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

ACUTE PAIN MANAGEMENT: SCIENTIFIC EVIDENCE

Third Edition 2010

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Acute Pain Management: Scientific Evidence

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

ANZCA
AUSTRALIAN AND NEW ZEALAND COLLEGE OF ANAESTHETISTS

FPM
FACULTY OF PAIN MEDICINE
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Copyright information for Tables 11.1 and 11.2

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NHMRC approval

These guidelines were approved by the NHMRC on 4 February 2010, under section 14A of the *National Health and Medical Research Council Act 1992*. Approval for the guidelines by NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years. Readers should check with the Australian and New Zealand College of Anaesthetists for any reviews or updates of these guidelines.

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.

This document can be downloaded from the ANZCA website: http://www.anzca.edu.au/resources/books-and-publications/. Copies of the document can be ordered through the Australian and New Zealand College of Anaesthetists on +61 3 9150 6299.

FOREWORD

Less than a generation ago the prevalent attitude towards acute pain was widespread acceptance as inevitable, and frequent indifference to its suboptimal management. Now, proper pain management is understood to be a fundamental human right and integral to the ethical, patient-centred and cost-effective practice of modern medicine. This progress is the result of dedicated efforts by health care professionals worldwide, including many in Australia and New Zealand who have contributed to past and present editions of *Acute Pain: Scientific Evidence.* The consistently high standards of *Acute Pain: Scientific Evidence* have established it as the foremost English-language resource of its type worldwide. Changes between successive editions reflect not simply accumulation of clinical evidence in this dynamic field, but also advancing sophistication in methods of evidence synthesis and decision support. Chaired by Associate Professor Pam Macintyre, assisted by many contributors and a distinguished editorial subgroup of Professor Stephan Schug, Associate Professor David Scott, Dr Eric Visser and Dr Suellen Walker, the working party responsible for the Third Edition of *Acute Pain: Scientific Evidence* have continued to aggregate new clinical evidence and to expand the range of topics. Even more, they have synthesised and presented the consolidated evidence in a clear, user-friendly fashion and highlighted instances where prior editions' conclusions have been altered by new findings.

The use of objective clinical evidence to provide a rational basis for practice is an old concept. In the Old Testament, the Book of Daniel clearly recounts a prospective case-controlled trial. Socrates advocated clinical outcomes assessment as the basis for annual reappointment of state physicians. Yet, aware that an evidence-informed approach to patient care has recently at times inappropriately been used as a rationale for restricting the range of therapