasons for this could include diminished memory, impairment of capacity to report, or it could be that less pain is experienced.

Dementia

Studies in patients with dementia suggest that they may not experience less pain (Hadjistavropoulos 2014 **NR**; Monroe 2014 **Level III-2**). Functional MRI responses following mechanical pressure stimulation showed no evidence of diminished pain-related activity in patients with Alzheimer's disease compared with age-matched controls, indicating that pain perception and processing were not diminished in these patients (Cole 2006 **Level III-2**). Moreover in those with dementia, facial expressions are increased in response to controlled levels of noxious stimulation (Kunz 2007 **Level III-2 EH**; Kunz 2009 **Level III-2 EH**) and immediately following a uniform clinical pain stimulus, such as venipuncture, pain on mobilisation (Hadjistavropoulos 2014 **NR**) or dental local anaesthetic injection (Hsu 2007 **Level III-2**). The increased facial expressions in response to pain could suggest an increased sensitivity to pain in persons with dementia (Kunz 2007 **Level III-2**) or that facial actions represent a different

aspect of the pain experience: a reflexive, automatic response which may be disinhibited in persons with cognitive impairment. In support of this conclusion, persons with dementia have also been found to display enhanced nociceptive flexion withdrawal reflexes (RIII) (Kunz 2007 **Level III-2 EH**; Kunz 2009 **Level III-2 EH**). In contrast, autonomic responses typically associated with the onset of acute pain (ie increased heart rate, blood pressure, galvanic skin resistance, breathing) appear to be blunted in persons with dementia (Plooij 2011 **Level III-2 SR EH,** 6 studies, n=395). Much of the typical elevation in autonomic indices occurs in anticipation of an impending painful stimulus, yet this anticipatory response is lacking in those with dementia (2 studies, n=135). Group differences in the poststimulus autonomic response, particularly in heart rate change, are less obvious (1 study, n=95) or unchanged (2 studies, n=103) including to stronger intensity pain (1 study, n=40).

Another study assessed the placebo component of analgesic therapies by looking at the effect of both "overtly applied" and "covertly applied" local anaesthetic on pain after venipuncture in patients with Alzheimer's disease (Benedetti 2006 **Level III-2**). The patients with reduced Frontal Assessment Battery scores (a measure of frontal executive function) had a reduced placebo component to their pain relief and dose increases were required to produce adequate analgesia (Benedetti 2006).

Undertreatment of acute pain is more likely to occur in cognitively impaired patients (Feldt 1998 **Level III-2**; Forster 2000 **Level III-2**; Morrison 2000 **Level III-2**), although this may be improving (Paulson 2014 **Level III-2**).

Delirium

A common form of acute cognitive impairment in the older patient is delirium; which is associated with increased postoperative morbidity, impaired postoperative rehabilitation and prolonged hospital stay (Fong 2006 **Level III-2 SR**, 7 RCTs and 3 studies, n= 1,269; Kalish 2014 **NR**). Delirium is more prevalent during acute illnesses in the older person and occurs in up to 80% of older postoperative patients, depending on the type of surgery. A systematic review confirms that POCD is relatively common after noncardiac surgery and that the older patient is particularly at risk (Newman 2007 **Level III-2 SR**, 46 studies, n=2,795). This is confirmed by subsequent large studies across a range of procedures (Evered 2011 **Level III-2**); the incidence at 3 mth was independent of the nature or the type of procedure or anaesthetic.

Risk factors associated with the development of delirium include old age, infection, pre-existing dementia, pre-existing depression and cognitive impairment, hypoxaemia and reduced cerebral oxygen saturation (Casati 2007 **Level IV**), anaemia, drug withdrawal (eg alcohol, benzodiazepines), fluid and electrolyte imbalance and unrelieved pain (Morimoto 2009 **Level IV**; Saczynski 2012 **Level III-2;** Lukas 2013 **Level IV**; Kalish 2014 **NR**). Medications are also often implicated, for example, those with central anticholinergic activity (eg atropine, TCAs, major tranquilisers, some antiemetics), benzodiazepines, opioids, ketamine, oral hypoglycaemics, NSAIDs and anticonvulsants. Delirium is associated with a larger drop in postoperative cognitive function (at d 1 and 28) and fewer patients with delirium return to baseline at 6 mth following CABG surgery (Saczynski 2012 **Level III-2**).

Delirium presents clinically in both hyperactive and hypoactive forms, of which the latter is more common (Rudolph 2011 **NR**). Although restlessness and agitation (hyperactive delirium) may trigger assessment, which identifies a trigger associated with pain, the more frequent hypoactive delirium may mask pain, especially in the elderly.

10.2.2.2 Measurement of pain

Patient self-report measures of pain

Unidimensional measures of pain intensity are more commonly used to quantify pain in the acute pain setting than multidimensional measures (see also Section 2.2). Unidimensional measures used in younger adult populations, and which have been shown to be appropriate for use in the older patient, include the VNRS, FPS, VDS alone and with calorimetry (Iowa pain thermometer) and the NRS, with equivocal support for use of the VAS (Hadjistavropoulos 2014 **NR;** Paulson 2014 **NR**). Completion rate is high for VNRS in the older patient but this

decreases with increasing cognitive impairment. Several studies confirm that VDS is often the preferred tool and use of familiar words such as "none, slight, mild, moderate, severe and extreme" is felt to be the most reliable in the older patient, including those with mild to moderate cognitive impairment. Trialling of different self-assessment scales may be warranted including in those with severe impairment and the patients may need more time to understand and respond to questions regarding pain. Immediate reports of present pain may be reasonably accurate and as valid as those of cognitively intact patients but recall of past pain is less likely to be as reliable. Further comparative studies in the elderly include patients with fractured hips (Leino 2011 **Level IV**) and after cardiac surgery (Pesonen 2008 **Level IV**), where VAS was also the least reliable and the VDS and Red Wedge Scale were most applicable.

Other measures of pain

Assessment of pain in noncommunicative patients is more difficult. Behaviours such as restlessness, frowning and grimacing or sounds such as grunting or groaning have been used in attempts to assess pain. In cognitively intact adults, some of these behaviours have been shown to correlate with patient self-report of pain (Bell 1997 **NR**). However, they may not always be valid indicators of pain in the nonverbal adult (Farrell 1996 **NR**) and can be difficult to interpret (Herr 2006 **NR**; Herr 2011 **NR**).

There is some argument that observations of facial expressions and sounds may be accurate measures of the presence of pain but not pain intensity in patients with advanced dementia (Herr 2006 **NR**), although this position has been challenged in recent studies (Lukas 2013 **Level III-2**).

More than 20 different observational pain assessment scales have been developed and used in patients with varying degrees of dementia (Herr 2011 **NR**). Scales with the strongest evidence of utility include: FPSs, Abbey Pain Scale, Pain Assessment in Advanced Dementia (a simple, reliable and validated five-item observational tool), Pain Assessment Checklist for Seniors with Limited Ability to Communicate and Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale.

For more detailed and critical review of pain-assessment tools for use with nonverbal adults see (Herr 2006 **NR**; Zwakhalen 2006 **NR**; Herr 2011 **NR**, Hadjistavropoulos 2014 **NR**).

10.2.3 Pharmacokinetic and pharmacodynamic changes

The changes in physiology and effects on pharmacokinetics and pharmacodynamics in older people, and consequent alterations that might be required in some drug regimens are summarised in Table 10.4. The information in this table centres on opioids, given their widespread use. These changes have variable prevalence and are generally attributable to ageing alone but may be compounded by the higher incidence of degenerative and other concurrent diseases in older people.

Assessment of the pharmacodynamic changes associated with ageing is difficult. When such studies have been done with opioids, most have used a surrogate measure of effect other than clinical pain relief. For example, in studying the effects of fentanyl and alfentanil on the EEG, the pharmacokinetics were shown to be unaffected by age, but the sensitivity of the brain to these opioids was increased by 50% in the older person (Scott 1987 **EH**). Whether this can be attributed to changes in the number or function of opioid receptors in the CNS (in older rats there are fewer mu- and kappa-opioid receptors) (Vuyk 2003 **NR**; Yezierski 2012 **NR BS**) or it is due to an increased penetration of opioids into the CNS is unclear. Some of the changes that may lead to increased drug sensitivity in the older patient are discussed below; see Section 10.2.2.

Table 10.4 Physiological changes in older people, resulting changes of pharmacokinetic variables and consequences for pharmacological treatment

Body system or process	Parameter and changes	Resulting pharmacokinetic/ pharmacodynamic changes	Changes in pharmacological treatment
Body composition	body fat ↑ 10–50%	for lipophilic medicines ↑ V_d ↑$t_{1/2}$	calculate doses of lipophilic medicines on total body weight
	muscle ↓20%	no relevant effect	none
	body water ↓10%	for hydrophilic medicines ↓ V_d	calculate doses of hydrophilic medicines based on lean body weight
	plasma volume↔	None	none
Liver	Liver size ↓25–40%	↑ bioavailability of oral medicines ↓ hepatic CL of high extraction medicines (eg morphine) ↓ hepatic CL of some low extraction medicines (eg ibuprofen	↔ IV bolus dose ↓ oral dose of some medicines ↓ maintenance doses of some medicines (eg morphine)
	Hepatic blood flow ↓25–40%		
	Phase 1 metabolism ↓25%		
Kidney	Kidney size ↓30%	↓ clearance of renally excreted medicines ↔ effect on opioids, but often ↓ clearance of metabolites (eg morphine [M6G], tramadol [M1])	↓ maintenance dose of renally excreted medicine (alpha-2-delta ligands) or medicines with renally excreted metabolites (morphine, tramadol, pethidine) monitor for accumulation of renally excreted medicines
	Renal blood flow ↓10% / decade		
	GFR ↓30–50%		
	Creatinine clearance (Cl) ↓50–70%		
Heart	Cardiac output ↔ or ↓ to 20%	↓ central compartment volume ↑ peak concentration after IV bolus	↓ initial IV bolus doses ↓ IV injection speed
CNS	Cerebral blood flow, volume and metabolism ↓ 20%	↓ distribution to the CNS ↓ apparent volume in the CNS	minimal clinically relevant changes for most drugs, but: ↓ bolus doses of medicines during titration ↓ maintenance doses of some medicines
	Blood brain barrier transport ↓ (medicine specific effect)	↑ apparent volume in the CNS ↑ apparent increase in CNS sensitivity	

Body system or process	Parameter and changes	Resulting pharmacokinetic/ pharmacodynamic changes	Changes in pharmacological treatment
Absorption of Medicines	oral and transmucosal absorption	no relevant effect of ageing	however oral bioavailability of some medicines ↑ due to ↓ first-pass effect
	IM absorption	↔	none
	SC absorption	↔	none
	transdermal absorption	↓ hydrophilic medicines ↔ lipophilic medicines	no clinically relevant effect for TD opioids
Protein binding of medicines	Plasma albumin ↓ 20% Alpha-1-acid glycoprotein ↑ 30–50%	↑ unbound fraction of medicines ↑ cerebral uptake of medicines ↔ hepatic clearance of high extraction medicines ↑ hepatic clearance of low extraction medicines	possibly changed clearance and oral bioavailability possibly changed cerebral effects

Source: Modified and adapted from Macintyre 2008 and Coldrey 2011.

10.2.4 Drugs used in the management of acute pain in older people

In general there is limited evidence about the use of analgesic medications in older patients; as because of their age, comorbidities or concurrent medications, they are often specifically excluded from clinical trials. However, these factors will need to be taken into consideration when a choice of analgesic regimen is made.

While this and the following section concentrate on the use of analgesic drugs and techniques in the older patient, physical and psychological strategies should also be employed as with other patients (Makris 2014 **NR**; Abdulla 2013 **GL**).

10.2.4.1 Paracetamol, nonselective NSAIDs and coxibs

Paracetamol is recommended as a first-line therapy in older adults for both mild to moderate pain (American Geriatrics Society 2009 **GL**; O'Neil 2012 **GL**; Abdulla 2013 **GL**; Makris 2014 **NR**). There is inconsistent evidence on the effect of ageing and frailty on clearance of paracetamol, with earlier authors recommending no dose adjustment (Divoll 1982 **PK**; Miners 1988 **PK**; Bannwarth 2001 **PK**) but more recent reviews recommending that dose adjustment is prudent (McLachlan 2011 **NR**; Mitchell 2011b **NR**). In a small cohort comparison (n=71), spot paracetamol plasma concentrations on d 5 of 3–4 g/d therapy were in the therapeutic range in 21 of 23 older and frail older patients and elevated in 2 (but less than twice therapeutic range) (Mitchell 2011a **Level III-3**). Plasma alanine aminotransferase levels after 5 d were not elevated in any of the older and frail participants.

Older patients are more likely to suffer gastric and renal adverse effects following administration of nsNSAIDs (Abdulla 2013 **GL**) and may also be more likely to develop cognitive dysfunction (Pilotto 2003 **Level III-2**; Peura 2004 **NR**; Juhlin 2005 **Level II**, n=14, JS 4) (see also Section 4.2). In elderly (age >65 y) medical inpatients, use of nsNSAIDs was a significant risk factor for renal function deterioration occurring in 6.1% of patients exposed; other risk factors were loop diuretics, hypernatraemia and low serum albumin levels (Burkhardt 2005 **Level IV**, n=343). Use of oral nsNSAIDs often does not align with current clinical guidelines in the older population and particularly regarding the prolonged duration of use and lack of PPI coadministration (Gnjidic 2014 **Level III-2**).

NSAIDs should be used with care in elderly patients given their cardiovascular, gastrointestinal and renal adverse effects, and patients should be monitored closely (O'Neil 2012 **GL**; Fine 2004 **GL**; Makris 2014 **NR**). For this reason, opioids are sometimes used in preference to NSAIDs. A cohort study of elderly patients (n=12,840) with arthritis (mean age 80 y) started on nsNSAIDs, coxibs or opioids challenge the assumption that opioids are safer in this population (Solomon 2010 **Level III-2**). This study found increased rates of fracture, hospital admission and all-cause mortality in the opioid cohort and similar or higher rates of cardiovascular, renal and gastrointestinal adverse effects. Overall the nsNSAID cohort appeared to have the lowest risk for adverse effects.

Coxibs have a significantly lower incidence of upper gastrointestinal complications (Jarupongprapa 2013 **Level I**, 9 RCTs, n=7,616) and have no antiplatelet effects (Munsterhjelm 2006 **Level II EH**, n=18, JS 4), which might be of some advantage in the older patient. The risk of other adverse effects, including effects on renal function (Zhang 2006 **Level I**, 114 RCTs, n=116,094), hypertension and exacerbation of cardiac failure may be lower too, at least for celecoxib (see Section 4.3.2.1). Compared with paracetamol and placebo, only transient reduction of creatinine clearance was seen after 3 d treatment with parecoxib 40 mg/d in elderly patients undergoing major orthopaedic surgery (Koppert 2006 **Level II**, n=75, JS 5).

Use of both coxibs and nsNSAIDs (possibly apart from naproxen and celecoxib) can increase the risk of cardiovascular and cerebrovascular events (Trelle 2011 **Level I**, 31 RCTs, n=116,429) and regular use of nsNSAIDs may interfere with the clinical benefits of low-dose aspirin (for details see Section 4.2). Extra precautions are therefore required in older patients.

Topical nsNSAID agents may be a preferred route of administration (due to lower systemic levels and less gastrointestinal adverse effects) in older adults where there is appropriate and localised pain (Zacher 2008 **Level I**, 19 RCTs, n>3,000; Massey 2010 **Level I** [Cochrane] 47 RCTs, n=3,455; Klinge 2013 **Level I**, 6 RCTs, n=600; Makris 2014 **NR)** (see also Section 4.3.3.6).

10.2.4.2 Opioids and tramadol

Despite the age-related changes listed in Table 10.4, there may be few differences in the older patient in fentanyl (Scott 1987 **EH**), morphine, oxycodone (Villesen 2007 **PK**) and buprenorphine pharmacokinetics (Kress 2009 **NR**).

After oral administration, the bioavailability of some drugs may be increased, leading to relatively higher plasma concentrations (Mangoni 2004 **NR**; Gupta 2012 **NR**).

Opioid dose

Older patients require less opioid than younger patients to achieve the same degree of pain relief (Macintyre 1996 **Level IV**; Woodhouse 1997 **Level IV**; Gagliese 2000 **Level IV**; Upton 2006 **PK**); however, a large interpatient variability still exists and doses must be titrated to effect in all patients. The decrease is much greater than would be predicted by age-related alterations in physiology and seems to have a significant pharmacodynamic component (Macintyre 2008 **NR**; Gupta 2012 **NR**).

In the clinical setting, there is evidence of an age-related 2–4-fold decrease in morphine and fentanyl requirements (Macintyre 1996 **Level IV**; Woodhouse 1997 **Level IV**; Gagliese 2000 **Level IV**). The decrease is in agreement with previous findings that the sensitivity of the brain to fentanyl and alfentanil was increased by 50% in older people (Scott 1987 **EH**). It has been suggested that doses of fentanyl, sufentanil and alfentanil should be reduced by up to 50% in older patients (Shafer 1997 **NR**); reductions in the doses of other opioids are also advised (Macintyre 2008 **NR**). In general, patients aged 80 y should receive 50% of the opioid dose of a 40-y-old patient due to pharmacodynamic changes and increased sensitivity (Gupta 2012 **NR**).

In patients >75 y, the elimination half-life of tramadol is slightly prolonged (Scott 2000 **NR**); lower daily doses have been suggested (Barkin 2005 **NR**). Awareness and consideration of drug interactions in the elderly is necessary, particularly with the high incidence of polypharmacy and antidepressant use (Makris 2014 **NR**).

Opioid metabolites

Reduced renal function in the older patient could lead to a more rapid accumulation of active opioid metabolites (eg M6G, M3G, H3G, nordextropropoxyphene, norpethidine and M1) (see Section 4.1).

Adverse effects of opioids

The concern regarding respiratory depression in older people, especially those with respiratory disease, often leads to inadequate doses of opioid being given for the treatment of their pain. However, as with other patients, significant respiratory depression can generally be avoided if appropriate monitoring (in particular, of sedation) is in place (see Section 4.1).

The incidence of nausea/vomiting and pruritus in the postoperative period lessens with increasing age (Quinn 1994 **Level IV**). In older patients, IV PCA fentanyl may cause less postoperative cognitive dysfunction than morphine (Herrick 1996 **Level II**, n=96, JS 2). However, administration of an appropriate opioid medication is often associated with higher levels of cognitive function and undertreatment of postoperative pain with lower levels (Lynch 1998 **Level IV**; Morrison 2000 **Level III-2**, n=541). Pethidine was associated with a higher incidence of confusion compared with morphine (Adunsky 2002 **Level III-3**) and a variety of other opioids (Morrison 2003 **Level III-2**). Constipation is a common adverse effect of treatment with opioids and is a relevant consideration in older adults, many of whom already exhibit altered gastrointestinal function. Prophylactic management of constipation should be commenced whenever opioids are prescribed (Hunold 2013 **Level IV**; Makris 2014 **NR**).

10.2.4.3 Local anaesthetics

Age-related decreases in clearance of bupivacaine (Veering 1987 **Level III-2**; Veering 1991 **PK**) and ropivacaine (Simon 2006 **PK**) have been shown. Older patients may be more sensitive to the effects of local anaesthetic agents because of a slowing of conduction velocity in peripheral nerves and a decrease in the number of neurons in the spinal cord (Sadean 2003 **NR**). Localised neuropathic pain may be suitable for treatment with topical lignocaine (lidocaine) patch, in particular in older patients with increased comorbidities and polypharmacy, as systemic adverse effects are rare (Fine 2012 **GL**; Makris 2014 **NR**).

10.2.4.4 Ketamine

There are no good data on the need or otherwise to alter ketamine doses in the older patient. In aged animals, however, changes in the composition of the NMDA-receptor site and function have been reported (Clayton 2002 **BS**; Magnusson 2002 **BS**; Vuyk 2003 **NR**). Young and elderly rats, given the same dose of ketamine on a mg/kg basis showed similar EEG changes but these changes were quantitatively greater in the older rats (Fu 2008 **BS**). These data suggest that, apart from any pharmacokinetic changes, the older person may be more sensitive to the effects of ketamine and doses may need to be lower in this patient group.

10.2.4.5 Tricyclic antidepressants

Clearance of TCAs may decrease with increasing patient age and lower initial doses are recommended in older people (Ahmad 2002 **NR**).

Older people may be particularly prone to the adverse effects of TCAs (Ahmad 2002 **NR**; Fine 2004 **GL**; Abdulla 2013 **GL**) including sedation, confusion, orthostatic hypotension, dry mouth, constipation and urinary retention. Adverse effects appear to be most common with amitriptyline, and so nortriptyline may be preferred in this patient group (Ahmad 2002 **NR**; Argoff 2005 **NR**). Clinical conditions that may require TCAs to be administered with caution are more common in older people and include prostatic hypertrophy, narrow-angle glaucoma, cardiovascular disease and impaired liver function; ECG abnormalities may be a contraindication to the use of TCAs in older people (Ahmad 2002 **NR**).

Overall in elderly patients, TCAs should generally be avoided, as the use of medications with anticholinergic activity increases the risk of cognitive impairment and even mortality in this patient group (Fox 2011 **Level III-2**).

10.2.4.6 Serotonin–norepinephrine-reuptake inhibitors

Duloxetine has been shown to be effective and safe for the treatment of painful diabetic peripheral neuropathy in older patients (mean age 60 y) (Goldstein 2005 **Level II**, n=547, JS 4). Duloxetine was effective and well tolerated for the treatment of osteoarthritis pain of the knee in older patients (mean age 62 y) (Chappell 2009 **Level II**, n=231, JS 4).

10.2.4.7 Anticonvulsants

As liver and renal function decline with increasing age, elimination of anticonvulsants such as carbamazepine and gabapentin may be reduced (Ahmad 2002 **GL**). As with TCAs, initial doses should be lower than for younger patients and any increases in dose should be titrated slowly.

The "second generation" drugs such as gabapentinoids and topiramate may be less likely to result in adverse effects in the older patient (Argoff 2005 **NR**), although the relatively high frequency of adverse effects such as somnolence and dizziness with pregabalin may be a problem in this group of patients (Guay 2005 **NR**). However, pooled data from RCTs with pregabalin in neuropathic pain showed an increase of adverse effects only with increasing doses, but not related to the age of patients (Semel 2010 **Level III-3**, n=2,516: 65–74 y n=766, ≥75 y n=514). Efficacy was comparable to that in younger age groups; the lack of drug interactions may be an advantage in particular in older patients.

10.2.5 Patient-controlled analgesia

PCA is an effective method of pain relief in older people (Gagliese 2000 **Level III-2**; Mann 2000 **Level II**, n=70, JS 3; Mann 2003 **NR**). Compared with younger patients (mean age 39 y), older patients (mean age 67 y) self-administered less opioid than the younger group but there were no differences in pain relief achieved, satisfaction with pain relief and pain scores or concerns about pain relief, adverse drug effects, risks of addiction or use of the equipment (Gagliese 2000 **Level III-2**).

Compared with IM morphine analgesia in older men, PCA resulted in better pain relief, less confusion and fewer severe pulmonary complications (Egbert 1990 **Level II**, n=83, JS 2). In older patients, PCA also resulted in significantly lower pain scores compared with intermittent SC morphine injections (Keita 2003 **Level II**, n=40, JS 3).

10.2.6 Epidural analgesia

In the general patient population, epidural analgesia can provide the most effective pain relief of all analgesic therapies used in the postoperative setting (see Section 5.6). Epidural analgesia significantly reduces many of the complications that occur in the elderly after surgery (Popping 2014 **Level I** [PRISMA], 125 RCTs, n=9,044). Older patients given epidural PCA (using a mixture of bupivacaine and sufentanil) had lower pain scores at rest and movement, higher satisfaction scores, improved mental status and more rapid recovery of bowel function compared with those using IV PCA (Mann 2000 **Level II**, n=70, JS 3). After hip fracture surgery, epidural analgesia with bupivacaine and morphine also provided better pain relief both at rest and with movement but this did not lead to improved rehabilitation (Foss 2005 **Level II**, n=60, JS 5). Epidural analgesia, after colectomy for cancer in patients aged >65 y of age, may be associated with improved long-term survival (Cummings 2012 **Level III-2**, n=42,151). Patients having colectomy for cancer had better 5-y survival in the epidural group vs the nonepidural group (61 v 55%; HR 0.91; 95%CI 0.87 to 0.94). In a retrospective study, epidural analgesia was associated with reduced cancer recurrence in patients aged >64 y having colectomy (Gottschalk 2010 **Level III-2**). The postulated mechanism is reduced impairment of immune function in patients having epidural analgesia, although overall data are contradictory (see also Section 5.6.1.2).

Older patients are more likely to have ischaemic heart disease and in such patients coronary blood flow may be reduced rather than increased in response to sympathetic stimulation. In a study of patients (average age 67 y) with multivessel coronary artery disease, high (T2–T3) thoracic epidural analgesia using 0.5% bupivacaine instituted before CABG surgery was able to partly normalise myocardial blood flow in response to sympathetic stimulation (Nygard

2005 **Level III-2**). In a small trial of perioperative analgesic regimens initiated preoperatively for hip fracture repaired under spinal anaesthesia, older patients who had received epidural bupivacaine/fentanyl analgesia had significantly better postoperative pain relief than those who were given IM oxycodone; there was no difference in the number of patients who developed postoperative continuous ECG-detected ischaemia or hypoxia (Scheinin 2000 **Level II**, n=77, JS 3). However, the number of episodes and total duration of ischaemia in each patient was markedly greater in the oxycodone group.

Epidural morphine requirements decrease as patient age increases (Ready 1987 **Level IV**). However, a comparison of PCA epidural fentanyl in patients aged >65 y with those aged 20–64 y showed no difference in fentanyl requirements although pain relief on coughing (at 24 h) was better in the older patient group; there was no difference in the incidence of pruritus (Ishiyama 2007 **Level III-3**).

Age was also a determinant of the spread of local anaesthetic in the epidural space and the degree of motor blockade (Simon 2002 **Level III-2**; Simon 2004 **Level III-2**). Thus smaller volumes may be needed to cover the same number of dermatomes than in a younger patient. When the same volume of local anaesthetic was given, the concentration required to produce effective motor block decreased as patient age increased (Li 2006 **Level III-1**). Combinations of a local anaesthetic and opioid are commonly used for epidural analgesia, so it would seem reasonable to use lower infusion rates in older patients (Macintyre 2008 **NR**).

Older patients may be more susceptible to some of the adverse effects of epidural analgesia, including hypotension (Crawford 1996 **Level IV**; Simon 2002 **Level III-2**; Veering 2006 **NR**).

10.2.7 Intrathecal opioid analgesia

IT morphine using a variety of doses provided more effective pain relief after major surgery compared with other opioid analgesia, although the risk of respiratory depression and pruritus was greater (Meylan 2009 **Level I**, 27 RCTs, n=645).

With neuraxial opioids, advanced patient age is considered by some to be a risk factor for respiratory depression and it has been suggested that patients >70 y be monitored in an ICU setting (Gwirtz 1999 **Level IV**). However, others report that older patients (average age 69 y) given up to 200 mcg IT morphine at the time of spinal anaesthesia for peripheral vascular and other surgery have been safely nursed on general wards by nursing staff who have received additional education and managed by an APS according to strict guidelines (Lim 2006 **Level IV**).

The optimal dose of IT morphine for older patients remains unknown. The evidence for the "best" dose is provided by data from small trials and remains inconsistent. IT morphine doses of 200 mcg given in addition to general anaesthesia in older patients (average age 70 y) undergoing abdominal aortic surgery led to better postoperative analgesia and reduced postoperative analgesia requirements compared with those given general anaesthesia only (Blay 2006 **Level II**, n=30, JS 4). No conclusion could be made about adverse effects, as total patient numbers were small. A comparison of three doses of IT morphine (50 mcg, 100 mcg and 200 mcg) given to older patients after hip surgery concluded that the 100 mcg dose provided the best balance between good pain relief and pruritus (Murphy 2003 **Level II**, n=60, JS 4). There was no difference seen in the incidences of nausea and vomiting or respiratory depression.

Use of IT morphine 300 mcg in addition to IV PCA morphine in elderly patients led to better pain relief and PCA morphine requirements compared with PCA morphine alone (Beaussier 2006 **Level II**, n=59, JS 5). However sedation was increased and there were no differences in time to ambulation, duration of hospital stay or incidence of confusion.

10.2.8 Other regional analgesia

Advantages of regional block in older patients include improved pain relief and reduction of adverse effects of opioids (Halaszynski 2009 **NR**). After fixation of a hip fracture, those who received patient-controlled femoral nerve analgesia, in addition to regular paracetamol and metamizol, were less likely to develop postoperative delirium, were able to sit at the bedside

at an earlier stage, and required no SC morphine compared with those given paracetamol and metamizol only, 28% of whom required additional morphine analgesia (Rosario 2008 **Level III-3**).

The duration of action of sciatic nerve (Hanks 2006 **Level III-2**) and brachial plexus blocks (Paqueron 2002 **Level III-2**) is prolonged in the older patient.

In older (>65 y) patients undergoing urological surgery via a flank incision, PVB of the lumbar plexus using either ropivacaine or bupivacaine has been shown to provide good analgesia with no changes in the patients' heart rate or blood pressure (Akin 2005 **Level II**, n=60, JS 1).

Unlike epidural analgesia, age did not influence the spread of bupivacaine in the thoracic paravertebral space (Cheema 2003 **Level III-2**).

Key messages

1. Topical nsNSAIDs for localised pain provide effective analgesia (**S**) (**Level I** [Cochrane Review] with lower plasma concentrations and fewer gastrointestinal adverse effects than oral nsNSAIDs (**S**) (**Level I**); this may improve safety in the elderly.
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).
3. Postoperative cognitive dysfunction is relatively common after surgery and the older patient is particularly at risk (**N**) (**Level III-2 SR**).
4. Experimental pain thresholds to thermal stimuli are modestly increased in older people (**W**) (**Level III-2 SR**).
5. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
6. Common unidimensional self-report measures of pain can be used in the older patient in the acute pain setting; in the clinical setting, the verbal descriptor and numerical rating scales are preferred (**S**) (**Level III-2**).
7. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**U**) (**Level III-2**).
8. The use of nsNSAIDs and coxibs in older people requires caution, although use of opioids may result in more complications (**Q**) (**Level III-2**); paracetamol is the preferred nonopioid analgesic (**S**) (**Level III-2**).
9. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
10. The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany ageing than to the changes in pharmacokinetics (**S**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ The assessment of pain and evaluation of pain relief therapies in the older patient may present problems, arising from differences in reporting, cognitive impairment and difficulties in measurement (**U**).
- ☑ Measures of present pain may be more reliable than past pain, especially in patients with some cognitive impairment (**U**).
- ☑ The physiological changes associated with ageing are progressive. While the rate of change can vary markedly between individuals and is related to frailty, these changes may decrease the dose (maintenance and/or bolus) of drug required for pain relief and may lead to increased accumulation of active metabolites (**U**).

10.3 Culturally responsive care for Culturally and Linguistically Diverse patients

Policy changes during the last few decades have resulted in a growth in the cultural, linguistic and religious diversity of the Australian community reflecting a plethora of migrant communities from Asia and other parts of the globe; a clear shift from early migrant communities predominantly of European background. The 2011 Census tells us that about 46% of Australians were born overseas or have at least one parent born overseas and 18.2% speak a language other than English with slight variations across the states (ABS 2012). Our Aboriginal and Torres Strait Islander community currently comprises 2.5% of the total population. The five most common languages spoken at home (other than English) were Mandarin (1.7%), Italian (1.5%), Arabic (1.4%), Cantonese (1.3%) and Greek (1.3%). The most common non-Christian religions in 2011 were Buddhism (2.5% of the population), Islam (2.2%) and Hinduism (1.3%).

Australia is not alone in its growing cultural, linguistic and religious diversity. Economic globalisation and current world events are compelling many communities to seek a home elsewhere. This facilitates an ever-growing migration, which has a direct impact on the cultural diaspora of many countries.

Culture, language and religious convictions have an impact on the clinical encounter, driving a need to understand different cultures when considering pain assessment and management. This extends beyond the language spoken, because an individual's culture, faith and migration history influences their linguistic expression, metaphorical language, beliefs, attitude, framework of meaning, health literacy, expectations, perception, methods of communication, norms of behaviour and pain relief preferences; as do the culture and attitudes of the health professional (Green 2003 **NR**; Davidhizar 2004 **NR**; Green 2010 **NR**; Incayawar 2010 **Level IV**; Rahim-Williams 2012 **Level III-2**; Campbell 2012 **NR**; Stewart 2014 **NR**; Pillay 2014 **NR**; Aziato 2015 **Level IV**).

Consequently, a health professional needs to consider their own cultural assumptions as well as address the cross-cultural elements that underpin their patients' individual responses. This is particularly the case when addressing verbal and nonverbal indicators of pain and being sensitive to stoic and emotive reactions to pain. Researchers have found significant cultural differences in self-care when managing pain which effect pain-relief seeking behaviour (Staton 2007 **Level III-2**; Merry 2011 **Level III-2**). Of note is that some cultural attitudes may limit pain-relief seeking behaviour and by extension an individual may appear stoic in managing pain. For example, it may be perceived by some patients as inappropriate to use a nurse's time to ask for analgesics or asking for pain relief may be seen as a weakness/shameful or an unnecessary interruption of his/her time (hence we often encounter the term of the "good" patient in this case; one who is compliant and respectful of the health professional). In fact, in a number of collectivist cultures the concept of patient autonomy is foreign and interdependence is preferred, which results in patients waiting for a health professional to offer pain relief as the latter is seen as the primary medical decision maker (Green 2003 **NR**, Pillay 2014 **NR**; Katz 2011 **Level III-2**). Health literacy influences a patient's ability to make sense of and act on medical advice (Chang 2007b **NR**; Monsivais 2007 **NR**; Adams 2009 **NR**; Singleton 2010 **NR**; Rothman 2010 **NR**; Magnusson 2011b **Level IV**; Shaw 2012 **Level IV**). A Turkish study demonstrates how a real fear of addiction in this culture impels patients to refuse pain relief (Bagcivan 2009 **Level IV**). Faith informs many patients to respond to pain positively without seeking pain relief. Hindu culture, for instance, understands pain and suffering to be a "just consequence and unfolding of karma" (Whitman 2007 **NR**). Confucianism and Buddhism emphasise the need for stoicism and fatalism, articulating that pain has the ability to strengthen the body, purify the soul and deepen the spirit (Chen 2008 **NR**). Stoicism and poor help-seeking skills were the result of self blame and guilt in a psychogeriatric nursing study involving older Irish adults (Cornally 2011 **Level IV**).

Communication problems caused by variable linguistic proficiency of either the patient or the health professional make it difficult to adequately help patients with interactive pain management (eg PCA use, requesting analgesia when needed), gain consent for invasive analgesic techniques (eg epidural or plexus catheters) and assess their degree of pain (Howe

1998 **Level IV**; Norris 2005 **Level IV**; Narayan 2010 **NR**). When language is an obstacle, care should be used when enlisting nonprofessional interpreters (eg family, friends or a bilingual staff member) to interpret, because their linguistic ability/accuracy in the other language has not been tested and may be incredibly variable. In addition, nonprofessional interpreters may inadvertently omit, edit and impose their own values when conveying the information to the clinician and the patient may be reluctant to openly express themselves in front of people they know.

Cultural differences in response to pain in both experimental and clinical settings have been reported. Early works on culture and pain argue that a person's pain experience is socialised and that therefore one will encounter cultural variances in language of distress when experiencing pain (Zborowski 1969 **NR**). A review of studies conducted between 1944 and 2011 using experimental pain stimuli found that cultural differences indeed influenced pain tolerance and threshold; although in the latter case effect sizes were only small to moderate across ethnic groups (Zatzick 1990 **NR**; Rahim-Williams 2012 **Level III-2 SR EH**, 25 studies, n unspecified). In a comparison of experimental pain sensitivity in three ethnic groups, African Americans and Hispanic Americans showed a greater sensitivity to laboratory-evoked pain compared with non-Hispanic white Americans (Rahim-Williams 2007 **Level III-2 EH**). Similarly, African American women were more sensitive to ischaemic pain than non-Hispanic white women (Klatzkin 2007 **Level III-2 EH**). In another experimental study, Asian Americans showed more sensitivity to pain than white Americans (Rowell 2011 **Level III-2 EH**). However, the implications of these results for the clinical setting are unclear.

A systematic review looked at the effect of patient race and ethnicity on pain assessment and management across a variety of clinical pain settings (Cintron 2006 **Level III-3 SR**, 35 studies, n unspecified). Marked disparities in effective pain treatment were reported; African Americans and Hispanics were less likely to receive opioid analgesics and were more likely to have their pain undertreated compared with Caucasian patients.

Differences have been reported in patients of different ethnic groups attending EDs and requiring analgesia. A study comparing opioid consumption differences after major abdominal surgery between Hong Kong patients and Caucasian patients in Australia found that the Chinese patients required less opioid but that their pain scores were higher (Konstantatos 2012 **Level III-2**).

A review of the treatment of pain in USA EDs showed that opioid prescribing for pain-related visits increased over the period 1993–2005 but that Caucasian patients with pain were more likely than African, Hispanic or Asian patients to receive an opioid; these differences did not diminish over time (Pletcher 2008 **Level III-3**). This disparity was reported for all types of pain visits, was more pronounced with increasing pain intensity and was unaffected by adjustment for pain severity.

Prescription of PCA and PCA prescription details also varied with patient ethnicity (Ng 1996 **Level III-3**; Salamonson 2005 **Level III-3**), although the actual self-administered doses of opioid were similar (Ng 1996 **Level IV**). After Caesarean delivery, significant ethnic group differences were noted in reported pain and morphine consumption; pain scores and morphine doses were higher in Indian patients compared with Chinese and Malay patients even after controlling for age, BMI and duration of operation (Tan 2008 **Level III-2**).

To ensure culturally responsive care, it is imperative that health professionals continually improve their cultural competence by increasing their cross-cultural knowledge, skills and self-awareness through cultural competency training (Kagawa-Singer 2003 **NR**; Khanna 2009 **Level III-3**; Betancourt 2010 **NR**; Lie 2011 **Level III-3 SR**, 7 studies, n unspecified) as well as request assistance of accredited medical interpreters to facilitate communication between health professionals and patients who have difficulty communicating in the main language (Norris 2005 **Level IV**) for the reasons noted above. Other strategies used to facilitate cross-cultural pain education and management include bilingual handouts describing varying methods of pain control and VAS scales with carefully chosen anchor terms or the use of faces scales (see Chapter 2); the NRS, for example has been translated and validated in many languages (Davidhizar 2004 **NR**). The South African cross-cultural adaptation of the PCS to include Afrikaans and Xhosa is another

good example of culturally sensitive care (Morris 2012 **Level IV**). A series of pain scales in a number of different languages has also been produced by the British Pain Society to assist in the assessment of people whose first language is not English and these are available on their website (BPS 2014). The only limitations with the latter are that they are not available in Italian (one of the largest cultural groups in Australia) and they assume a certain level of literacy of the patient. The WBPRS offers an alternative (although not available in Arabic) by providing a visual cue as well.

While there is some evidence of differences in pain reports and analgesic use in different cultures or ethnic groups, this should not be used to stereotype patients or promote assumptions about differences in assessment and management of pain or response to pain therapies. Rather, it should only be used to inform of possible cultural preferences. Provision of effective analgesia requires sensitivity to a patient's ethnicity, spirituality, cultural practices and beliefs, level of acculturation and their behavioural expression of pain. However, the large interindividual differences in pain behaviours and analgesic requirements that exist in any patient group mean that pain is best assessed and managed on an individual basis rather than on the basis of what might be "expected" in a patient from a particular cultural, ethnic or spiritual background (Im 2009 **Level IV**; Narayan 2010 **NR**; Shavers 2010 **NR**).

Key messages

1. Disparities in assessment, analgesic requirements and effective treatment of pain exist across ethnic groups (**N**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Cultural competence of health professionals supported by cultural competency training improves health outcomes for culturally and linguistically diverse patients (**N**).
- ☑ If language proficiency poses a communication barrier, an accredited medical interpreter should be included when conducting a pain assessment, to facilitate a positive outcome for the patient (**N**).
- ☑ Ethnic and cultural background of both health professional and patient can significantly affect the ability to assess and treat acute pain (**U**).
- ☑ Multilingual printed information and pain measurement scales are useful in managing patients from different cultural or ethnic backgrounds (**U**).
- ☑ Pain assessment and management should be done on an individual patient basis. Differences between ethnic and cultural groups should not be used to stereotype patients but should only be used to inform of possible cultural preferences (**N**).

10.3.1 Aboriginal and Torres Strait Islander peoples

High quality literature to inform acute pain management in Aboriginal and Torres Strait Islander peoples is limited; as a result, all findings should be interpreted with caution, as should any translation into clinical practice. Likewise, this field is undergoing a major shift in the research methodology used to obtain data from researcher-driven studies of the past to consultative practices used by contemporary authors. This will allow for improved translation of research findings in the future. As the literature reflects the heterogeneity of this population, findings may not be applicable to all Aboriginal peoples, however some key concepts can be derived.

Studies of pain experience have identified high levels of both prevalence and chronicity when assessing musculoskeletal complaints in New South Wales Aboriginal peoples (Vindigni 2004 **Level IV**) and long-term low-back pain in Central Australian peoples (Honeyman 1996 **Level IV**). Literature does however provide conflicting findings regarding the impact of pain on an individual, which ranged from pain causing minimal avoidance of activities (Honeyman 1996 **Level IV**) to chronic low-back pain affecting multiple domains of a participant's life (Lin 2012 **Level IV**). Explanations offered for these conflicting findings include that the study populations

were geographically and culturally different and that findings stemmed from the use of differing research methodology (Lin 2012 **Level IV**).

When considering pain behaviour of Central Australian and Northern Territory Aboriginal peoples, Fenwick's personal communication highlights "Given the opportunity, Indigenous people do demonstrate just as prominently and regularly unique pain behaviours and language, albeit differently from European culture" (Fenwick 2006 **NR**). This statement suggests that health professionals may be required to change their methods of assessment in order to identify pain expression in this population. Examples in the literature include study populations where pain is not vocally communicated in a manner "expected" by Western health professionals (Honeyman 1996 **Level IV**; Fenwick 2004 **Level IV**; McGrath 2006 **Level IV**). In some Central Australian peoples, "silent" pain performance may include the feigning of sleep, turning a head away or grimacing (Fenwick 2001 **Level IV**). Authors propose multiple reasons for this style of pain expression, ranging from respect for the health professional (Fenwick 2006 **NR**), a belief that the practitioner can "see within" the patient akin to the skills of a traditional healer (Fenwick 2004 **Level IV**), fear of the healthcare system (Fenwick 2001 **Level IV**) or due to fear of the cause of pain, which may include the breaking of cultural rules (Fenwick 2004 **Level IV**). Beliefs regarding the cause of pain should however be contrasted with the findings in regional and remote Western Australia, where the majority of participants with chronic low-back pain believed their pain resulted from problems in spinal anatomy or structure (Lin 2013 **Level IV**).

Other considerations influencing pain expression may include an individual's position within their community as highlighted in Northern Territory palliative care literature where men in "leadership roles within the community may not express pain for fear of appearing 'weak' " (McGrath 2006 **Level IV**).

10.3.1.1 Assessment

Problems with frequently used assessment tools have been identified in different studies. In a review of the impact of an APS on postoperative pain, 15.8% of the Aboriginal and Torres Strait Islander participants within a Queensland health service were unable to complete an NRS (Sartain 1999 **Level III-3**). However all participants were able to complete a VRS. One suggested explanation is that this may result from numerical nuances of some Australian Aboriginal languages (Fenwick 2006 **NR**). In these settings, use of a VRS may be preferable.

When non-Aboriginal nurses assessed postoperative pain in Central Australian Aboriginal women, both parties had differing expectations about the interaction (Fenwick 2004 **Level IV**). Non-Aboriginal nurses expected pain to be expressed in a manner familiar to their own culture (eg vocalising pain); likewise the Aboriginal women expected pain to be interpreted in a manner similar to traditional healers such as "to see within". Not appreciating individual differences in pain expression and expectations in the pain-assessment interaction may lead to inadequate pain management (Fenwick 2006 **NR**)

Communication difficulties between the patient and health professional were identified as another barrier to optimal pain management. A prospective study identified that anaesthetists were far more likely to be unsure if Aboriginal or Torres Strait Islander patients understood explanations when compared to non-Aboriginal patients (Howe 1998 **Level III-3**); subsequently leading to a higher rate of change to the patient's proposed treatment plan. This also raises concern regarding the ability for health professionals to ensure informed consent in the presence of communication difficulties.

The health professional may be required to modify their methods of history-taking within some populations in order to improve communication (Fenwick 2001 **Level IV**). Resources developed for pain management in Central Australian Aboriginal peoples highlight that asking two questions in one sentence or asking questions with obvious answers may cause confusion or result in no answer from the patient respectively. They recommend the health professional ask one question at a time and avoid asking "nonsense" questions where the answer is clear, such as asking about the presence of pain when the experience of pain is obvious. Likewise, health professionals should be aware that periods of silence may occur following asking

questions of some Australian Aboriginal peoples, possibly out of respect for the individual asking the question(Fenwick 2006 **NR;** Taylor 2014 **NR**).

Additional options offered by the literature to address barriers to optimal pain management include

- seeking the assistance of caretakers in assessment of pain (Fenwick 2006 **NR**);
- using a conversational style of history taking (Fenwick 2006 **NR**; Taylor 2014 **NR**; Lin 2013 **Level IV**);
- developing trust (Fenwick 2006 **NR**; McGrath 2006 **Level IV**);
- providing support and giving information (McGrath 2006 **Level IV**);
- seeking the assistance of an Aboriginal health worker or interpreter to assist in the bilateral communication between patient and health care team (Howe 1998 **Level III-3;** Taylor 2014 **NR**).

10.3.1.2 Treatment

Higher levels of medical comorbidities such as renal failure were identified within the Aboriginal population (Howe 1998 **Level III-3** ; AIHW 2011 **Level IV**). These comorbidities may influence analgesic choice as reflected within other chapters.

Key messages

1. The verbal descriptor scale may be a better choice of pain measurement tool than verbal numerical rating scales in Aboriginal and Torres Strait Islander peoples (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander peoples and may influence the choice of analgesic agent (**U**) (**Level IV**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

☑ Heterogeneity between differing populations of Aboriginal peoples may require tailoring of the service delivered to the population being serviced (**N**).

☑ Pain expression in Aboriginal and Torres Strait Islander peoples may not reflect that which is expected by the health professional's cultural background. This places the onus on the health professional to understand nuances of pain expression and beliefs within such populations (**N**).

10.3.2 Māori peoples and pain

Māori peoples make up 15% and Pacific Islanders 7% of the New Zealand population (New Zealand Statistics 2006). Cultural factors play a role in pain experiences in terms of a person's pain expression, threshold and tolerance (McGavock 2012 **NR**; Davidhizar 2004 **NR**) and also influence interaction with health professionals and adherence to advice provided (Magnusson 2011b **Level IV**). Māori views on health and healing and the care of Māori people who are in pain are different to the biomedical views prevalent in Western culture (McGavock 2012 **NR**). Māori perceive pain as a multidimensional experience affecting them physiologically, psychologically and socially (Magnusson 2011b **Level IV**). For example, in the Te Whare Tapa Whā model, health is seen as the interaction between te taha tinana (physical health), te taha hinengaro (mental health), te taha wairua (spirituality) and te taha whānau (family) (Durie 1985 **NR**; Pitama 2011 **NR**). Commonly used and widely accepted descriptors and phrases relating to pain and established pain measures are appropriate to use when assessing Māori patients (Magnusson 2011a **Level IV**; Pitama 2011 **NR**).

Little has been published about Māori perspectives on pain (Magnusson 2011b **Level IV**). Quantitative research of Māori health has covered experimental acute pain (Azariah 1984 **Level III-2**; Mahmoud 2006 **Level IV**), pain associated with giving birth (Nelson 2006 **Level IV**),

dental pain in children (Jamieson 2006 **Level III-2**) and prescription rates for analgesia (Crengle 2005 **Level III-2**).

Using the ischaemic arm test, Māoris were able to tolerate ischaemic pain for longer durations compared to their European counterparts (n=60) (Azariah 1984 **Level III-2**).

After accounting for various behavioural and material factors, Māori children were more likely to experience dental pain (OR 1.35; 95%CI 1.08 to 1.70) in a model considering demographic factors only, and Pacific Islander children were less likely to have received a general anaesthetic for dental work than Pakeha (New Zealand European) children (OR 0.44; 95%CI 0.24 to 0.82) (n=3,275) (Jamieson 2006 **Level III-2**).

Māori women were less likely to receive a range of medical interventions during childbirth, including Caesarean delivery and epidural analgesia compared with non-Māori women (Harris 2007 **Level III-2**; Nelson 2006 **Level IV**; Sadler 2002 **Level III-2**). Māori and Pacific Islander women had a 15% epidural analgesia rate compared with 25% in other New Zealand women, despite the fact that Māori and Pacific women were more likely to have pre-existing health conditions that would dictate a higher need for epidural analgesia (Nelson 2006 **Level IV**).

From accident registry data, high levels of adverse outcomes were observed 3 mth post-trauma among a Māori cohort (n=566) (Maclennan 2013 **Level IV**). Almost half were experiencing problems with mobility. A majority were having difficulties performing their usual activities and most were suffering some or extreme pain or discomfort. Over half were experiencing an increased level of psychological distress as well. Prevalence of disability due to injury in a household survey was also higher among Māori (31.4%) than non-Māori (29.3%) aged ≥15 y (Office for Disability Issues and Statistics New Zealand 2010 **Level III-2**). This highlights the importance of identifying improved strategies to prevent injury.

New Zealand continues to have some of the highest healthcare inequalities in the world with Māori having a two to three times higher mortality from noncommunicable disease than non-Māori populations (Di Cesare 2013 **Level IV**; Lilic 2015 **Level III-2**; Hsiang 2013 **Level IV**; Kerr 2014 **Level III-2**).

Māori were slightly less likely to consult general practitioners for back pain or regional pain disorders than Pakeha (New Zealand Europeans) but were more likely to present with gout (Taylor 2004 **Level III-3**). In a prospective observational study, patients with gout for <10 y were recruited from primary and secondary care settings (n = 291; 37 Māori, 35 Pacific Islanders and 219 who were neither Māori nor Pacific Islanders) (Dalbeth 2013 **Level III-2**). Māori and Pacific Islander participants had earlier age of onset (by 9 y), higher flare frequency and more features of joint inflammation. Māori and Pacific Islander patients also reported greater pain and activity limitation and lower health-related quality of life.

Similarly, joint replacement registry data collected between 2005 and 2009 demonstrated that Maori patients experience higher pain and poorer mobility on self report questionnaires 1 y following total joint arthroplasty than non-Maori patients (Singleton 2013 **Level III-2**).

Alongside inequalities in access to and quality of care, Māori also experience greater racial discrimination than non-Māori (Harris 2006 **Level III-2**). Research on acute pain suggests that experiences of Māori may differ from those of other New Zealanders in terms of tolerance, healthcare access or treatment, including receipt of pain-relief medication (McGavock 2012 **NR**). Given entrenched health disparities across a wide range of conditions and diseases, Māori carry a disproportionate burden of pain. The development and implementation of cultural competence training should provide pathways for health professionals to work more effectively with Māori patients (Pitama 2011 **Level IV**).

Key messages

1. Experimental ischaemic pain is tolerated for longer in Māori people than in European New Zealanders (**N**) (**Level III-2**).
2. Māori people report higher levels of pain and/or disability with dental pain, gout and after trauma and joint replacement surgery than European New Zealanders (**N**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ High healthcare inequalities exist regarding access and quality of care (across age ranges, genders and for various medical conditions) between the Māori and Pacific Islander peoples compared with New Zealanders of European origin (**N**).
- ☑ Māori culture embraces the multidimensional aspects of pain experiences (**N**).

10.4 The patient with sleep-disordered breathing including obstructive sleep apnoea

Sleep disordered breathing is a term for a spectrum of disorders where partial or complete cessation of breathing occurs many times during sleep. OSA is the most common form of sleep-disordered breathing and is the condition most studied in surgical patients. In patients with OSA having surgery, there is accumulating evidence of adverse outcomes. As the prevalence of OSA is increasing and numbers of patients having surgery is large, the population at risk is significant (Memtsoudis 2013 **NR**). Acute pain management in a patient with OSA presents several potential problems; identification of patients at significant risk, choice of the most appropriate form of analgesia, the most suitable location in which to provide care and the level of monitoring required. These difficulties arise primarily from the risk of exacerbating OSA by the administration of opioid or other medicines with sedative effects (in particular benzodiazepines but also butyrophenone or phenothiazine antiemetics and alpha-2-delta ligands).

Approximately one in five men and one in ten women have at least mild OSA (Jordan 2014 **NR**). One in fifteen adults have moderate or more severe OSA, and 75–80% of those who could benefit from treatment remain undiagnosed (Young 2004 **NR**). Therefore, many patients with undiagnosed OSA will have had treatment for acute pain without significant morbidity. The risk will depend on the severity of OSA, the nature and extent of surgery, the type of anaesthesia and analgesia and the extent of postoperative monitoring. The availability of a simple screening tool (STOP-Bang questionnaire) can help to identify those with OSA (Chung 2012 **Level IV**).

Despite the apparent overall low risk, patients with known OSA are at increased risk of postoperative complications compared with other patients (Memtsoudis 2013 **NR**). However, the main risk may lie more with the body size and build of the patient, especially those who are morbidly obese, rather than the fact they have a specific diagnosis of OSA (Loadsman 2009 **NR**).

A large retrospective database study using the USA Nationwide Inpatient Sample (n=6,051,703) compared postoperative respiratory outcomes in surgical patients either with or without OSA based on ICD-9 coding on discharge and matched by propensity scoring (Memtsoudis 2011 **Level III-2**). Coding for OSA was associated with respiratory complications after both orthopaedic and general surgery; aspiration pneumonia (OR 1.41; 95%CI 1.35 to 1.47 respectively OR 1.37; 95%CI 1.33 to 1.41), acute respiratory distress syndrome (OR 2.39; 95%CI 2.28 to 2.51 respectively OR 1.58; 95%CI 1.54 to 1.62) and requiring intubation/mechanical ventilation (OR 5.20; 95%CI 5.05 to 5.37 respectively OR 1.95; 95%CI 1.91 to 1.98). The relative contribution of each component of perioperative care (eg type of analgesia or anaesthesia) is impossible to ascertain. OSA has also been associated with a higher risk of postoperative cardiac adverse effects (OR 2.07; 95%CI 1.23 to 3.50) and also acute respiratory failure (OR 2.43; 95%CI 1.34 to 4.39) (Kaw 2012 **Level III-2 SR**, 13 studies, n=3,942). Desaturation

and ICU transfer were also more likely but these two findings were hindered by a high degree of heterogeneity in the studies. A subsequent prospective cohort study (n=14,962) screened patients for OSA risk and after surgery instituted extra care and observation for those identified as high risk (options included continuous pulse oximetry, oxygen, CPAP/bilevel positive airway pressure [BiPAP] and others but the actual usage of these interventions was not recorded) (Lockhart 2013 **Level III-2**). There was no increase in 30-d or 1-y postoperative mortality; however, it is not possible to determine if this was due to the use of the targeted interventions.

Several other studies have analysed patient outcomes using the Nationwide Inpatient Sample database. These studies found:

- sleep-disordered breathing was independently associated with postoperative cardiopulmonary complications (atrial fibrillation, intubation with mechanical ventilation, noninvasive ventilation) but not with an increased rate of inhospital death (n=1,058,710) (Mokhlesi 2013b **Level III-2**);
- for the subgroup of bariatric surgery patients (n=91,028), a diagnosis of sleep-disordered breathing/OSA was surprisingly negatively associated with inhospital mortality (OR 0.34; 95%CI 0.23 to 0.50) (Mokhlesi 2013a **Level III-2**), while being positively associated with increased risk of atrial fibrillation (OR 1.25; 95%CI 1.11 to 1.41), need for intubation (OR 4.35; 95%CI 3.97 to 4.77) and of noninvasive ventilation (OR 14.12; 95%CI 12.09 to 16.51);
- for patients having shoulder arthroplasty (n=22,988), there was no association with adverse outcomes (Griffin 2013 **Level III-2**);
- in patients having revision hip or knee arthroplasty (n=258,455), OSA was associated with increased inhospital mortality (OR 1.9; 95%CI 1.3 to 2.8) as well as pulmonary embolus (OR 2.02; 95%CI 1.3 to 2.9) and wound complications (D'Apuzzo 2012 **Level III-2**).

Two studies have failed to demonstrate an association between preoperative diagnosis of OSA and an increase in adverse effects or unplanned hospital admission after outpatient surgery (Sabers 2003 **Level III-3**, n=234; Bryson 2012b **Level III-2**, n=674).

10.4.1 Opioids and obstructive sleep apnoea

One of the main concerns in patients with OSA is that administration of opioids for the treatment of acute pain may lead to an increase in the number and severity of obstructive episodes and oxygen desaturation. OSA is associated with an increased sensitivity to opioid analgesia and decreased sensitivity to pain in both adult volunteers (Doufas 2013 **Level III-2**) and children (Brown 2009 **NR**).

Two early studies concluded that opioid administration in the postoperative period led to episodes of pronounced oxygen desaturation while the patients were asleep and this was more commonly the result of obstructive and central apnoea than the regular decrease in respiratory rate (Catley 1985 **Level III-2**; Clyburn 1990 **Level III-2**). Those studies, however, involved bolus doses of opioids in the PACU and subsequent infusion rates of IV morphine that would now be considered much larger than current practice. A subsequent study using continuous infusion doses of remifentanil calculated to be analgesic in volunteers with moderate OSA demonstrated a substantial increase in the number of central events, while the number of obstructive events was reduced (Bernards 2009 **Level II**, n=19, JS 4). Overall, there remains a paucity of information regarding the effects of analgesics, including opioids, in the acute pain setting in patients with OSA and therefore limited data on which to base recommendations for their postoperative care (ASA 2014 **GL**).

Patients assessed to be at risk of having OSA (by history, BMI and physical examination) (n=63) compared to control patients had more obstructive events during the first postoperative night (39±22 vs 14±10 events/h) and spent more time with oxygen saturation levels <90% (Blake 2008 **Level III-2**). There was no difference between the groups in the cumulative morphine dose over that time or frequency of central and mixed apneas. Classification of risk for OSA correlated with an increased number of desaturation events/h in patients monitored for 48 h postoperatively (Gali 2009 **Level III-3**).

In a number of case reports, the use of opioid medications in patients with OSA appeared to be a common factor for complications, including death, following intermittent IM, patient-controlled IV and epidural analgesia (Reeder 1991 **CR**; VanDercar 1991 **CR**; Etches 1994 **Level IV**; Ostermeier 1997 **Level IV**; Cullen 2001 **CR**; Lofsky 2002 **NR**; Parikh 2002 **Level IV**). However, caution is required when interpreting these reports. Most of the cases involved excessive opioid doses (eg excessive bolus dose or a background infusion with PCA) and/or inadequate monitoring for respiratory depression (Macintyre 2005 **NR**). It appeared there was an over-reliance on monitoring respiratory rate; however sedation levels were not checked and/or increasing sedation was not recognised as an early indicator of respiratory depression.

A small study in children undergoing adenotonsillectomy for OSA showed a trend to fewer episodes of postoperative desaturation in children given tramadol compared with morphine but the difference was only significant for the second h after surgery (Hullett 2006 **Level II**, n=66, JS 4). In patients with a BMI ≥28 and with signs or symptoms suggestive of OSA, there was no difference in the numbers of respiratory events (obstructive apnoeas, hypopnoeas or central apnoeas) in patients receiving IV morphine PCA and those receiving an "opioid-sparing" analgesic regimen (IV tramadol PCA, parecoxib and "rescue-only" morphine); however there was a correlation between >15 respiratory events/h and total morphine dose (Blake 2009, **Level II**, n=65, JS 4).

An updated ASA task force report on the perioperative management of patients with OSA concluded that there remains only limited evidence to evaluate the effects of various postoperative analgesia techniques in patients with OSA and no good comparisons between pure agonist opioids, such as morphine, and tramadol or nonopioid analgesics (ASA 2014 **GL**). Expert opinion, however, consistently suggests that nonopioid analgesics and regional techniques should be considered, either as an alternative to opioids or to help limit the amount of opioid required both for adults (ASA 2014 **GL**) and children (Patino 2013 **NR**).

10.4.2 Obesity as a risk factor

Morbid obesity is strongly associated with OSA (Young 2004 **NR**) and, using polysomnography, OSA was identified in 71% of patients presenting for bariatric surgery (Frey 2003 **Level IV**). It is still unclear if the use of PCA, with appropriate bolus doses and monitoring, in morbidly obese patients is less safe than regional analgesia or other systemic opioid analgesic techniques.

In 797 patients having bariatric surgery, all of whom underwent preoperative polysomnography and were prescribed CPAP therapy preoperatively if indicated, complications were common (33%) but, while age, open surgery and BMI were associated with those complications, OSA severity was not (Weingarten 2011a **Level III-2**). In 100 morbidly obese children having tonsillectomy, obesity was similarly associated with adverse outcome, independently of OSA (Gleich 2012 **Level III-2**).

10.4.3 Approaches to treatment

Oxygen

While oxygen therapy alone may not prevent the disruptions of sleep pattern or symptoms such as daytime somnolence and altered mental function that may occur in patients with OSA, it can reduce the likelihood of significant hypoxaemia (Phillips 1990 **Level III-3**; Landsberg 2001 **Level III-3**). As patients with OSA are more at risk of hypoxaemia after surgery or when given opioids, the use of supplemental oxygen would seem appropriate (ASA 2014 **GL**) despite concerns about reducing respiratory drive during the apnoeic periods (Lofsky 2002 **NR**).

Continuous positive airway pressure

The perioperative use of CPAP may theoretically help to reduce postoperative risk and is recommended for patients with OSA (ASA 2014 **GL**). The effectiveness of CPAP (used appropriately and in highly supervised environments) for the management of OSA in the postoperative setting was initially supported by case reports (Reeder 1991 **CR**; Rennotte 1995 **Level IV**; Mehta 2000 **NR**). A number of studies examining perioperative initiation of both fixed and autotitrated CPAP for patients considered or known to be at risk, however, have

demonstrated very poor adherence by those accepting the therapy (Guralnick 2012 **Level IV**; Liao 2013 **Level II**, n=177, JS 2), with no obvious outcome benefit (O'Gorman 2013 **Level II**, n=133, JS 2). Poor patient adherence may be improved by initiation of CPAP prior to surgery with more effective education and individualisation of therapy.

The effective *de-novo* use of CPAP in the setting of acute pain management likely requires a higher level of supervision than that available in the general surgical ward; most reports of the successful use of postoperative CPAP utilise extended periods of high-dependency nursing with staff educated and experienced in its use (Reeder 1991 **CR**; Rennotte 1995 **Level IV**; Mehta 2000 **NR**). Established CPAP use may, however, be associated with a lower risk of perioperative complications, as cardiovascular complications in particular (cardiac arrest and shock) were increased in patients with untreated OSA compared with those previously established on CPAP in a study using a Manitoban health administrative database (OR 2.20; 95%CI 1.16 to 4.17) (Mutter 2014 **Level III-3**). Patients with a known diagnosis of OSA, who are currently using CPAP at home, should therefore have CPAP continued while in hospital (ASA 2014 **GL**).

Concerns about the risk of CPAP causing gastric distension and anastomotic leaks after upper gastrointestinal surgery appear to be unfounded (Huerta 2002 **Level III-2**; Weingarten 2011b **Level III-2**).

Monitoring and environment

Advice on the most appropriate environment for the care of OSA patients requiring analgesia, along with the level of monitoring required, is based on expert opinion only and suggests that the severity of sleep-disordered breathing, efficacy of any current therapy, relevant comorbidities (eg cardiac) and the analgesia required all be taken into consideration both for adults (ASA 2014 **GL**; Joshi 2012 **GL**) and children (Patino 2013 **NR**).

Key messages

1. Patients with sleep-disordered breathing, including obstructive sleep apnoea, having surgery are at increased risk of adverse cardiac and respiratory effects (**S**) (**Level III-2 SR**), in particular cardiac arrest/shock, atrial fibrillation, aspiration pneumonia, acute respiratory distress syndrome and need for intubation, mechanical and noninvasive ventilation (**N**) (**Level III-2**).
2. Patients with obstructive sleep apnoea have an increased risk of exacerbation of obstructive episodes and hypoxaemia during the postoperative period (**Q**) (**Level III-2**).
3. Morbidly obese patients may be at increased risk of postoperative hypoxaemia, independent of a diagnosis of obstructive sleep apnoea (**S**) (**Level III-2**).
4. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**U**) (**Level III-2**).
5. Increasing severity of obstructive sleep apnoea is associated with increased risk of postoperative respiratory complications (**N**) (**Level III-3**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ The incidence of obstructive sleep apnoea in the surgical patient population is high and the majority (80%) of these patients are undiagnosed (**N**).
- ☑ Preoperative screening for obstructive sleep apnoea combined with treatment (ideally instituted preoperatively) and increased postoperative observation may decrease postoperative morbidity and mortality; the STOP-Bang questionnaire can be used to identify patients at risk of significant obstructive sleep apnoea (**N**).
- ☑ Patients with obstructive sleep apnoea may have increased sensitivity to opioids (**N**).

☑ Management strategies that may increase the efficacy and safety of pain relief in patients with obstructive sleep apnoea include multimodal nonsedating opioid-sparing analgesia including regional techniques, continuous positive airway pressure, monitoring and supervision (in a high-dependency area if necessary) and supplemental oxygen (**S**).

☑ Perioperative commencement of continuous positive airway pressure may be beneficial in patients with obstructive sleep apnoea but requires high levels of supervision and poor patient acceptance and postoperative adherence are significant problems (**N**).

10.5 The patient with concurrent renal or hepatic disease

The clinical efficacy and effects of most analgesic medicines is altered by impaired renal or hepatic function. This change in drug effect is not only because of altered clearance of the parent medicine but also through the accumulation of therapeutically active or toxic metabolites. Some analgesic agents can aggravate pre-existing renal and hepatic disease, causing direct damage and thus altering their metabolism.

A brief summary of the effects that renal or hepatic disease may have on some of the medicines used in pain management, as well as alterations that might be required in analgesic medicine regimens, is given in Tables 10.5 and 10.6.

10.5.1 Patients with renal disease

The degree to which analgesic medicine regimens require alteration in patients with renal impairment depends largely on the extent of renal impairment and whether the medicine has active metabolites that are dependent on the kidney for excretion, or if the medicine or its metabolites may further impair renal function.

A standard definition for chronic kidney disease (CKD) is provided by the National Kidney Foundation Kidney Disease Outcome Quality Initiative Advisory Board; patients with CKD should have either a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 mth or structural/functional kidney damage with or without changes in GFR (National Kidney Foundation 2002 **GL**). This definition quantifies five stages from Stage 1 (kidney damage with normal or increased GFR) via Stage 2 (mild reduction in renal function and GFR), Stages 3 and 4 (moderate to severe impairment of renal function and reduction in GFR) to Stage 5 (end-stage kidney disease requiring dialysis or renal replacement therapy).

There is some limited information about the ability of dialysis to clear the medicines and/or their metabolites. Molecules are more likely to be removed by dialysis if they have a low molecular weight, greater water solubility and lower volume of distribution; while a higher degree of protein binding and use of lower-efficiency dialysis techniques will reduce removal (Dean 2004 **NR**; Trainor 2011 **NR**).

The available data indicate the following (see Table 10.5 for references).

- Analgesics that exhibit the safest pharmacological profile in patients with renal impairment are alfentanil, buprenorphine, fentanyl, ketamine, paracetamol (except with compound analgesics) and sufentanil. None of these medicines deliver a high active metabolite load or has a significantly prolonged clearance.
- Oxycodone can usually be used without any dose adjustment in patients with renal impairment. Its metabolites do not appear to contribute to any clinical effect in patients with normal renal function.
- Amitriptyline, bupivacaine, levobupivacaine, lignocaine, ropivacaine, clonidine, gabapentin, pregabalin, codeine, hydromorphone, methadone, morphine and tramadol have been used in patients with renal disease but depending on the degree of impairment. For local anaesthetics and prolonged administration, a reduction in dose may be required. Levobupivacaine, with similar clearance mechanisms, and ropivacaine may be safer than bupivacaine due to a higher therapeutic ratio. Haemodialysis clears some medicines and a supplemental dose may be needed at the end of dialysis (eg gabapentin, pregabalin).

- NSAIDs (both nsNSAIDs and coxibs), dextropropoxyphene and pethidine should not be used in the presence of significant renal impairment.

Detailed reviews of pain management in patients with CKD have been published (Nayak-Rao 2011 **NR**), also with an emphasis on the perioperative period (Tawfic 2015 **NR**). A review of perioperative management of the dialysis patient has also been published (Trainor 2011 **NR**). Additional information can be found in the *Australian Medicines Handbook* (AMH 2015).

Table 10.5 Analgesic medicines in patients with renal impairment

Medicine	Comments	Recommendations*
Opioids		
Alfentanil	No active metabolites 92% protein bound; increases in free fraction may result from alterations in protein binding Davies 1996; Mercadante 2004; Murtagh 2007; Craig 2008; King 2011; Tawfic 2015	No dose adjustment required unless renal failure is severe
Buprenorphine	Pharmacokinetics unchanged; predominantly biliary excretion of metabolites Pharmacokinetics also unchanged with dialysis Davies 1996; Mercadante 2004; Launay-Vacher 2005; Boger 2006; Filitz 2006; Niscola 2010	No dose adjustment required
Codeine	Accumulation of active metabolites can occur; prolonged sedation and respiratory arrest have been reported in patients with renal impairment No good data on removal by dialysis Davies 1996; Dean 2004; Mercadante 2004; Craig 2008; Niscola 2010; Nayak-Rao 2011; Tawfic 2015	Dose adjustment recommended or use an alternative opioid
Dextro-propoxyphene	Accumulation of active metabolite (nordextropropoxyphene) can lead to CNS and cardiovascular system toxicity. Contraindicated if creatinine clearance <40 mL/min. Blood concentrations not significantly changed during dialysis Mercadante 2004; Launay-Vacher 2005; Murtagh 2007; Niscola 2010	Use of alternative agent recommended
Dihydrocodeine	Metabolic pathway probably similar to codeine Time to peak concentration and terminal half-life prolonged Barnes 1985; Davies 1996; Murtagh 2007; Craig 2008	Insufficient evidence: use not recommended
Fentanyl	No active metabolites Not removed to any significant degree by dialysis Dean 2004; Mercadante 2004; Launay-Vacher 2005; Murtagh 2007; Craig 2008; Nayak-Rao 2011; Tawfic 2015	No dose adjustment required; may be used in patients with severe renal impairment
Hydromorphone	Neurotoxicity from accumulation of H3G possible H3G is effectively removed during dialysis Dean 2004; Mercadante 2004; Davison 2008; Niscola 2010; Nayak-Rao 2011; Tawfic 2015	Dose adjustment recommended or use alternative opioid

Medicine	Comments	Recommendations*
Methadone	Methadone and its metabolites are excreted in urine and faeces; in anuric patients it may be mostly in faeces	Dose adjustment may be required in severe renal impairment
	High protein binding, high volume of distribution and moderate water solubility would suggest that it is likely to be poorly removed by dialysis	
	Dean 2004; Mercadante 2004; Launay-Vacher 2005; Lugo 2005; Murtagh 2007; Nayak-Rao 2011	
Morphine	Major metabolites M3G and M6G excreted via kidney and accumulate in renal impairment	Dose adjustment recommended or use alternative opioid
	M6G is an opioid agonist that crosses the blood-brain barrier slowly; delayed sedation from M6G has been reported in renal failure	
	Neurotoxicity from accumulation of M3G possible	
	Oral administration results in proportionally higher metabolite load	
	Morphine and its metabolites are cleared by most haemodialysis procedures but may not be significantly affected by peritoneal dialysis	
	M6G also removed but slow diffusion from CNS delays response	
	Richtsmeier 1997; Pauli-Magnus 1999; Angst 2000; Mercadante 2004; Dean 2004; Launay-Vacher 2005; Craig 2008; Nayak-Rao 2011; Tawfic 2015	
Oxycodone	The metabolite oxymorphone is active but plasma levels are normally negligible and therefore it has an insignificant clinical effect in patients with normal renal function	No dose adjustment required in most patients Monitor and adjust if necessary
	Higher blood concentrations of oxycodone and metabolites with moderate to severe renal impairment; half-life significantly increased in end-stage renal disease	
	Oxycodone and its metabolites are dialysable	
	Dean 2004; Kalso 2005; Lee 2005; Riley 2008; Niscola 2010	
Pethidine	Norpethidine is the only active metabolite and is renally excreted; it is dialysable	Use of alternative agent recommended
	Accumulation of norpethidine can lead to neuroexcitation including seizures	
	Simopoulos 2002; Mercadante 2004; Launay-Vacher 2005; Craig 2008; Tawfic 2015	
Sufentanil	Minimally active metabolite	No dose adjustment required
	Murphy 2005; King 2011	
Tramadol	Increased tramadol-like effects from active metabolite O-desmethyltramadol (M1)	Dose adjustment recommended
	Tramadol is removed by dialysis	Use of alternative agent recommended with significant renal impairment
	Mercadante 2004; Launay-Vacher 2005; MIMS 2014; Pham 2009; Tawfic 2015	

Medicine	Comments	Recommendations*
Tapentadol	Metabolised by glucuronidation Major metabolite will accumulate in renal failure but significance unknown Xu 2010; AMH 2015	Do not use in severe renal impairment Creatinine clearance <30 mL/min
Other medicines		
Local anaesthetics	There may be no significant difference in plasma concentration of levobupivacaine, bupivacaine or ropivacaine in patients with chronic renal failure unless renal failure is severe, continuous infusions are used or repeated doses are used Increases in free fraction may result from alterations in protein binding Higher peak plasma concentrations of ropivacaine in uraemic patients but no difference in free fraction; uraemic patients have significantly higher alpha-1-acid glycoprotein plasma concentrations Rice 1991; Crews 2002; Jokinen 2005; De Martin 2006; AMH 2015	Risk of toxicity may be affected by abnormalities in acid-base balance and/or potassium levels Doses may need to be reduced if prolonged or repeated administration (eg continuous infusions)
Paracetamol	Terminal elimination half-life may be prolonged Is dialysable Craig 2008; Launay-Vacher 2005; Kuo 2010; Nayak-Rao 2011	May need to increase dose interval if renal impairment is severe Some evidence that it may increase the rate of progression to chronic renal failure
NsNSAIDs and coxibs	Can affect renal function Behaviour during dialysis not clearly elucidated for most NSAIDs Launay-Vacher 2005; Kuo 2010; Nayak-Rao 2011	Use with caution in patients with mild renal impairment and avoid in patients with severe renal impairment Progression of renal disease more likely with nsNSAIDs than coxibs
Clonidine	Half-life is increased in severe renal failure 50% metabolised by the liver; remainder excreted unchanged by the kidney Lowenthal 1993; Khan 1999	Limited data; dose adjustment has been recommended
TCAs	Amitriptyline is metabolised in the liver to nortriptyline, the active agent Not significantly removed by dialysis Lieberman 1985; Murphy 2005; Dargan 2005; Raymond 2008	Limited data; metabolite accumulation may occur and increase the risk of adverse effects but little evidence to indicate need for dose reduction
SNRIs	Duloxetine Venlafaxine Raymond 2008; AMH 2015	Dose reduction if creatinine clearance <30 mL/min

Medicine	Comments	Recommendations*
Ketamine	Dehydronorketamine levels are increased but it has only 1% of potency of ketamine Ketamine is not removed well by dialysis Koppel 1990; Tawfic 2015	Limited data; probable that no dose adjustment is required
Alpha-2-delta ligands	Gabapentin: impaired renal function reduces clearance in direct proportion to creatinine clearance; about 35% cleared by dialysis Blum 1994; Wong 1995; Asconape 2014	Dose adjustment recommended on basis of creatinine clearance
	Pregabalin: Impaired renal function reduces clearance in direct proportion to creatinine clearance; highly cleared by dialysis Randinitis 2003; Asconape 2014	Dose adjustment recommended on basis of creatinine clearance

Note: * *Doses must still be titrated to effect for each patient.*

10.5.2 Patients with hepatic disease

Not all patients with hepatic disease have impaired liver function. In patients with hepatic impairment, most analgesic medicines have reduced clearance and increased oral bioavailability but the significance of these changes in the clinical setting has not been studied in depth.

Patients with cirrhotic liver disease may have renal impairment despite a normal serum creatinine. This can affect clearance of renally excreted medications and dose adjustment may be required.

The available data indicate the following (see Table 10.6 for references).

- While there are limited data, dose adjustments are usually not required for alfentanil, buprenorphine, fentanyl, morphine, oxycodone and sufentanil. However, all opioids carry an increased risk of toxicity and hepatic encephalopathy.
- Tramadol may need to be given at lower doses.
- Methadone should be used with caution in the presence of severe liver disease because of the potential for accumulation due to impaired clearance.
- Combined preparations of oxycontin and naloxone (Targin®) should be avoided in hepatic impairment as the reduced naloxone clearance leads to increased systemic levels and potential antagonism of the analgesic action of the oxycodone.
- The clearance of local anaesthetics may be significantly impaired; doses may need to be decreased if use is prolonged.
- Carbamazepine and valproate should be avoided in patients with severe hepatic impairment.
- It may be wise to reduce the dose of paracetamol in patients with significant degrees of hepatic impairment.

Detailed reviews of analgesic use in hepatic disease have been published (Dwyer 2014 **NR**; Imani 2014 **NR**). Additional information can be found in the *Australian Medicines Handbook* (AMH 2015).

Table 10.6 Analgesic medicines in patients with hepatic impairment

Medicine	Comments	Recommendations*
Opioids		
Alfentanil	No significant difference in half-life found in children undergoing liver transplant In alcoholic cirrhosis, plasma clearance and protein binding decreased and elimination half-life increased after single dose Davis 1989; Ferrier 1985	Limited data: no dose adjustment required in most patients
Buprenorphine	Lower blood concentrations of buprenorphine and norbuprenorphine Johnson 2005; Dwyer 2014	Limited data: no dose adjustment required
Dextro-propoxyphene	Reduced oxidation leading to reduced clearance Tegeder 1999	Limited data: dose adjustment may be required
Fentanyl	Disposition appears to be unaffected Tegeder 1999; Chandok 2010; Dwyer 2014	Limited data: no dose adjustment required
Methadone	Increased half-life but limited significance Lugo 2005; Novick 1985; Dwyer 2014	Limited data: no dose adjustment required in stable chronic liver disease
Morphine	Hepatic impairment does not appear to have a significant effect on morphine pharmacokinetics; even in patients with cirrhosis there is a large hepatic reserve for glucuronidation Blood concentrations of morphine but not morphine metabolites higher after liver resection; blood concentrations also higher in patients with liver cancer Increased oral bioavailability of morphine due to its normal high first pass metabolism when given via this route Kotb 2005; Rudin 2007;	In most patients no dose adjustment required
Hydromorphone	 Chandok 2010; AMH 2015	Consider dose reduction
Oxycodone	Decreased oxycodone clearance with mild to moderate hepatic impairment Avoid fixed dose combination with naloxone (Targin®) in moderate to severe hepatic impairment as systemic absorption of naloxone may be increased Kalso 2005; Riley 2008; AMH 2015	Limited data: no dose adjustment required in most patients
Pethidine	Reduced clearance Tegeder 1999	Limited data: dose adjustment may be required; use not recommended

Medicine	Comments	Recommendations*
Sufentanil	No difference in clearance or elimination	No dose adjustment required
	Chauvin 1989; Tegeder 1999	
Tramadol	Reduced clearance	Limited data: dose adjustment may be required if impairment is severe
	Tegeder 1999; Kotb 2008; Dwyer 2014	
Tapentadol	Elimination by hepatic glucuronidation	Avoid in severe hepatic impairment (Child-Pugh score 10–15)
		Adjust dose in moderate hepatic impairment (Child-Pugh score 7–9)
	Xu 2010; AMH 2015	
Other medicines		
Local anaesthetics	Amide-type local anaesthetics undergo hepatic metabolism and clearance may be reduced in hepatic disease	Limited data; dose adjustment may be required with prolonged or repeated use
	Increased plasma concentrations of ropivacaine after continuous infusion but not single dose	
	Bodenham 1990; Jokinen 2005; Jokinen 2007; AMH 2015	
Paracetamol	Metabolised in the liver; small proportion metabolised to the potentially hepatotoxic metabolite Nacetyl-p-benzoquinone imine. This is normally inactivated by hepatic glutathione	Commonly suggested that it should be used with caution or in reduced doses or frequency with active liver disease, alcohol-related liver disease and glucose-6-phosphate dehydrogenase deficiency
	Clearance is reduced	However, others report that it can be used safely in patients with liver disease and is preferred to NSAIDs, and that therapeutic doses of paracetamol, at least for short-term use, are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol
		Dose reduction for chronic use
	Benson 2005; Graham 2005; Zapater 2004; Chandok 2010; Graham 2013; Dwyer 2014; Imani 2014	
nsNSAIDs	Metabolised in liver. Altered metabolism and bioavailability in cirrhosis.	May be used in mild chronic liver disease
	Avoid if renal impairment present or risk of hepatorenal syndrome	Avoid in cirrhosis
		COX2 selective agents may be safer
	Chandok 2010; Dwyer 2014; Imani 2014	
TCAs	Amitriptyline is metabolised in the liver to nortriptyline, the active agent	Reduce dose if hepatic impairment is severe
	Chandok 2010; Dwyer 2014	

Medicine	Comments	Recommendations*
SNRIs	Duloxetine Venlafaxine Chandok 2010; Dwyer 2014	Duloxetine should not be used in hepatic impairment Venlafaxine dose reduction in hepatic impairment Desvenlafaxine may be safer
Alpha-2-delta ligands	Eliminated renally Chandok 2010; Asconape 2014; Dwyer 2014	Safe in liver disease
Carbamazepine	Transient rises in hepatic enzymes occur in 25–61% of patients treated; has been reported to cause hepatic failure (rare) Primarily metabolised in the liver Ahmed 2006; Asconape 2014	Dose adjustment may be required; use not recommended in severe hepatic impairment
Valproate	Transient rises in hepatic enzymes occur in 10–15% of patients treated; has been reported to cause hepatic failure (rare) Primarily metabolised in the liver Ahmed 2006; Asconape 2014	Dose adjustment may be required; use not recommended in severe hepatic impairment

Note: * *Doses must still be titrated to effect for each patient*

Key message

The following tick box represents conclusions based on clinical experience and expert opinion.

☑ Consideration should be given to choice and dose regimen of analgesic agents in patients with hepatic and particularly renal impairment (**U**).

10.6 The opioid-tolerant patient

10.6.1 Definitions and clinical implications

Misunderstandings in the terminology related to addiction (see also Section 10.7), tolerance, and physical dependence may confuse health professionals (and patients) and lead to inappropriate and/or suboptimal acute pain management as well as stigmatisation. Terms such as addiction, substance abuse, substance dependence and dependence are often used interchangeably. With this in mind, a consensus statement with agreed definitions for addiction, tolerance and physical dependence has been developed by the American Pain Society, the American Academy of Pain Medicine and the American Society of Addiction Medicine (AAPM 2001 **GL**).

Table 10.7 Definitions of relevant terms

Tolerance (pharmacological)	A predictable physiological decrease in the effect of a drug over time so that a progressive increase in the amount of that drug is required to achieve the same effect Tolerance develops to desired (eg analgesia) and undesired (eg euphoria, opioid-related sedation, nausea or constipation) effects at different rates
Physical dependence	A physiological adaptation to a drug whereby abrupt discontinuation or reversal of that drug, or a sudden reduction in its dose, leads to a withdrawal (abstinence) syndrome Withdrawal can be terminated by administration of the same or similar drug

Addiction	A disease that is characterised by aberrant drug-seeking and maladaptive drug-taking behaviours that may include cravings, compulsive drug use and loss of control over drug use, despite the risk of physical, social and psychological harm While psychoactive drugs have an addiction liability, psychological, social, environmental and genetic factors play an important role in the development of addiction Unlike tolerance and physical dependence, addiction is not a predictable effect of a drug
Substance use disorder	The essential feature of a substance use disorder is a cluster of cognitive, behavioural and psychological symptoms indicating that the individual continues using the substance despite significant substance-related problems (American Psychiatric Association 2013)
Pseudoaddiction	Behaviours that may seem inappropriately drug-seeking but are a result of undertreatment of pain and resolve when pain relief is adequate (Weissman 1989)
Diversion	Sharing, selling or trading prescribed drugs to someone for whom they are not prescribed (Arria 2011) Sourcing activities or paths which redirect psychoactive prescription drugs from legitimate production or medical-use environments into the hands of nonmedical consumers (Fischer 2010)
Aberrant drug-related behaviours	"Behaviours that may be suggestive of the development of abuse, addiction or misuse" (Moore 2009)
Chemical coping	"A state observed in certain patients on chronic opioid therapy who have a mixed response to opioid therapy and in whom aberrant drug-related behaviours are sometimes (but not consistently) exhibited. Chemical coping has been described as a 'middle ground' between compliance and addiction" (Pergolizzi 2012)
OIH	"State of nociceptive sensitisation caused by exposure to opioids" (Ramasubbu 2011)

*Source: Adapted from (*AAPM 2001*) and the references in the table.*

10.6.1.1 Clinical implications of opioid tolerance and opioid-induced hyperalgesia

The relative roles played by tolerance and OIH in the patient who is taking opioids on a long-term basis are unknown and both may contribute to increased pain (Hay 2009 **Level III-2 EH**; Lee 2011 **NR**; Chu 2012 **Level II**, n=103, JS 4). It is also possible that different opioids vary in their ability to induce OIH and tolerance (see Section 4.1.1). Studies of OIH are confounded by factors such as pain modality tested, route of administration and type of opioid (Bannister 2010 **NR**). Psychological factors such as pain-related distress and catastrophising might also affect pain sensitivity in those taking opioids for chronic pain (Edwards 2011 **Level III-2**; Eyler 2013 **NR**).

There are some features of OIH that may help to distinguish it from pre-existing pain. With OIH, pain intensity may be increased above the level of the pre-existing pain; the distribution tends to be beyond that of the pre-existing pain as well as more diffuse; and QST may show changes in pain thresholds and tolerability (Chang 2007a **NR**; Hay 2009 **Level III-2 EH**; Bannister 2010 **NR**; Lee 2011 **NR**; Ramasubbu 2011 **NR**).

In the experimental setting, patients with opioid (morphine or methadone) managed chronic noncancer pain (Hay 2009 **Level III-2 EH**), those abusing heroin (Ho 2011 **Level III-2 EH**) and those in methadone-maintenance programs (Compton 2000 **Level III-2 EH**; Doverty 2001b **Level III-2 EH**; Athanasos 2006 **Level III-2 EH**; Hay 2009 **Level III-2 EH**; Compton 2012 **Level III-2 EH**) have been shown to be hyperalgesic, when assessed with cold-pressor testing but not with electrical pain stimuli. Other studies have demonstrated tolerance without evidence of OIH in patients taking opioids for chronic pain (Edwards 2011 **Level III-2**; Chu 2012 **Level II**, n=103, JS 4).

In comparisons of subjects in methadone-maintenance programs with and without chronic pain, the presence of chronic pain may differentially increase pain thresholds and there may be a dose-related effect on abnormal pain processing (Chen 2009 **Level III-2 EH**; Hooten 2010 **Level IV EH**; Peles 2011 **Level III-3 EH**). There is controversy about the impact of opioid cessation with some evidence suggesting resolution of OIH after a few months of abstinence from opioids (Treister 2012 **Level III-3 EH**) and others showing that heat and pain perception remain abnormal even after abstinence for at least 6 mth (Prosser 2008 **Level III-2 EH**).

After intraoperative use of remifentanil (at ≥0.1 mcg/kg/min), there is evidence of acute opioid tolerance and OIH of limited clinical relevance (Kim 2014 **Level IV SR**, number of studies unspecified, n unspecified; Rivosecchi 2014 **Level IV SR**, 35 studies, n unspecified). Another meta-analysis confirms clinically small but statistically significant OIH only after high-dose remifentanil use (≥0.3 mcg/kg/min) with insufficient data on fentanyl and sufentanil (Fletcher 2014 **Level I** [PRISMA] 27 RCTs, n=1,494). Patients had increased postoperative pain scores at 1 h (MD 9.4/100; 95%CI 4.4 to 14.5) up to 24 h (MD 3/100; 95%CI 0.4 to 5.6) and higher opioid requirements over 24 h (SMD 0.7; 95%CI 0.37 to 1.02). In this meta-analysis, propofol attenuates OIH.

NMDA-receptor antagonists (mainly ketamine [8 RCTs] but also magnesium [5 RCTs] and amantadine [1 RCT]) reduce the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 14 RCTs, n=729). Pregabalin had an attenuating effect (Lee 2013b **Level II**, n=93, JS 5; Jo 2011 **Level II**, n=60, JS 5) as did N_2O (Echevarria 2011 **Level II**, n=50, JS 4).

The challenge faced by the health professional is that if inadequate pain relief is due to OIH, a reduction in opioid dose may help; if it is due to opioid tolerance, increased doses may provide better pain relief (Mao 2008 **NR**; Huxtable 2011 **NR**). There are case reports of patients with cancer and chronic noncancer pain taking high doses of opioid who developed OIH and whose pain relief improved following reduction of their opioid dose (Angst 2006 **CR**; Chang 2007a **CR**); there are no data in the acute pain setting.

When a patient who has been taking opioids for a while (either legally prescribed or illicitly obtained) has new and ongoing tissue injury with resultant acute pain, a reasonable initial response to inadequate opioid analgesia, after an evaluation of the patient and in the absence of evidence to the contrary, is a trial of higher opioid doses (Chang 2007a **NR**; Huxtable 2011 **NR**). If the pain improves, this would suggest that the inadequate analgesia resulted from tolerance; if pain worsens, or fails to respond to dose escalation, it could be a result of OIH (Chang 2007a **NR**). Fortunately, some of the strategies that may be tried in an attempt to attenuate opioid-tolerance in the acute pain setting may also moderate OIH (see below).

Other reasons for increased pain and/or increased opioid requirements should also be considered. These include acute neuropathic pain, pain due to other causes including postoperative complications, major psychological distress and aberrant drug-seeking behaviours (see Section 10.7) (Macintyre 2015 **NR**; Gourlay 2008 **NR**; Edwards 2011 **Level III-2**).

10.6.1.2 Chronic opioid use and sleep-disordered breathing

Opioids can affect ventilatory function via decreases in central respiratory drive, level of consciousness and upper airway tone (Macintyre 2011 **NR**). Long-term opioid use may be a risk factor for sleep-disordered breathing, although the evidence for this association is primarily at the level of case series and case reports (Webster 2008 **Level IV**; Farney 2013 **Level IV**).

In patients undergoing methadone-maintenance treatment, subjective sleep complaints were common and in 60% were not due to sleep-disordered breathing (Sharkey 2010 **Level IV**). A small observational study showed that patients on methadone-maintenance programs were more likely to have sleep abnormalities, especially central sleep apnoea, than were matched controls, although the effect was confounded by greater use of benzodiazepines in the methadone group (Teichtahl 2001 **Level III-2**). The effect of chronic opioid use on sleep-disordered breathing may be dose-related (Walker 2007 **Level III-3**).

Particular care should be taken when the total opioid dose is rapidly escalated above the usual dose and when other sedative agents are coadministered.

10.6.2 Patient groups

Four main groups of opioid-tolerant patients are encountered in acute pain settings.

- Patients with noncancer pain being treated with opioids, where acute presentations may be due to a new acutely painful condition (eg surgery, trauma) or to exacerbation of the underlying chronic condition (eg sickle cell crisis, pancreatitis) (Quinlan 2012 **NR**). Some of these patients may exhibit features of opioid addiction. This was increased in certain subgroups eg younger adults, those who catastrophise (Martel 2013 **Level III-2**; Morasco 2013 **Level IV**), have a personal history of addiction, more severe pain, and other comorbid psychiatric disorders (Sehgal 2012 **NR**; Pergolizzi 2012 **NR**) (see Section 10.7).
- Patients with cancer pain being treated with opioids may be at various stages of their illness ranging from active treatment (including surgery) or palliation to remission. In the latter case, survivors of cancer may experience specific issues relating to "survivorship" (Yazdani 2014 **NR**). Some of the issues will be similar to those in patients with noncancer pain.
- Patients with a substance use disorder who are either using illicit opioids or on an opioid-maintenance treatment program; some will have chronic pain (see Section 10.7).
- Patients who have developed acute or subacute opioid tolerance (or OIH) due to perioperative or postoperative opioid administration, particularly opioids of high potency.

Similar opioid-tolerant groups are seen in the paediatric population. Although a greater proportion of children and adolescents treated with opioids will have cancer pain, subacute tolerance also occurs (related primarily to prolonged ICU admission) and some adolescents experience addiction (Geary 2012 **NR**). However, paediatric patients with opioid tolerance have been even less well studied than have adults and recommendations have been primarily based upon extrapolation from their opioid-naïve counterparts and the adult literature.

Recognition of the presence of opioid tolerance or OIH may not be possible if the patient's history is not available or accurate (eg following major trauma with ICU admission or if the patient is unconscious at presentation). If a patient is requiring much larger than expected opioid doses and other factors that might be leading to the high requirements have been excluded, opioid tolerance or OIH should be considered.

10.6.3 Assessment and management of acute pain

While the discussion below will focus on assessment and management of the opioid-tolerant patient, it is recognised that these patients may also have OIH.

A number of articles, chapters and a book (Bryson 2012a **NR**) have been published outlining suggested strategies for the assessment and management of acute pain in the patient taking long-term opioids for chronic pain or because they have a substance use disorder, perhaps treated in a drug treatment program (Haber 2009 **NR**; Huxtable 2011 **NR**; De Pinto 2012 **NR**; Geary 2012 **NR**; Quinlan 2012 **NR**; Schug 2012 **NR**; Eyler 2013 **NR**; Buckley 2014 **NR**; Tumber 2014 **NR**). Evidence for the most appropriate assessment and management in these patients is very limited and the advice given in these papers remains based primarily on case series, case reports, expert opinion and personal experience. Opioid-tolerant patients are heterogeneous and thus difficult to study, and thus are usually excluded from studies of acute pain management. The past few years have seen a small number of RCTs in opioid-tolerant patients or inclusion of these patients in broader studies, often after spinal surgery. However, details of the opioid tolerance and pre-existing pain are sometimes not well described.

In general, assessment and management of these patients should focus on:

- effective analgesia;
- use of strategies that may attenuate tolerance or OIH;
- prevention of withdrawal; and
- close liaison with other treating health professionals and specialist teams as required, and appropriate discharge planning to ensure continuity of long-term care.

10.6.3.1 Assessment

Considerations in assessment of acute pain in opioid-tolerant patients include:

- unidimensional measures may not be adequate in these complex patients (Gandhi 2011 **NR**; Radnovich 2014 **NR**);
- it is important to consider psychological and social, as well as pathological, triggers for pain deterioration in those with chronic pain (Quinlan 2012 **NR**);
- in addition to usual pain assessment, there are specific factors that should be sought in all opioid-tolerant patients, those with chronic pain and those with addiction (see Table 10.8) (Huxtable 2011 **NR**);
- practitioners determining the need for elective procedures (eg surgeons, physicians, radiologists) or for labour analgesia planning (obstetricians, general practitioners) should refer patients early for pain management planning (Tumber 2014 **NR**);
- previous records should be reviewed and information about previous experiences of acute pain management should be sought to avoid or optimise strategies that were ineffective and to replicate those that were effective (Tumber 2014 **NR**);
- engagement of the patient, and their family in the case of paediatric patients (Geary 2012 **NR**), is key to assessment, management and adherence to the proposed plan (Haber 2009 **NR**); and
- communication should involve engagement, empathising, educating, enlisting and end by summarising, reviewing and indicating next steps (Jamison 2011 **NR**).

Table 10.8 Pain-related assessment in opioid-tolerant patients

Information from all opioid-tolerant patients	Additional information in patients with CNCP or cancer pain	Additional information in patients with a substance use disorder
Current treatment providers	Pain diagnosis	Opioid substitution therapies and doses (methadone, buprenorphine)
Opioid and nonopioid medications	Usual pain scores	Other prescribed or diverted prescription medicine or illicit substance use (polyabuse is common)
Dose verification of all relevant medications	Functional status	Routes of administration
Nonprescribed drugs (eg over-the-counter and illicit drugs, alcohol, nicotine)	Prognosis (cancer pain)	Where relevant, registered prescriber and dispensing pharmacy
Drug allergies and reactions	Psychospiritual issues (including end-of-life issues, anxiety, depression, coping style and strategies)	Medical and psychiatric comorbidities (eg blood-borne viruses, hepatic disease, other infections, chronic pain, personality disorder)
Experiences and expectations of acute pain management	Where relevant, the authorised prescriber of any opioids	

Information from all opioid-tolerant patients	Additional information in patients with CNCP or cancer pain	Additional information in patients with a substance use disorder
Support systems after discharge	Presence of invasive pain treatment (eg IT pump, spinal cord stimulator)	
	Medication misuse, evidence of aberrant drug-related behaviour or addiction	
	Expectations about their admission (eg expectation that chronic back pain will be improved after spinal surgery; palliative vs curative surgery in patients with cancer)	

Source: From Huxtable 2011*; reproduced with permission and slightly modified.*

10.6.3.2 Effective analgesia

Even more than in other patients, the basis for successful pain management in opioid-tolerant patients must be the utilisation of multimodal analgesia strategies (Huxtable 2011 **NR**; Schug 2012 **NR**).

Opioids

It is known that opioid requirements are usually significantly higher in opioid-tolerant compared with opioid-naïve patients and that the interpatient variation in the doses needed is even greater. After a variety of surgical procedures, opioid-tolerant patients using PCA (Rapp 1995 **Level III-2**) or epidural analgesia (de Leon-Casasola 1993 **Level III-2**) required approximately three times the dose (on average, standard deviation larger) compared with their opioid-naïve counterparts.

Opioid-tolerant patients reported higher pain scores (both resting and dynamic) and remained under the care of an APS longer than other patients (Rapp 1995 **Level III-2**). Compared with opioid-tolerant patients with cancer pain, opioid-tolerant patients with noncancer pain had higher rest and dynamic pain scores and required longer APS input but there was no difference in opioid requirements (Rapp 1995 **Level III-2**). In addition, staff relied more on functional measures of pain than on pain scores to assess pain intensity in these patients (Rapp 1994 **Level IV**). Their postoperative pain also resolved more slowly than that in opioid-naïve patients (Chapman 2009 **Level III-2**). Opioid-tolerant patients also had significantly longer length of hospital stay and higher readmission rates (Gulur 2014 **Level IV**).

The incidence of opioid-induced nausea and vomiting may be lower in opioid-tolerant patients, although the risk of excessive sedation/ respiratory depression may be higher (Rapp 1995 **Level III-2**) and may be particularly likely if opioid doses are rapidly escalated above the baseline level (Huxtable 2011 **NR**).

IV PCA is a useful modality for pain relief in opioid-tolerant patients, including those with an addiction disorder, provided that pain intensity and opioid consumption are carefully monitored and background requirements are provided if the patient cannot take their usual opioid; larger bolus doses will often be needed (Mitra 2004 **NR**; Macintyre 2015 **NR**; Huxtable 2011 **NR**). The size of an appropriate dose (on an individual patient basis) has been calculated by one group of investigators by using a preoperative fentanyl infusion until the patient's respiratory rate was <5/min; pharmacokinetic simulations were then used to predict the size of the PCA bolus dose and the rate of a background infusion that would be required for postoperative analgesia (Davis 2005 **Level IV**). It may also be based on the dose of opioid the patient is already taking (Hadi 2006 **NR**; Macintyre 2015 **NR**). Regardless of the initial dose prescribed, subsequent doses will need to be titrated to effect for each patient.

Neuraxial opioids have been used effectively in opioid-tolerant patients; although higher doses may be required and may not result in an increase in adverse effects (de Leon-Casasola

1993 **Level III-2**). Effective analgesia using IT or epidural opioids will not necessarily prevent symptoms of opioid withdrawal (Carroll 2004 **NR**; Huxtable 2011 **NR**).

Nonpharmacological strategies

Behavioural and cognitive techniques may minimise anxiety and reduce catastrophising, and physical techniques should also be considered (Tumber 2014 **NR**); however, there is no evidence for their effectiveness in opioid-tolerant patients in acute pain settings.

10.6.3.3 Attenuation of tolerance and opioid-induced hyperalgesia

There are a number of strategies that may help attenuate opioid tolerance and OIH. These include:

- use of NMDA-receptor antagonists
- use of opioid-receptor antagonists;
- opioid rotation; and
- use of other adjuvant medicines.

NMDA-receptor antagonists

As noted in Section 4.6, the NMDA receptor is involved in the development of tolerance and OIH (Chang 2007a **NR**). In rodents, use of the NMDA-receptor antagonist ketamine has been shown to attenuate both the development of tolerance (Shimoyama 1996 **BS**; Laulin 2002 **BS**) and OIH (Laulin 2002 **BS**; Haugan 2008 **BS**; Minville 2010 **BS**; Van Elstraete 2011 **BS**).

In patients taking opioids on a long-term basis, the administration of ketamine has been reported to lead to improved pain relief and reduced opioid requirements (Eilers 2001 **CR**; Sator-Katzenschlager 2001 **CR**; Mitra 2008 **NR**). NMDA-receptor antagonists (mainly ketamine [8 RCTs], but also magnesium [5 RCTs] and amantadine [1 RCT]) reduce the development of acute tolerance/OIH associated with remifentanil use (Wu 2015 **Level I** [QUOROM], 14 RCTs, n=729); this assessment is based on reduced postoperative pain scores and opioid requirements and increased time to first analgesic request and satisfaction scores in the NMDA-receptor antagonist vs the placebo groups.

After spinal surgery in opioid-tolerant patients (due to preceding long-term opioid use), perioperative ketamine use resulted in significantly less pain but did not reduce PCA opioid requirements (Urban 2008 **Level II**, n=26, JS 3) and reduced opioid requirements and pain scores in the early postoperative period and at 6 wk (Loftus 2010 **Level II**, n=101, JS 4). After noncancer general surgery in a similar patient group, a postoperative ketamine infusion at 0.2 mg/kg/h decreased average pain scores (13.5% decrease vs 15.5% increase; p=0.0057) but not opioid requirements (Barreveld 2013 **Level II**, n=64, JS 4).

Opioid receptor antagonists

In rodents, ultra-low doses of naloxone have been shown to attenuate opioid tolerance (Crain 1995 **BS**; Crain 2000 **BS**; Wang 2005 **BS**) and remifentanil-induced OIH (Aguado 2013 **BS**).

In the experimental pain setting in healthy volunteers, the coadministration of ultra-low doses of naloxone (La Vincente 2008 **EH**) or naltrexone (Hay 2011 **Level II EH**, n=10, JS 5) to buprenorphine significantly increased tolerance to cold-pressor pain.

Clinical studies have concentrated on the use of both naloxone and an opioid given acutely, with conflicting results; improved postoperative pain and reduced opioid requirements as well as no differences in either have been reported (Angst 2006 **NR**; Sloan 2006 **NR**). The use of low-dose naloxone added to postoperative opioid analgesia (most commonly by PCA) decreases the risk of pruritus (OR 0.40; 95%CI 0.21 to 0.79) and nausea (OR 0.62; 95%CI 0.43 to 0.89), but not vomiting, pain intensity or opioid requirements (Murphy 2011 **Level I**, 8 RCTs, n=800). Use over 3 mth of a combination of oxycodone/ultra-low-dose naltrexone in patients with chronic pain, in comparison with oxycodone alone, showed that those given the combination had similar pain relief but with 12% lower daily oxycodone use, as well as less constipation, sedation, pruritus and physical dependence as assessed by a withdrawal scale (Webster 2006 **Level II**, n=719, JS 4).

Opioid rotation

Opioid rotation (also called "switching") is commonly used in the treatment of chronic noncancer and cancer pain when a change to another opioid can improve analgesia and reduce adverse effects (Mercadante 2012 **Level IV;** Nalamachu 2012 **NR**). Opioid rotation (eg using an opioid that is different from the preadmission opioid) may also be of use in the acute pain setting (Hadi 2006 **NR**; Huxtable 2011 **NR**). The concept is based on the rationale that the different opioids do not act to the same degree on different opioid receptor subtypes, are metabolised differently, that cross-tolerance is likely to be incomplete (Jage 2005 **NR**; Mitra 2008 **NR**; Huxtable 2011 **NR**) and that the degree of OIH and tolerance appears to vary between opioids (see Section 4.1.1).

Adjuvants

Adjuvants are primarily used for their antitolerance, antiallodynic and antihyperalgesic effects (Huxtable 2011 **NR**).

In rats, intraoperative use of paracetamol, metamizol, ketoprofen and parecoxib abolished acute tolerance caused by remifentanil infusion (Benito 2010 **BS**). In an experimental pain setting using intradermal electrical pain stimuli, parecoxib given before but not during a remifentanil infusion modulated the hyperalgesia after withdrawal of remifentanil (Troster 2006 **Level II EH**, n=15, JS 5).

Gabapentin has also been shown to attenuate opioid tolerance (Lin 2005 **BS**; Aguado 2012 **BS**) and OIH (Wei 2012 **BS**) in rats and this effect was synergistic to ketamine (Van Elstraete 2011 **BS**). Pregabalin shows similar effects in animal models (Hasanein 2014 **BS**). In methadone-maintained patients, gabapentin increased cold-pressor pain threshold and pain tolerance (Compton 2010, **Level II EH**, n=26, JS 2). In the setting of OIH associated with remifentanil, 150–300 mg pregabalin preoperatively attenuated this effect after hysterectomy (Jo 2011 **Level II**, n=60, JS 5) and laparoscopic urological surgery (Lee 2013b **Level II**, n=93, JS 5).

Other adjuvants that may influence tolerance and OIH but for which there is limited evidence include alpha-2 receptor antagonists (clonidine and dexmedetomidine) and buprenorphine (Lee 2011 **NR**; Ramasubbu 2011 **NR**).

10.6.3.4 Prevention of withdrawal

Withdrawal from opioids is characterised by excitatory and autonomic symptoms including abdominal cramping, muscle aches and pain, insomnia, dysphoria, anxiety, restlessness, nausea and vomiting, diarrhoea, rhinorrhoea and sneezing, trembling, yawning, watery eyes (epiphora) and piloerection (or "gooseflesh") (Tetrault 2008 **NR**; Rehni 2013 **NR**). The time of onset of withdrawal symptoms after cessation of the drug will depend on the duration of action of the opioid.

Withdrawal should be prevented by maintenance of normal preadmission opioid regimens where possible (including on the day of surgery) or appropriate substitutions with another opioid or the same opioid via another route (Macintyre 2015 **NR**; Huxtable 2011 **NR**; Schug 2012 **NR**). It may be of benefit to check preadmission opioid doses with the patient's doctor or pharmacist; the use of unauthorised additional opioids (licit or illicit) or of lower doses than prescribed may affect both pain relief and the risk of adverse effects.

While multimodal analgesic regimens (eg NSAIDs, paracetamol, ketamine, tramadol, regional analgesia) are of analgesic benefit (Rajpal 2010 **Level III-3**), opioid-tolerant patients are at risk of opioid withdrawal if a purely nonopioid analgesic regimen or tramadol or tapentadol is used (Macintyre 2015 **NR**; Huxtable 2011 **NR**).

For this reason, opioid antagonists (naloxone, naltrexone) should be avoided as their use may precipitate acute withdrawal reactions (Alford 2006 **NR**; Schug 2012 **NR**).

Alpha-2 agonists such as clonidine and lofexidine are more effective than placebo in the management of opioid-withdrawal symptoms (Gowing 2014 **Level I** [Cochrane], 25 RCTs, n=1,668).

Pregabalin attenuated naloxone-induced withdrawal symptoms in opioid-tolerant rats (Hasanein 2014 **BS**). During a 10-d buprenorphine detoxification procedure, gabapentin reduced

opioid use compared with placebo (Sanders 2013 **Level II**, n=30, JS 5) and in a dose of 1,600 mg/d reduced withdrawal symptoms in patients during methadone-assisted detoxification (Salehi 2011 **Level III-1**). Pregabalin added to methadone in maintenance program patients reduced methadone requirements and withdrawal symptoms compared with placebo (Moghadam 2013 **Level II**, n=60, JS 5).

10.6.3.5 Management on discharge

Discharge planning of opioid-tolerant patients must take into account any regulatory requirements (eg the authority to prescribe an opioid may have to be delegated to a particular physician only), the duration of use of any additional opioids prescribed for the short-term management of acute pain and the weaning of those drugs and, in a small minority of patients, the potential for prescribed opioids to be abused, misused or diverted. Without robust discharge systems, there is a significant risk of unintended opioid dose escalation (Huxtable 2011 **NR**; Quinlan 2012 **NR**; Schug 2012 **NR**).

A "reverse analgesic ladder" approach is recommended, with the aim being stepwise return of the patient to their usual opioid regimen (Huxtable 2011 **NR**). Considerations include the likely duration of acute pain (and thus the amount of opioid that should be prescribed), the choice of opioid and its "abuse liability" and the use of nonopioid agents. Appropriate use of nonopioid analgesics where possible, use of abuse-deterrent formulations, provision of small quantities and staged pharmacy supply, communication with the primary physician and other treating health care professionals (including a plan for cessation) and patient education and support must all be considered.

An ethical dilemma arises where the preadmission opioid regimen is not consistent with widely accepted professional guidelines for opioid prescription in chronic pain or addiction (FPM, 2010 **GL**). In these cases and/or when there is a high risk of opioid misuse, referral to a pain specialist and/or an addiction service may be considered (Huxtable 2011 **NR**).

For more details on discharge medication see Section 8.11.

Key messages

1. Alpha-2 agonists (clonidine and lofexidine) reduce opioid-withdrawal symptoms (**N**) (**Level I** [Cochrane Review]).
2. Remifentanil use leads to opioid-induced hyperalgesia (**N**), which is attenuated by propofol (**N**) (**Level I** [PRISMA]), NMDA-receptor antagonists (**N**) (**Level I**) and pregabalin (**N**) (**Level II**).
3. Gabapentin and pregabalin attenuate opioid-induced hyperalgesia/tolerance and reduce opioid-withdrawal symptoms (**N**) (**Level II**).
4. In opioid-tolerant patients, ketamine improves pain relief after surgery (**S**) (**Level II**) and may reduce opioid requirements (**N**) (**Level II**).
5. Opioid-tolerant patients report higher pain scores (**U**), have slower pain resolution leading to longer hospital stay and increased readmissions (**N**) but have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
6. Opioid-tolerant patients may have significantly higher opioid requirements and interpatient variation in the doses needed than opioid-naïve patients (**N**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ Usual preadmission opioid regimens should be maintained where possible or appropriate substitutions made (**U**).
- ☑ Liaison with all health care professionals involved in the treatment of the opioid-tolerant patient is important (**U**).

- ☑ Opioid-tolerant patients are at risk of opioid withdrawal if nonopioid analgesic regimens or tramadol or tapentadol alone are used (**S**).
- ☑ PCA settings may need to include a background infusion to replace the usual opioid dose and a higher bolus dose (**U**).
- ☑ Neuraxial opioids can be used effectively in opioid-tolerant patients, although higher doses may be required and these doses may be inadequate to prevent withdrawal (**S**).
- ☑ Adjuvants are used for their antitolerance, antihyperalgesic, and antiallodynic effects and there is some evidence upon which to base the choice of agent (**S**).
- ☑ In patients with escalating opioid requirements, management considerations are the development of tolerance or opioid-induced hyperalgesia (**N**).
- ☑ Long-term opioid use may increase the risk of sleep-disordered breathing, which requires appropriate assessment, monitoring and management in the perioperative period (**N**).
- ☑ Following short-term opioid dose escalation for acute pain, a "reverse analgesic ladder" approach, using stepwise reduction to the patient's usual opioid regimen is recommended (**N**).

10.7 The patient with an addiction

An addiction exists when the extent and pattern of substance use interferes with the psychological and sociocultural integrity of the person (see Table 10.7). For example, there may be recurring problems with social and personal interactions or with the legal system, recurrent failures to fulfil work or family obligations, and these patients may put themselves or others at risk of harm (Haber 2009 **NR**).

Use of the term addiction is recommended in the consensus statement from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine (AAPM 2001 **GL**; Ballantyne 2007 **NR**). This separates the behavioural component (addiction) from tolerance and physical dependence, the latter two factors are likely to exist if a patient is taking opioids long-term but may not be present in all patients with an addiction; it also reduces the risk of stigmatisation of patients who have a physical dependence because of long-term opioid therapy (Ballantyne 2007 **NR**).

Effective management of acute pain in patients with an addiction may be complex due to:

- psychological, social and behavioural characteristics associated with an addiction;
- presence of the drug (or drugs) of abuse;
- medications used to assist with drug withdrawal, relapse prevention and/or rehabilitation;
- complications of drug abuse including organ impairment, infectious diseases and increased risk of traumatic injury; and
- the presence of tolerance, physical dependence and withdrawal.

Many health professionals (and some patients) have misconceptions about acute pain management in these patients (Bounes 2014 **NR**). Evidence for the most appropriate management of acute pain in patients with an addiction is limited and thus advice is based primarily on case series, case reports, expert opinion and personal experience.

Effective analgesia may be difficult, may be required for longer periods than in other patients (Rapp 1995 **NR**) and often requires significant deviations from "standard" treatment protocols (Macintyre 2015 **NR**). In addition, ethical dilemmas can arise from the need to balance concerns of undermedication against anxieties about safety and possible drug abuse or diversion (Basu 2007 **NR**). Behavioural issues, including discharge against medical advice, are more common in this patient population (Hines 2008 **Level III-3**).

Identification of patients at risk of drug abuse or abusing drugs may be difficult. The ability of health professionals to predict which patients may misuse or abuse opioids is poor (Jung 2007

Level IV SR, 6 studies, n unspecified) and patient self-reports of drug use may not correlate with evidence from drug screening (Sehgal 2012 **NR**).

The first step in managing patients with an addiction is identifying the problem, although obtaining an accurate history can sometimes be difficult. Polysubstance use is common and many patients use drugs from different groups, the most common being CNS-depressant drugs (such as opioids, alcohol, benzodiazepines and cannabinoids) and CNS-stimulant drugs (including cocaine, amphetamines and amphetamine-like drugs). The group from which the drugs come determines their withdrawal characteristics (if any) and their interaction with acute pain treatment (Mitra 2004 **NR**; Peng 2005 **NR**). Patients should be asked about the route of administration used, as some may be injecting prescription drugs intended for oral, TD or SL use. Verification of opioid doses should be undertaken where possible or else a divided dose given with monitoring of effect, in case the reported dose is incorrect or being diverted (Alford 2006 **NR**; Huxtable 2011 **NR**).

A number of centres worldwide monitor the use of illicit drugs on a regular basis, including prescription opioids. These include:

- worldwide, the World Health Organization (WHO 2014);
- in Australia, the National Drug and Alcohol Research Centre (Roxburgh 2014);
- in New Zealand, the Centre for Social and Health Outcomes Research and Evaluation (SHORE 2014);
- in the UK, the surveillance systems set up by the National Health Service under the Health and Social Care Information Centre (HSCIC 2013); and
- in the USA, the Substance Abuse and Mental Health Services of the USA Department of Health and Human Services (SAMHSA 2014) or other schemes specifically tracking prescription opioid abuse, such as Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) (Jones 2014).

Management of pain in patients with an addiction should focus on:

- engaging the patient in the management plan through empathic and open communication and negotiation of pragmatic clinical goals (Haber 2009 **NR**; Jamison 2011 **NR**);
- effective analgesia, use of strategies that may attenuate tolerance, and prevent withdrawal (as outlined in Section 10.6 above);
- symptomatic treatment of affective disorders and behavioural disturbances; and
- the use of secure drug administration procedures.

Pain management in patients with an addiction often presents significant challenges because of their fears of being stigmatised, concerns about inadequate pain relief, past experiences, expectations, and responses to interventions (Roberts 2008 **NR**; Eyler 2013 **NR**; Buckley 2014 **NR**). Inappropriate behaviours can be prevented to a significant extent by the development of a respectful, honest and open approach to communication and, as with all other patients, an explanation of treatment plans and the fact that complete relief of pain may not be a realistic goal, as well as involvement of the patient in the choice of plan (within appropriate boundaries) (Roberts 2008 **NR**; Haber 2009 **NR**; Jones 2014 **NR**).

A proactive, rather than reactive, discussion about medications and behaviours is recommended (Haber 2009 **NR**) and sometimes limit setting (Huxtable 2011 **NR**). Episodes of acute pain may negatively impact upon long-term retention in addiction treatment programs and better acute pain control may improve such retention (Bounes 2013 **Level III-2**).

The acute pain setting is not one in which to attempt opioid withdrawal, although it may provide a "teachable moment" to initiate changes such as referral to a chronic pain service or for addiction treatment (Buckley 2014 **NR**).

In all cases, close liaison with other treating health professionals and drug and alcohol services is required. This is especially important if the management plan includes additional opioids for pain relief for a limited period after discharge or if any alteration has been made, after

consultation with the relevant services, to methadone or buprenorphine doses while in hospital. In many countries, regulatory requirements will dictate that only one physician has the authority to prescribe for these patients. However, restricted use of additional opioids after discharge may be possible in some circumstances. For example, it could be arranged for the patient to also pick up a limited and progressively decreasing number of tablets each day or every other day, along with their usual methadone or buprenorphine (Peng 2005 **NR**).

For those with concurrent chronic pain, referral to an outpatient pain service may be required and the patient not currently in treatment may require referral to a drug and alcohol service (Huxtable 2011 **NR**).

10.7.1 Management of acute pain in pregnant patients with an addiction

The majority of women with an addiction are of childbearing age; 0.76% of all births at one obstetric institution were to women using opioids and 0.42% to those using amphetamines (Ludlow 2007 **NR**). The prevalence of prescription-opioid abuse is rising in this population, along with the prevalence of NAS (Jones 2014 **NR**).

The management of acute pain in pregnant patients with an addiction must take into account treatment of the mother, as well as possible effects on the fetus and newborn.

Identification of these patients during pregnancy allows time for assessment and appropriate management planning; however this is not always possible as antenatal care is often suboptimal (Jones 2014 **NR**). Routine screening may increase the rate of addiction detection (Jones 2014 **NR**) and validated screening tools include the 4Ps and CRAFFT (ACOG 2012 **GL**; Jones 2014 **NR**). Care is complicated in these patients by other factors related to their use of drugs such as respiratory infections, endocarditis, untreated cellulitis, abscesses, HIV/AIDS, hepatitis and social factors such as abuse, interpersonal violence and homelessness (Ludlow 2007 **NR**; Jones 2014 **NR**).

Reviews of pain management in these patients have been published (Stanhope 2013 **NR**; Buckley 2014 **NR**; Jones 2014 **NR**). Collaborative team care is essential.

Methadone maintenance is regarded as the gold standard for antenatal opioid replacement (ACOG 2012 **GL**). There is less evidence for the use of buprenorphine in pregnancy. The largest study of opioid-replacement therapy in pregnancy, the Maternal Opioid Treatment Human Experimental Research study compared methadone and buprenorphine-maintenance therapy and showed similar maternal outcomes (Jones 2012b **NR** summarising results of 1 RCT, n=175). Buprenorphine resulted in less fetal cardiac and movement suppression, lower rates of preterm labour, less severe NAS (a treatable condition) but lower maternal satisfaction and lower treatment retention rates, when compared with methadone maintenance (Bandstra 2012 **NR** secondary analysis of 1 RCT, n=175; Jones 2012a **NR**).

Pregnant patients taking methadone as part of a drug-dependence treatment program should receive whatever dose is needed to prevent heroin use, and the dose may need to be increased in the third trimester because the physiological changes associated with pregnancy can alter the pharmacokinetics of the drug (Ludlow 2007 **NR**; Jones 2012a **NR**). Both methadone and buprenorphine should be continued without interruption or, if the patient cannot take these medications, then an alternative route (or opioid) should be used (Jones 2008 **NR**; Meyer 2010 **NR**).

As with any opioid-tolerant patient, additional opioids will be required for any pain post Caesarean delivery and the newborn will require high-level neonatal care because of the risk of NAS (Ludlow 2007 **NR**; Jones 2008 **NR**; Jones 2012a **NR**). Pain scores after Caesarean delivery are also higher (Meyer 2010 **Level III-3**). Those taking buprenorphine will also have higher opioid requirements after surgery and the newborn is still at risk (albeit maybe a lower risk) of NAS (Ludlow 2007 **NR**; Jones 2010 **NR**; Jones 2012a **NR**).

Opioid requirements during labour were not significantly increased, although methadone- (Meyer 2007 **Level III-3**) and buprenorphine-maintained patients had higher pain scores and higher opioid requirements postpartum than did controls (Meyer 2010 **Level III-3**). In another study, opioid-maintained patients required epidural analgesia more often than controls

(38.1 vs 14.3%) but had no higher opioid requirements after Caesarean delivery (Hoflich 2012 **Level III-2**).

Opioid requirements and the risk of withdrawal, for the patient and the newborn, will be higher in patients still using heroin prior to childbirth (Ludlow 2007 **NR**). For further information on maternal and neonatal outcomes see Section 10.1.1.1.

Opioid requirements in those addicted to substances other than opioids should be similar to other patients.

10.7.2 CNS depressant drugs

Although not inevitable, abuse of CNS-depressant drugs (eg opioids, alcohol, benzodiazepines) is often associated with physical dependence and the development of tolerance (see Section 10.6). Withdrawal from CNS depressant drugs produces symptoms of CNS and autonomic hyperexcitability, the opposite of the effects of the CNS-depressant drugs themselves.

10.7.2.1 Opioids

In general, when opioids are used in the short-term to treat acute pain, they are usually effective and the risk of abuse is considered to be low; although there are few data and the exact incidence is unknown (Wasan 2006 **Level IV SR**, 9 studies, n unspecified; Clarke 2014 **Level III-2**). However, when opioids are prescribed for chronic noncancer pain, the risk of abuse of these drugs may be higher (Ballantyne 2007 **NR**; Chou 2009 **GL**; RACP 2009 **GL**). Both patients with chronic pain and those with an addiction have a high rate of psychiatric conditions (such as anxiety and depression). Patients with chronic pain may therefore be at increased risk of developing behavioural problems associated with opioid use (Ballantyne 2007 **NR**). Medical inpatients with acute pain and opioid addiction (nonmedical use of opioids) had similar characteristics (younger, positive score on addiction questionnaires, life time history of substance-use disorder) to chronic pain outpatients misusing opioids (Suzuki 2013 **Level IV**).

Opioid abuse involves heroin and also legally prescribed opioids or prescription opioids obtained illegally. The number of opioid prescriptions continues to increase in many countries, along with the incidence of abuse of these drugs (Fischer 2010 **NR**; Degenhardt 2013 **Level IV**). Illicitly obtained prescription opioids now account for a large proportion of all opioids used by patients with an addiction (NDARC 2009 **Level IV**; Roxburgh 2011 **Level IV**), in many countries exceeding the use of heroin (Fischer 2006 **Level IV**; Okie 2010 **NR**; Imtiaz 2014 **Level IV**).

Not all aberrant drug-related behaviours indicate opioid addiction. Suggestive behaviours include unsanctioned dose escalations, "lost" or "stolen" medications, obtaining the drugs from a number of different prescribers, polysubstance abuse, use of opioids obtained illicitly, and forging prescriptions (Turk 2008 **NR**). Other features of addiction are listed under the definition of addiction in Table 10.7. Other aberrant behaviours may be indicative of factors other than addiction (Ballantyne 2007 **NR**).

A large survey, to which over 9,000 patients with chronic noncancer pain responded (a 64% response rate), found that users of prescription opioids had higher rates of opioid and nonopioid illicit drug misuse and of alcohol abuse, compared with those not using prescription opioids (Edlund 2007 **Level III-2**). However, it is difficult to get accurate information on the rate of opioid addiction in patients with chronic pain, especially as a variety of definitions are used that may not differentiate between problematic drug use and true addiction (Ballantyne 2007 **NR**). The prevalence of addiction in patients with chronic pain prescribed opioids is reported to range from 0–50% (Hojsted 2007 **Level IV**). Others have reported that, on the basis of urine toxicology, up to 30–40% of patients prescribed opioids for the management of their chronic pain misuse those drugs (Turk 2008 **Level IV**). A community-based study in Denmark identified that those prescribed long-term opioids for chronic pain were more likely to smoke, use cannabis and exhibit "addictive behaviours" than were those not prescribed opioids (Hojsted 2013, **Level III-2**).

More recently, focus has turned to the use of "abuse deterrent" or "tamper-resistant" formulations (Schaeffer 2012 **NR**); strategies that are being assessed include the use of

technologies that prevent the release of active opioid when tablets are crushed or attempts are made to extract the drugs by other means, combinations of the opioid with an opioid antagonist such as naloxone or with a second substance with aversive effects (Webster 2011 **NR**; Passik 2014 **NR**). It is important to note that such formulations are not preventing abuse in principle but are making it more difficult to abuse these opioids by routes other than the oral one (ie injecting, snorting). For example, addition of ultra-low-dose naltrexone to oxycodone did not reduce its abuse liability in experienced drug users (Tompkins 2010 **Level II**, n=14, JS 3).

Those with addiction to opioids should be treated using the strategies outlined in Section 10.7 and in the remainder of this section.

10.7.2.2 Alcohol and benzodiazepines

Excessive alcohol use predisposes to particular types of acute pain eg trauma (77% of screened Australian trauma patients had a probable alcohol-related injury or were engaging in risky drinking regularly (Browne 2013 **Level IV**) and pancreatic disease (RR 1.37; 95%CI 1.19 to 1.58) (Alsamarrai 2014 **Level IV SR**, 51 studies, n≈3,000,000). It may also lead to hepatic dysfunction, which may affect the metabolism of other drugs, including analgesics.

There is no cross-tolerance between opioids and alcohol or benzodiazepines in animal studies (Bell 1998 **BS**). The effective concentrations of remifentanil were not different between alcoholic and nonalcoholic patients (Liang 2011 **Level II**, n=60, JS 5). There is therefore no pharmacological reason to use higher than "standard" initial opioid doses in patients with an alcohol or benzodiazepine dependence.

Alcohol and/or benzodiazepine use disorders are relatively common and prevention of withdrawal should be a clinical priority in all patients. Benzodiazepines are effective for alcohol-withdrawal symptoms, especially prevention of seizures (Amato 2010 **Level I** [Cochrane], 64 RCTs, n=4,309). If benzodiazepines are administered for the treatment of withdrawal symptoms and signs, patient sedation levels must be monitored, especially if patients are receiving concurrent opioids or other sedating drugs (Macintyre 2011 **NR**). Excessive sedation will limit the amount of opioid that can be given safely.

There are inconclusive results on the effect of pregabalin on alcohol withdrawal (Guglielmo 2012 **Level IV SR**, 3 studies [withdrawal], n=271).

10.7.2.3 Cannabinoids

"Recreational" cannabis users had approximately 50% greater rescue pethidine requirements, as well as higher pain intensity and dissatisfaction scores, than nonusers over the first 6 h after orthopaedic surgery (Jefferson 2013, **Level III-2**).

Synthetic cannabinoids may contain a large number of components and are more potent than the naturally occurring drug, resulting in agitation, hypertension, hypokalaemia, vomiting and seizures (Hermanns-Clausen 2013, **Level IV**).

For information about the use of cannabinoids for acute pain, see Section 4.11.

10.7.3 CNS-stimulant drugs

Abuse of CNS-stimulant drugs (eg cocaine, amphetamines, ecstasy) is associated with psychological rather than physical dependence and only a low degree of tolerance; these drugs do not exhibit any cross-tolerance with opioids (Buckley 2014 **NR**). While behavioural and autonomic effects are seen during acute exposure, withdrawal symptoms are predominantly affective rather than physical. Stimulants are associated with particular types of acute pain (eg cocaine use and chest pain including acute coronary syndromes).

Cocaine and ecstasy (N-Methyl-3,4-methylenedioxyamphetamine or MDMA) are known to enhance the analgesic effects of morphine in animal studies (Nencini 1988 **BS**; Kauppila 1992 **BS**; Gatch 1999 **BS**). This effect may be age-dependent as exposure to metamphetamine in adolescent rats enhances morphine antinociception (and tolerance development) with inverse effects in adult rats (Cyr 2012 **BS**). There are currently no data from human studies.

In experimental-pain settings, subjects taking ecstasy have been shown to have a reduced pain tolerance (O'Regan 2004 **Level III-2 SR**); this was also true for abstinent previous users (lower pressure pain thresholds, increased cold pain ratings, increased pain ratings during testing of DNIC) (McCann 2011 **Level III-2**). Those taking cocaine also had reduced cold-pressor pain thresholds (Compton 1994 **Level III-2**). There are no data from the clinical setting of any differences in opioid requirements.

Withdrawal from methamphetamines is characterised by increases in sedation and appetite that can last for a few days; the severity of sleepiness correlated with amount used (calculated by cost per month) and length of regular use (McGregor 2005 **NR**).

10.7.4 Drugs used in the treatment of addiction disorders

Close liaison with all treating clinicians and drug and alcohol services should occur. In the case of those receiving opioid substitution therapy, this may include arrangements with the usual prescriber and pharmacist for a "takeaway" dose on the day of elective surgery/procedure admission, as well as liaison at discharge to ensure continuity of ongoing therapy (Huxtable 2011 **NR**; Schug 2012 **NR**).

Good acute pain management is particularly important for patients on opioid-maintenance treatment as acute pain exposure was associated with reduced retention in treatment (adjusted OR 0.46; 95%CI 0.23 to 0.93) (Bounes 2013 **Level III-2**).

10.7.4.1 Methadone

Methadone is a long-acting opioid agonist used in the management of patients with an opioid addiction (see Section 4.1). It is commonly prescribed in doses in the range 50–120 mg and once/d, which is adequate to suppress symptoms of opioid withdrawal; the duration of any analgesic effect from the dose is much shorter (Alford 2006 **NR**); although this is sometimes not well understood by treating physicians (Bounes 2014 **Level IV**). Dividing the daily dose on a temporary basis (eg giving half the usual daily methadone doses twice a day or one third of the usual dose every 8 h) may result in a better analgesic effect (Basu 2007 **NR**).

In the acute pain setting, methadone should be continued, where possible, at the usual dose. If there is any doubt about the dose (eg there is suspicion that the patient is diverting all or part of the prescribed amount), it is prudent to give part of the reported dose and repeat this over the day if needed, monitoring the patient for sedation (Peng 2005 **NR**; Huxtable 2011 **NR**). If the patient is unable to take methadone by mouth, substitution with parenteral methadone or another opioid will be required in the short-term (Mitra 2004 **NR**; Huxtable 2011 **NR**). Parenteral methadone doses were 0.7 of the oral dose (Gonzalez-Barboteo 2008 **Level IV**); half to two-thirds of the oral maintenance dose can be given in equal divided doses by SC or IM injection 2–4 times/d or by continuous infusion (Alford 2006 **NR**; Huxtable 2011 **NR**).

Patients in methadone-maintenance programs have been shown to be hyperalgesic when assessed with cold-pressor testing (Compton 2000 **Level III-2**; Doverty 2001a **Level III-2**; Athanasos 2006 **Level III-2**; Hay 2009 **Level III-2**; Compton 2012 **Level III-2**). QST shows abnormal thermal pain sensitivity, which is influenced by the methadone dose and the presence of chronic pain (Peles 2011 **Level III-3**). Abnormalities may persist for months after methadone is ceased (Prosser 2008 **Level III-2**). In subjects taking methadone, sensitivity to cold-pressor pain stimuli is attenuated by gabapentin (Compton 2010 **Level II**, n=26, JS 2).

Care should also be taken with concurrent administration of other drugs that prolong the corrected QT interval; although this is thought to be an issue only with very high methadone doses (Andrews 2009 **NR**).

10.7.4.2 Buprenorphine

Buprenorphine is a partial opioid agonist used effectively in the treatment of opioid addiction (Mattick 2014 **Level I** [Cochrane], 31 RCTs, n=5,430) and commonly prescribed in doses of 8–32 mg (Roberts 2005 **NR**).

Administered SL, it has a mean terminal half-life of 28 h (Johnson 2005 **NR**). It is usually given once every day or every second day, which is adequate to suppress symptoms of opioid

withdrawal; like methadone the duration of any analgesic effect from the dose is much shorter (Alford 2006 **NR**). Preparations that combine buprenorphine and naloxone (the latter is poorly absorbed by the SL route) are available (Orman 2009 **NR**); naloxone is added to buprenorphine with the aim of reducing parenteral abuse of the drug.

In opioid-naïve subjects, administration of buprenorphine resulted in decreased hyperalgesia following transcutaneous pain stimuli compared with those given a placebo, suggesting that unlike morphine and methadone, buprenorphine may exert an antihyperalgesic effect (Koppert 2005 **Level III-2**). However, both methadone-maintained and buprenorphine-maintained patients were similarly more sensitive to cold-pressor pain than opioid-naïve controls (Compton 2012 **Level III-2**).

If shorter-acting opioid agonists are required, a decision whether to continue the buprenorphine or not needs to be made. Traditional approaches to management vary from withholding the buprenorphine and substituting an alternative opioid (eg methadone) to continuing the buprenorphine as usual (Roberts 2005 **NR**; Alford 2006 **NR**). More recent evidence supports continuing usual buprenorphine and managing acute pain with the combination of a short-acting pure opioid agonist as well as other multimodal analgesic strategies (Macintyre 2015 **Level III-2**; Kornfeld 2010 **Level IV**) ie managing the patient as per any other opioid-tolerant patient. Compared with those for whom buprenorphine was ceased, those who continued buprenorphine had similar pain scores and adverse effects, with lower opioid requirements, reduced requirement for ketamine and shorter duration of PCA therapy and APS involvement (Macintyre 2013 **Level III-2**). As with methadone, dividing the daily doses on a temporary basis (every 8 or 12 h) may take advantage of the analgesic properties of the buprenorphine (Alford 2006 **NR**).

If buprenorphine has been ceased (eg unconscious patient, intraoral surgery or trauma preventing SL administration), its reintroduction should be managed in consultation with the prescribing health professional who should also be involved in discharge planning to ensure continuity of long-term care and availability of usual replacement therapy on discharge (Huxtable 2011 **NR**).

10.7.4.3 Naltrexone

Naltrexone is a pure opioid antagonist used in the management of patients with opioid or alcohol dependence. While there is good evidence for its effectiveness in alcohol dependence (Rosner 2010 **Level I** [Cochrane], 50 RCTs, n=7,793), this is not the case in opioid dependence. Here neither oral naltrexone (Minozzi 2011 **Level I** [Cochrane], 13 RCTs, n=1,158) nor long-acting naltrexone implants (Larney 2014 **Level I**, 5 RCTs, n=576 & **Level IV**, SR of 4 studies, n=8,358) have good evidence of efficacy and safety. On the contrary, there is a significant excess mortality in patients on oral naltrexone compared to methadone-maintenance treatment (RR 3.5; 95%CI 2.2 to 5.8) (Degenhardt 2015 **Level III-2**).

The usual oral maintenance dose is 50 mg/d; orally administered, naltrexone has an apparent half-life of about 14 h and binds to opioid receptors for over 24 h following a single dose (Vickers 2006 **NR**); this can create difficulties in the acute pain setting as opioid agonists will be antagonised. It has been recommended that, where possible, naltrexone should be stopped for at least 24 h before surgery (Mitra 2004 **NR**; Vickers 2006 **NR**).

These difficulties are even greater when the patient has an active implant (Vickers 2006 **NR**; O'Brien 2006 **NR**); the duration of efficacy of the 1.1 g implant is approximately 95 d and that of the 2.2 and 3.3 g implants approximately 140 d (Ngo 2008 **PK**). In cases where effective opioid analgesia is required, removal of the implant should be considered (Sadleir 2011 **Level IV**).

In patients receiving naltrexone therapy, multimodal analgesic regimens (eg NSAIDs, paracetamol, ketamine, tramadol and regional analgesia) should also be employed.

There is experimental evidence of mu-opioid receptor upregulation following antagonist withdrawal (Millan 1988 **BS**) and abrupt discontinuation of naltrexone may therefore lead to a period of increased opioid sensitivity (Vickers 2006 **NR**). As the effect of naltrexone diminishes after it has been ceased, the amount of opioid required to maintain analgesia may also need to be decreased in order to avoid opioid overdose (in particular OIVI).

Reintroduction of naltrexone should be done in consultation with the prescribing health professional.

10.7.5 Patients in recovery from addictive disorders

Patients in drug-treatment programs or in drug-free recovery may be concerned about the risk of relapse if they are given opioids for the management of their acute pain (Eyler 2013 **NR**; Markowitz 2010 **NR**). However, there is no evidence that the use of opioids to treat acute pain increases the rate of relapse; a more likely trigger is unrelieved pain, although this is primarily based on expert opinion (Alford 2006 **NR**; Markowitz 2010 **NR**; Buckley 2014 **NR**). Those at particular risk of relapse when given opioids may include younger patients, males and those using multiple illicit drugs, especially cocaine (Markowitz 2010 **NR**). Effective communication and planning, the use of multimodal analgesic strategies, reassurance that the risk of reversion to an active addiction is small, and information that ineffective analgesia can paradoxically lead to relapses in recovered patients, are important and help avoid undertreatment (Mitra 2004 **NR**; Huxtable 2011 **NR**).

10.7.6 Contribution of acute pain management to the community supply of opioids

There is a contribution of discharge opioid prescribing for acute pain management to the broader community use of prescription opioids, through personal abuse and diversion to others (Passik 2014 **NR**). "Left over" medications from resolved acute pain episodes also represent a source for abuse and diversion; deaths attributable to diverted discharge opioid medication are not uncommon.

It has been suggested that the lessons learnt in the management of chronic pain should also be applied to acute pain management, with formal risk assessment tools applied also for short-term opioid prescription (Passik 2014 **NR**; Macintyre 2014 **NR**). Certainly the need to treat pain in the individual patient should be balanced against risk to that person of abuse and diversion, and the broader community concern.

For discharge medication see also Section 8.11.

Key messages

1. Benzodiazepines are effective for alcohol-withdrawal symptoms, in particular reducing seizures (**N**) (**Level I** [Cochrane Review]).
2. Poorly managed acute pain episodes may decrease retention in opioid-maintenance programs (**N**) (**Level III-2**).
3. Methadone- and buprenorphine-maintenance regimens should be continued throughout acute pain episodes wherever possible (**S**) (**Level III-2**).

The following tick boxes represent conclusions based on clinical experience and expert opinion.

- ☑ There is no cross-tolerance between alcohol or benzodiazepines or central nervous system stimulants and opioids (**S**).
- ☑ To achieve better analgesic efficacy, daily methadone and buprenorphine maintenance doses should be divided and given 8 to 12 hourly (**N**).
- ☑ Oral naltrexone should be stopped at least 24 hours prior to elective surgery (**U**); naltrexone implants may need surgical removal in cases of severe acute pain and no opioid responsiveness (**N**).
- ☑ Patients who have completed naltrexone therapy should be regarded as opioid naïve; in the immediate post-treatment phase they may be more opioid sensitive (**U**).

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Appendix A

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Multidisciplinary consultative committee

Area of expertise	Member	Affiliation
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Addiction Medicine (Drug and Alcohol)	Dr Allan Quigley	Director of Clinical Services Next Step, Mental Health Commission Perth, Western Australia
Australian Medicines Handbook	Louise Quinn	Editor Australian Medicines Handbook Pty Ltd Adelaide, South Australia
Burns and Plastic Surgery	Prof Fiona Wood	Director of the Burns Service of WA and Director of the Burn Injury Research Unit of UWA. Perth, Western Australia

Chiropractic	A/Prof Philip S Bolton	School of Biomedical Sciences & Pharmacy, Faculty of Health and Medicine, University of Newcastle Callaghan, New South Wales
Clinical Pharmacology	Prof Paul Rolan	Affiliate Professor School of Medicine Faculty of Health Sciences The University of Adelaide Adelaide, South Australia
Consumer representative	Helen Maxwell Wright	Consumer Representative ANZCA Melbourne, Victoria
Complementary Medicine	Professor Caroline Smith	National Institute of Complementary Medicine, Western Sydney University, Sydney, New South Wales
Emergency Medicine	Prof Daniel M Fatovich	Emergency Medicine, Royal Perth Hospital and University of Western Australia Head, Centre for Clinical Research in Emergency Medicine, Harry Perkins Institute of Medical Research Perth, Western Australia
General Practice	Dr Stephen Leow	Clinical Director at GP Plus Elizabeth GP Axis Munno Para South Australia
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Rheumatology	Prof Milton Cohen	Specialist Pain Medicine Physician and Rheumatologist Conjoint Professor, St Vincent's Clinical School, UNSW Australia Sydney, New South Wales
Rural and Remote Medicine	A/Prof Kirsten Auret	Deputy Head of School, Rural Clinical School of WA Albany, Western Australia

Appendix B

Process report

This is the fourth edition of the document *Acute Pain Management: Scientific Evidence*. The first edition was written by a multidisciplinary committee headed by Prof Michael Cousins and published by the National Health and Medical Research Council (NHMRC) in 1999.

The second edition was written by multiple contributors and a working group chaired by A/ Prof Pam Macintyre. It was approved by the NHMRC and published by the Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) in 2005. It was also endorsed by other major organisations worldwide.

The third edition was written by multiple contributors and a working group chaired by A/ Prof Pam Macintyre. It was approved by the NHMRC and published by ANZCA and its FPM in 2010. It was also endorsed by other major organisations — the International Association for the Study of Pain, the Royal College of Anaesthetists and its Faculty of Pain Medicine, the Australian Pain Society, the Australasian Faculty of Rehabilitation Medicine, the College of Anaesthesiologists of the Academies of Medicine of Malaysia and Singapore, the College of Intensive Care Medicine of Australia and New Zealand, the Faculty of Pain Medicine of the College of Anaesthetists of Ireland, the Hong Kong College of Anaesthesiologists, the Hong Kong Pain Society, the Malaysian Association for the Study of Pain, the New Zealand Pain Society, the Pain Association of Singapore, the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Psychiatrists and the Royal Australasian College of Surgeons — and recommended to its members by the American Academy of Pain Medicine.

In accord with the NHMRC requirement that guidelines be revised as further evidence accumulates, and as there has been a continuing and substantial increase in the quantity of information available about acute pain management, it was seen as timely to reassess the available evidence. ANZCA and the FPM therefore again took responsibility as an "external body" for revising and updating the document – this fourth edition.

Since the third edition was published in 2010, a sizeable amount of new evidence relating to the management of acute pain has been published. The aim of this fourth edition is, as with the first three editions, to combine a review of the best available evidence for acute-pain management with current clinical and expert practice, rather than to formulate specific clinical practice recommendations. Accordingly, the document aims to summarise, in a concise and easily readable form, the substantial amount of evidence currently available for the management of acute pain in a wide range of patients and acute pain settings using a variety of treatment modalities. It aims to assist those involved in the management of acute pain with the best current (up to August 2014) evidence-based information.

It is recognised that while knowledge of current best evidence is important, it plays only a part in the management of acute pain for any individual patient and many factors in addition to scientific evidence should be considered if such treatment is to be effective.

Evidence-based medicine has been defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" and that must "integrate research evidence, clinical expertise and patient values" (Sackett 1995 **NR**). Therefore evidence, clinical expertise and, importantly, patient participation (ie including the patient as part of the treating and decision-making team, taking into account their values, concerns and expectations) are required if each patient is to get the best treatment. The information provided in this document is not intended to over-ride the clinical expertise of health professionals. There is no substitute for the skilled assessment of each individual patient's health status, circumstances and perspectives, which health professionals will then use to help select the treatments that are relevant and appropriate to that patient.

This process report provides examples of the decision-making processes that were put in place to deal with the plethora of available evidence under consideration.

Development process

A working group was convened to coordinate and oversee the development process. An editorial subgroup of the working group (Prof Stephan A Schug [Chair], A/Prof Greta M Palmer, A/Prof David A Scott, Dr Richard Halliwell, Dr Jane Trinca) coordinated the development process and edited and/or wrote the sections. The working group also included Dr Mark Rockett (representing the Faculty of Pain Medicine, Royal College of Anaesthetists in the United Kingdom) and Prof Karen Grimmer from the International Centre for Allied Health Evidence, University of South Australia, who had been the NHMRC-appointed Guidelines Assessment Register representative for the third edition. She provided expert advice on the use of evidence-based findings, the methodology and the application of NHMRC criteria for this edition.

A large panel of contributors was appointed to draft sections of the document and a multidisciplinary consultative committee was chosen to review late drafts and contribute more broadly as required. A list of panel members is given in Appendix A, together with a list of contributing authors and working group members.

Structures and processes for the revised edition were developed, and within these frameworks, contributors were invited to review the evidence and submit content for specific sections according to their area of expertise. All contributors were given instructions about the process of the literature search and the requirements for submission of their section, referred to the website of the NHMRC document *How to Use the Evidence: Assessment and Application of Scientific Evidence* (NHMRC 2000 **GL**) and directed to the ANZCA website for copies of the third edition of the document.

Members of the editorial subgroup of the working group were responsible for the initial editing of each section, the evaluation of the literature submitted with the contributions and checking for further relevant references. In a series of meetings, the working group compiled and edited an initial draft. Once the draft of the document had been prepared, it was sent to all contributors for comment before being redrafted for public consultation as well as parallel review by members of the multidisciplinary panel. To ensure general applicability, there was a very wide range of experts among contributors and on the multidisciplinary committee, including medical, nursing, allied health and complementary medicine clinicians and consumers (see Appendix A).

The fourth edition of *Acute Pain Management: Scientific Evidence* is based on the NHMRC's recommendations for guideline development. That is, this review of the best available evidence for acute pain management focuses on improving patient outcomes, is based on the best evidence available, includes statements concerning the strength of levels of evidence underpinning recommendations and uses a multidisciplinary approach involving all stakeholders (including consumers).

Competing interests

Conflicts of interest were managed by each of the five editors responsible for writing the content of the document by completing an International Committee of Medical Journal Editors *Uniform Disclosure Form for Potential Conflicts of Interest*. A list of conflicts of interest is provided below.

Member	Conflicts of interest
Prof Stephan A Schug (Chair)	Chair of Anaesthesiology at University of Western Australia; Director of Pain Medicine at Royal Perth Hospital. Member of Board of FPMANZCA and various committees of ANZCA and FPMANZCA. Vice Chair of SIG Acute Pain of IASP and Chair of SIG Acute Pain of ACECC. Member of advisory boards of various educational organisations on pain (AIM, Pain in Practice, PRISM), of PROSPECT group, of Faculty of 1000 (F1000), the Board of AOSRA, Musculoskeletal Health Network "Pain Health Working Group", WA Opioid Pharmacotherapy Mortality Review Committee, Leitliniensteuergruppe S3-Leitlinie "Behandlung akuter perioperativer und posttraumatischer Schmerzen" DGSS, DGCh, DGAI, Journal PAIN Advisory Board, Review Board ICD-11 Pain. External Advisor PAIN OUT (EC Research Project). Current recipient of competitive research funding from ANZCA The Anaesthesiology Unit of the University of Western Australia chaired by Prof Schug, but not he privately, has received research and travel funding and speaking and consulting honoraria from bioCSL, Bionomics, Eli Lilly, Gruenenthal, Janssen Pharmaceuticals, Mundipharma, Pfizer, Phosphagenics and iX Biopharma within the last 5 years.
A/Prof Greta M Palmer	Paediatric and Adult Pain Specialist and Specialist Anaesthetist, Royal Children's and Royal Melbourne Hospitals; Deputy Head of the Children's Pain Management Service, Royal Children's Hospital; Research Associate, Murdoch Childrens Research Institute; Associate Professor, University of Melbourne. Small industry project grants received from Mundipharma and dolasetron for blinded drug preparation in a postoperative nausea and vomiting RCT and for paracetamol serum assay data access to support FDA application for paediatric listing of IV paracetamol. No further industry support has been received in the last 7 years.
A/Prof David A Scott	Associate Professor, University of Melbourne; Director of the Department of Anaesthesia and Acute Pain Medicine, St Vincent's Hospital Melbourne; Elected Councillor (honorary) and Vice President of ANZCA. No industry support or funding, either directly or indirectly, has been received in the last 10 years. Current recipient of competitive research funding from ANZCA and the NHMRC.
Dr Richard Halliwell	Deputy Director of Anaesthesia, Westmead Hospital, Sydney; Director of Acute Pain Service Westmead Hospital; Clinical Senior Lecturer, Discipline of Anaesthesia, Sydney Medical School. No industry support has been received in the last 10 years.
Dr Jane Trinca	Director of Barbara Walker Centre for Pain Management, St Vincent's Hospital, Melbourne; Honorary Clinical Research Fellow, Bionic institute. No industry support has been received in last 10 years.

Member	Conflicts of interest
Editorial Advisory Group	
Representative of FPMRCA:	Consultant anaesthetist and specialist in pain medicine, Derriford Hospital, Plymouth, UK.
Dr Mark Rockett	Honorary Associate Professor, Plymouth University Peninsula School of Medicine and Dentistry.
	Co-opted board member Faculty of Pain Medicine of the Royal College of Anaesthetists.
	Speaking and/or consultative honoraria from Pfizer, Grunenthal and Astellas Pharma within the last 10 years. Recipient of competitive research funding from NIAA and NIHR.
Methodology:	Professor of Allied Health, University of South Australia
Prof Karen Grimmer	Director, International Centre for Allied Health Evidence, University of South Australia (www.unisa.edu.au/cahe)
	Scientific lead, Project SAGE, Medical Research Council, South Africa, Flagship Grant 2014-2017
	No industry support, or grants funding relevant to this project has been received in the last 10 years

No disclosures of interests were requested from contributors. Contributors conducted searches and summarised the new literature and had no influence on the content or the decisions about inclusion or exclusion of material.

Review of the evidence

This document is a revision of the third edition of *Acute Pain Management: Scientific Evidence* published in 2010. Therefore most of the new evidence included in this fourth edition has been published from August 2009 onwards, which was the cut-off date of literature inclusion in the third edition. Literature was considered when published between this date and the cut-off date for this fourth edition (August 2014). However, in rare circumstances, references published after this cut-off were considered but only if of high relevance and encountered in the editorial process. These were identified by team members. Moreover, evidence-based guidelines had been published independently by a number of organisations in the areas of acute back and musculoskeletal pain and recommendations relevant to the management of acute pain were drawn directly from these.

Search strategies

Searches of the electronic databases Medline or PubMed, Embase and Cochrane were conducted for each of the main topics included in the review, from August 2009 until August 2014. Searches were limited to articles concerning humans. Included literature was required to be full text and written in English.

The initial searches were inevitably broad, given the very wide scope of the topic. “Pain”, “acute pain”, “postoperative pain” or “analgesia” was searched with the key headings of the various sections and subsections of the document such as “neuropathic”, “patient-controlled”, “epidural”, “paracetamol” and so on. For drugs and techniques, a search was also made for “efficacy”, “complications” and “adverse effects”. Hand searches were also conducted of a large range of relevant journals from August 2009 onwards and bibliographies of relevant papers were checked to identify references that may not have been identified from database searching.

Levels of evidence

Levels of evidence were documented according to the NHMRC designation (NHMRC 1999 **GL**) and, as for the second and third edition of this document, clinical practice points have been added.

Levels of evidence were documented according to the NHMRC designation (NHMRC 1999 **GL**).

Levels of evidence	
I	Evidence obtained from a systematic review of all relevant randomised-controlled trials (RCTs)
II	Evidence obtained from at least one properly designed randomised-controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post test or pretest and post-test
Clinical practice points	
☑	Recommended best practice based on clinical experience and expert opinion

Foreign language evidence

Where new systematic reviews or meta-analyses were identified with an English abstract, but written substantially in another language, these were considered for inclusion if there was enough information in the abstract to establish it as valid NHMRC Level I evidence. In this instance, these were included and then classified as Level I evidence for this review. Similarly, where relevant, studies with lower levels of evidence in a foreign language were also considered, if there was enough information in the English abstract to establish study validity (eg critical appraisal score and relevant findings). If there was insufficient information in the abstract to establish its validity then such references were excluded. Where available in the review team, speakers of the language would be engaged for translation.

Preferred evidence

A review of acute pain management requires a broad focus on a range of topics (eg postoperative pain, musculoskeletal pain, migraine, pain associated with spinal cord injury etc). This broad focus inevitably produces a very large number of research publications. In order to provide the best information to inform practice, it was important to concentrate on the highest ranked, highest quality evidence where available (eg Cochrane review).

Secondary evidence: High-quality systematic reviews of RCTs (NHMRC Level I) were the preferred evidence source. Reference lists of such designated Level I evidence were then scanned for the included RCTs. If these studies had also been identified in the literature search, they were excluded from subsequent analysis as their findings had already been accounted for in the Level I evidence. Relevant RCTs identified in the search, which had not been included in the systematic reviews or meta-analyses and relevant RCTs published since the cut-off date for literature inclusion in the systematic reviews or meta-analyses, were included in the update, to provide additional primary evidence. In case of multiple systematic reviews or meta-analyses published in parallel, or a lower-ranked meta-analysis published after a previous higher-ranked one (eg an older Cochrane Review), their results were considered after identification of the number of overlapping studies. Cochrane Reviews, which had been withdrawn due to age and lack of an update, were considered in conjunction with subsequently published Level I evidence.

Systematic reviews that included non-randomised controlled studies were assigned the level of evidence of their lowest level component studies, as outlined in the NHMRC designation of evidence levels (NHMRC 1999 **GL**) and identified by "SR" following the level of evidence eg (Roberto 2014 **Level III-2 SR**).

Primary evidence: Where Level I reviews were not available, the next preferred level of evidence was RCTs (NHMRC Level II). Where these were not available, other experimental evidence or case series were accepted as the best available evidence (reflecting NHMRC Level III and Level IV). According to NHMRC guidelines, Level IV evidence is obtained from

case series, either post-test or pretest and post-test; these levels refer to evidence about interventions (NHMRC 1999 **GL**). Publications describing results of audits or surveys were also included as Level IV evidence in the absence of any other higher-level evidence.

Expert opinion: In the few instances where no relevant published evidence was available, expert opinion was included as the best available information. Narrative reviews containing such evidence are identified by NR following the reference eg (Graham 2013 **NR**). Where no opinion-based studies were available, the working group provided expert input.

Other evidence types: Not all evidence relating to the management of acute pain is intervention-based. In a number of instances, best practice has been derived from studies such as record audit, quality processes or single case reports, pharmacokinetic studies, human experimental data and basic science or animal data. These studies were included where relevant and the type of research indicated following the reference. Thus readers will find CR (for case report) eg (Madadi 2010 **CR**), **GL** for clinical practice guidelines eg (Kowalski 2011 **GL**), BS if presenting basic science or animal data eg (LaCrois-Fralish 2011 **BS**), PK if presenting pharmacokinetic studies eg (Holford 2012 **PK**) and EH if presenting human experimental data eg (Saxena 2013 **EH**). The latter two were also assigned an evidence level in line with NHMRC hierarchy if suitable eg (Williams 2002 **Level II PK**, n=96, JS 4).

Quality scoring

Systematic reviews and meta-analyses: These studies were not directly assessed for quality using a critical appraisal instrument. The quality assessment was based on the quality criteria that were reported to underpin the review. These were rated and reported in the following manner, on the assumption that if the study was reported as having been conducted along the lines of a specific quality approach, then the methodological quality of the study could be assumed.

- Reviews performed by the Cochrane Collaboration are identified as [Cochrane] in the text eg (Derry 2013 **Level I** [Cochrane]);
- Reviews that overtly state that the review conformed with an evidence-based minimum set of items for reporting referred to as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati 2009 **GL**) are identified as PRISMA eg (Moore 2014 **Level I** [PRISMA]);
- Reviews that overtly state that the review conformed with standards previously published as Quality of Reporting of Meta-analyses (QUOROM) (Moher 1999 **GL**), a precursor of PRISMA, are identified as QUOROM eg (Macedo 2006 **Level I** [QUOROM]);
- Non-Cochrane meta-analyses that did not provide evidence of using PRISMA or QUOROM quality and reporting methods are only labelled Level I eg (Thorlund 2014 **Level I**).

For all systematic reviews and meta-analyses, the number of RCTs for Level I and the number of studies for all other levels is reported as well as the number of subjects included in these, if reported or immediately obvious eg (Rabbie 2013 **Level I** [Cochrane], 9 RCTs, n=4,473); if this is not the case, the term unspecified is used eg (Hughes 2011 **Level IV SR**, 5 studies, n unspecified).

Randomised controlled trials: The Jadad scoring instrument was used to score the quality of all RCTs.

Item	Maximum points	Description	Examples
Randomisation	2	1 point if randomisation is mentioned	"The patients were randomly assigned into two groups"
		1 additional point if the method of randomisation is appropriate	The randomisation was accomplished using a computer-generated random number list, coin toss or well-shuffled envelopes
		Deduct 1 point if the method of randomisation is inappropriate (minimum 0)	The group assignment was accomplished by alternate assignment, by birthday, hospital number or day of the week
Blinding	2	1 point if blinding is mentioned	"The trial was conducted in a double-blind fashion"
		1 additional point if the method of blinding is appropriate	Use of identical tablets or injectables, identical vials Use of tablets with similar looks but different taste
		Deduct 1 point if the method of blinding is inappropriate (minimum 0)	Incomplete masking
An account of all patients	1	The fate of all patients in the trial is known. If there are no data the reason is stated	"There were 40 patients randomised but the data from 1 patient in the treatment group and 2 in the control were eliminated because of a break in protocol"

Source: Jadad 1996.

Considering the reporting of dropouts throughout trials, a Jadad score point was withheld if the numbers randomised were greater than the numbers analysed and insufficient explanation was provided. No dropouts were assumed if the text did not state this but the descriptive reporting was comprehensive (ie 60 started, 60 finished, 60 analysed, therefore assume no dropouts). If there were obvious dropouts (ie 60 in, 56 completed), reviewers sought information on the percentage completing the study and the analysis approach that was taken to account for the dropouts.

In addition to the Jadad score, the number of patients randomised (prior to dropouts) is reported for all Level II references eg (Chan 2010 **Level II**, n=4,484, JS 5) including those carried forward from the third edition.

No quality evaluation was undertaken for lower ranked evidence (**Level III** and **Level IV**), when this was the highest available level of evidence. However, the number included is reported if the size of the study subtracts from, or adds to the quality of the evidence eg (Morton 2010 **Level IV**, n=5,065).

Thus this document is underpinned by the highest level, highest methodological quality evidence available for each review question.

Conflicting evidence

If evidence was consistent, the most recent, highest hierarchy and highest quality references were used. If evidence was conflicting, the same approach was taken (identifying highest level, highest quality evidence), however examples were given of differences within the literature so that readers could appreciate the ongoing debate. In some instances, particularly in acute pain management in various patient populations, evidence was limited to case reports only, which was made clear in the document as the best available evidence in this instance.

Cost analyses

The area of acute pain management remains remarkably deficient in research on costs and health economics, one obvious example is the costs associated with the adverse effects of treatment. Where available, relevant health economic information was reported to assist health professionals to better manage both pain and some of the adverse effects of treatment, as well as better individualise treatment for each patient, and to minimise overall expenditure. This is again noted as an area warranting further research.

Key messages

These levels of evidence were also used for the key messages, which are presented in order of level of evidence from the highest to the lowest. Key messages referring to information extracted from Cochrane meta-analyses were marked "Level I [Cochrane Review]", and these were listed first, followed by those marked "Level I [PRISMA]" and "Level I [QUOROM]".

Updating the evidence base from the third edition of the guidelines

There is no standard approach to updating wording or strength of evidence of existing guideline recommendations (Vernooij 2014 **GL**). The system used by Johnston et al, as applied to the updating process in the third edition of this document, was again used in this update to reflect the implications of new evidence on clinical recommendations (Johnston 2003). The working group found this approach to be simple and straightforward when considering the implications of new research, layered onto existing recommendations. To indicate New, Unchanged, Strengthened, Weakened, Qualified and Reversed in the key messages, the letters N, U, S, W, Q and R respectively were used — see table below for examples.

Review and revision of key messages	
New	New evidence leads to new key message(s).
Unchanged	The new evidence is consistent with the data used to formulate the original key message. The key message in the previous edition remains unchanged.
Strengthened	The new evidence is consistent with the data used to formulate the original key message. The key message in the previous edition remains unchanged or expanded. The level of evidence and/or content of the key message in the previous edition has been strengthened to reflect this additional evidence.
Weakened	The new evidence is inconsistent with the data used to inform the original key message(s). However, the new evidence does not alter the key message but weakens the level of evidence.
Qualified	The new evidence is consistent with the data used to formulate the original key message. The key message in the previous edition remains unchanged but applicability may be limited to specific patient groups/ circumstances.
Reversed	The new evidence is inconsistent with the data used to inform the original key message(s). The strength of the new evidence reverses the conclusions of the previous edition.
NB	*Clinical and scientific judgment informed the choices made by the Working Group members; there was no mandatory threshold of new evidence (eg number of studies, types of studies, magnitude of statistical findings) that had to be met before classification of categories occurred.* *The first letter of each of the words (**N** for **N**ew, **U** for **U**nchanged etc) was used to denote the classification, and changes (if any) from the previous edition of this document.*

An example of the use of this system is taken from the key messages in the paediatric Section 9.5 – Opioid infusions and patient-controlled analgesia.

Key messages

1. In ventilated preterm neonates, routine use of morphine infusions does not affect mortality, duration of ventilation or neurological outcomes (**Q**) (**Level I** [Cochrane Review]), including when followed up as older children (**N**) (**Level III-3**).
2. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**U**) (**Level II**).
3. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).
4. Patient-controlled analgesia can provide safe and effective analgesia for children as young as 5 years old (**S**) (**Level III-3**).

Where the new evidence led to reversal of a conclusion and key message, this was noted in a grey text box and labelled R in the key message. For example, this appears in the text:

Note: reversal of conclusion
This reverses the Level I key message in the previous edition of this document; a preceding meta-analysis had described no effect of IV magnesium on postoperative pain scores or opioid requirements.

and the related key message reads:

7. IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect and improves pain scores (**R**) (**Level I**).

INN drug names

This document uses the generic names of drugs that apply in Australia and New Zealand (Australian Approved Names [AAN]). Where this differs from the International Nonproprietary Name (INN) or the United States Adopted Name (USAN), these are given in brackets on first use within each of the chapters.

Bibliographic citations

Citations and bibliographic style are based on a modified Harvard (Author-Date) style. In-text citations use the format "First Author" then "Year of Publication" eg (Madden 2012). A decision was made to omit "et al" for in-text citations that had more than one author, for brevity and improved readability.

Small letters further qualify multiple publications by the same first author in the same year in in-text citations eg (Anderson 2014a) (Anderson 2014b) as in the reference lists eg

Anderson BJ & Dare T (2014b) We need to confirm, not relearn old information. *Paediatr Anaesth* **24**(6): 549–52.

Web pages are shown with their uniform resource locator (URL) and the date assessed by a member of the working group.

Public consultation

Following finalisation of the draft, its availability was advertised in a national newspaper (*The Australian*) and on the ANZCA website. Fellows of ANZCA and FPMANZCA as well as members of the multidisciplinary consultative committee were notified of the availability of the draft by email. The public was also invited to provide comments on the draft.

The public consultation period was from 2 to 30 November 2015. The draft was made available via the publically accessible website (www.anzca.edu.au/APMSE4).

Submissions and comments were received from the following 12 individuals.

Name	Affiliation
Dr Steven Fowler	Staff Specialist Anaesthetist, Head — Sandringham Anaesthesia Melbourne, Victoria
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Lauren Short	Medical Product Specialist Sequirus Parkville, Victoria
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Topics raised

The main topics raised in these submissions and comments related to:

- prevention of phantom limb pain and treatment of stump pain;
- anticoagulation and epidural analgesia;
- prevention of chronic postsurgical pain;
- safety and efficacy of regional and epidural analgesia;
- prescription of discharge medications;
- anticoagulation and regional anaesthesia;
- OIVI;
- safety and efficacy of methoxyflurane;
- efficacy of parenteral ibuprofen;
- listing of contributors;
- off-label prescribing;
- definitions of pain states;
- nomenclature of nociceptive pathways;
- personality disorder in chronic pain patients;
- red flags for acute back pain;
- naltrexone use; and
- error in a Cochrane Review.

Implementation, dissemination and revision

- ANZCA and its FPM will be responsible for the dissemination, implementation, and updating of this document. The document will be initially available on the internet via the ANZCA website (formatted to allow for downloading and printing as a PDF and a 'flip book' file) as well as later in hard copy.
- ANZCA will also notify other Colleges and professional groups and organisations of the availability of the document and ask them to disseminate the information to their members. In addition, information will be sent to relevant national and international organisations with the request to endorse this document and to distribute this information to their members. This is further expected to heighten awareness of the availability of this document. It will also be promoted at relevant professional meetings and conferences and by editorials in professional journals.

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Acronyms and abbreviations

5-HT	5-hydroxytriptamine (serotonin)
AAN	Australian Approved Names
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
AIDS	acquired immunodeficiency syndrome
ALA	adrenaline, lignocaine, amethocaine
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ANZCA	Australia and New Zealand College of Anaesthetists
APS	acute pain service
ASA	American Society of Anesthesiologists
ASIC	acid-sensing ion channel
ASRAPM	American Society of Regional Anesthesia and Pain Medicine
ATP	adenosine triphosphate
BiPAP	bilevel positive airway pressure
BK	bradykinin
BMI	body mass index
BPS	Behavioural Pain Scale
CABG	coronary artery bypass graft
CAIP	channelopathy-associated insensitivity to pain
CAM	complementary and alternative medicine
CB_1	cannabinoid type 1
CB_2	cannabinoid type 2
CCK	cholecystokinin
CCL3	chemokine (C-C motif) ligand 3
CGRP	calcitonin gene-related peptide
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CIPA	congenital insensitivity to pain with anhydrosis
CIPN	chemotherapy-induced peripheral neuropathy
CKD	chronic kidney disease
C_{max}	maximum serum concentration
CNS	central nervous system
CO_2	carbon dioxide
COMT	catechol-O-methyltransferase
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
COX-2	cyclooxygenase-2
coxib	COX-2 selective inhibitor

CPAP	continuous positive airway pressure
CPNB	continuous peripheral nerve block
CPOT	Critical-Care Pain Observation Tool
CPSP	chronic postsurgical pain
CR	controlled-release
CRIES	Cries, Requires oxygen, Increased vital signs, Expression, Sleeplessness
CRPS	chronic regional pain syndrome
CSE	combined spinal epidural
CSF	cerebrospinal fluid
CT	computer tomography
CTG	cardiotocograph
DALY	disability-adjusted life years
DAMP	damage-associated molecular pattern
DIS	daily interruption of sedation
DLF	dorsolateral funiculus
DN4	Douleur Neuropathique en 4
DNIC	diffuse noxious inhibitory control
DRG	dorsal root ganglia
DRt	dorsal reticular nucleus
EBP	epidural blood patch
ECF	extracellular fluid
ECG	electrocardiogram
ED	emergency department
EDIN	Échelle Douleur Inconfort Nouveau-Né
EEG	electroencephalogram
EMA	European Medicines Agency
EMG	electromyelograph
ER	extended release
ERCP	endoscopic retrograde cholangiopancreatography
EREM	extended-release epidural morphine
ESA	European Society of Anaesthesiology
EVENDOL	Evaluation ENfant DOuLeur
FANS	Faceless Acute Neonatal Pain Scale
FAS	Functional Activity Scale
FBSF	fentanyl buccal soluble film
FBT	fentanyl buccal tablets
FDA	Food and Drugs Administration (USA)
FLACC	Faces, Legs, Activity, Cry and Consolability
fMRI	functional magnetic resonance imaging
FNB	femoral nerve block
FPM	Faculty of Pain Medicine

FPS	Faces Pain Scale
FPS-R	Faces Pain Scale-Revised
G-CSF	granulocyte-colony stimulating factor
GABA	gamma-amino butyric acid
GANB	greater auricular nerve block
GDNF	glial-derived neurotrophic factor
GFR	glomerular filtration rate
GM-CSF	granulocyte macrophage-colony stimulating factor
H3G	hydromorphone-3-glucuronide
HIV	human immunodeficiency virus
HSAN	hereditary sensory and autonomic neuropathy
IASP	International Association for the Study of Pain
IC	intercostal
ICB	intercostal block
ICD	International Classification of Diseases
ICF	intracellular fluid
ICU	intensive care unit
ICV	intracerebroventricular
ID	intellectual disability
IL	interleukin
IM	intramuscular(ly)
IN	intranasal(ly)
INN	International Nonproprietary Name
INR	International Normalised Ratio
INRS	Individualised Numeric Rating Scale
IR	immediate-release
IT	intrathecal(ly)
IU	International Unit
IV	intravenous(ly)
IVRA	intravenous regional anaesthesia
IVRB	intravenous regional block
JIA	juvenile idiopathic arthritis
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LAST	local anaesthetic systemic toxicity
LEA	lumbar epidural analgesia
LIA	local infiltration analgesia
LMWH	low molecular weight heparin
LTP	long-term potentiation
M1	O-desmethyltramadol
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide

MAM	monoacetylmorphine
MDMA	N-Methyl-3,4-methylenedioxyamphetamine (ecstasy)
MDR	multidrug resistance protein
mGluR	metabotropic glutamate receptor
mL	millilitre
MLAC	minimum local anaesthetic concentration
MPQ	McGill Pain Questionnaire
MRI	magnetic resonance imaging
N-PASS	Neonatal Pain, Agitation and Sedation Scale
N_2O	nitrous oxide
NAC	Nacetylcysteine
NAS	neonatal abstinence syndrome
NCA	nurse-controlled analgesia
NCCPC-PV	Non-Communicating Children's Pain Checklist — postoperative version
NCCPC-R	Non-Communicating Children's Pain Checklist
NFCS	Neonatal Facial Coding Scale
NGF	nerve growth factor
NGT	nasogastric tube
NHMRC	National Health and Medical Research Council
NICU	neonatal intensive care unit
NIRS	near infrared spectroscopy
NK1	neurokinin-1
NMDA	N-methyl-D-aspartate
NNH	number-needed-to-harm
NNS	non-nutritive sucking
NNT	number-needed-to-treat
NOAC	new oral anticoagulant
NOMS	neurologic, oncologic, mechanical, systemic
NPQ	Neuropathic Pain Questionnaire
NRS	numerical rating scale(s)
NSAID	nonsteroidal anti-inflammatory drug
nsNSAID	nonselective nonsteroidal anti-inflammatory drug
OCT1	organic cation transporter
ODI	Oswestry Disability Index
ODT	orally disintegrating tablet
OIH	opioid-induced hyperalgesia
OIVI	opioid-induced ventilatory impairment
ONJ	osteonecrosis of the jaw
OPG	osteo protegerin
OPRM1	opioid receptor mu-1
OSA	obstructive sleep apnoea

OTFC	oral transmucosal fentanyl citrate
P_2X_3	purinergic receptor subtype
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PACU	postanaesthesia care unit
PAG	periaqueductal grey
PaO_2	partial pressure of oxygen in arterial blood
PAR	proteinase-activated receptor
PCA	patient-controlled analgesia
PCC	percutaneous cervical cordotomy
PCEA	patient-controlled epidural analgesia
PCINA	patient-controlled intranasal analgesia
PCS	Pain Catastrophising Scale
PDA	patent ductus arteriosus
PDPH	postdural puncture headache
PET	positive emission tomogram
PGE_2	prostaglandin E2
PGI_2	prostacyclin
PICC	peripherally inserted central catheter
PICU	paediatric intensive care unit
PIEB	programmed intermittent boluses
PIPP	Premature Infant Pain Profile
PNB	peripheral nerve block
PNS	peripheral nerve stimulation
POCD	postoperative cognitive dysfunction
PONS	postoperative neurological symptoms
PONV	postoperative nausea and vomiting
PPDA	postoperative pain days averted
PPI	proton pump inhibitor
PPP	Paediatric Pain Profile
PPPM	Parents Postoperative Pain Measure
PRAN	Pediatric Regional Anesthesia Network (USA)
prn	*pro re nata* (as needed)
PROSPECT	PROcedure-SPECific postoperative pain management
PTA	Polymyxin E, tobramycin and amphotericin B
PVB	paravertebral block
QALY	quality-adjusted life years
QOL	quality of life
QoR	quality of recovery
QST	quantitative sensory testing
RANKL	receptor activator of nuclear factor kappa-B ligand
RASS	Richmond Agitation-Sedation Scale

ROP	retinopathy of prematurity
RSB	rectus sheath block
rTMS	repetitive transcranial magnetic stimulation
RVM	rostroventromedial medulla
SACD	subacute combined degeneration
SaO_2	oxygen saturation
SAS	Sedation-Agitation Scale
SC	subcutaneous(ly)
SCC	spinal cord compression
SCI	spinal cord injury
SF-12	Short Form 12 of Medical Outcomes Study
SF-36	Short Form 36 of Medical Outcomes Study
SF-MPQ	Short Form of McGill Pain Questionnaire
SIP	Sickness Impact Profile
SL	sublingual(ly)
SNP	single-nucleotide polymorphism
SNRI	serotonin–norepinephrine-reuptake inhibitors
SPID	summed pain intensity difference
SSRI	selective serotonin-reuptake inhibitor
SUNCT	Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing
TAP	transversus abdominis plane
TCA	tricyclic antidepressant
TD	transdermal(ly)
TdP	Torsades de Pointes
TEA	thoracic epidural analgesia
TENS	transcutaneous electrical nerve stimulation
TGA	Therapeutic Goods Administration
THC	tetrahydrocannabinol
T_{max}	time to reach maximum serum concentration
TMD	temperomandibular disorder
TMJ	temporomandibular joint
TNF	tumour necrosis factor
TNS	transient neurological symptoms
TOTPAR	total pain relief
TrkA	tyrosine kinase receptor
TRP	transient receptor potential
TRPV1	transient receptor potential vanilloid 1
TTH	tension-type headache
UK	United Kingdom
URL	uniform resource locator

US	ultrasound
USA	United States of America
USAN	United States Adopted Name
VAS	visual analogue scale(s)
Vd	volume of distribution
VDS	verbal descriptor scale(s)
VIGOR	Vioxx Gastrointestinal Outcomes Research
VNRS	verbal numerical rating scale(s)
VPL	ventral posterolateral nucleus of the thalamus
VPM	ventral posteromedial nucleus of the thalamus
VR	virtual reality
VZV	varicella-zoster virus
WBFPRS	Wong-Baker Faces Pain Rating Scale
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Units

d	day(s)
g	gram
h	hour(s)
L	litre
mcg	microgram
mcL	microlitre
mg	milligram
min	minute(s)
mL	millilitre
mm	millimetre
mmHg	millimetres of mercury
mth	month(s)
ng	nanogram
s	second(s)
y	year(s)

Methodological terms

BS	basic science or animal data
CCT	case-controlled trial
CI	confidence interval
CR	case report
EH	experimental human studies
ES	effect size
GL	clinical practice guideline
HR	hazard ratio
IQR	interquartile range

JS	Jadad Score
MD	mean difference
NR	narrative review
OR	odds ratio
PK	pharmacokinetic study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUOROM	Quality of Reporting of Meta-analyses
RCT	randomised controlled trial
RR	relative risk
SMD	standardised mean difference
SR	systematic review
SRW	standardised regression weight
WMD	weighted mean differen

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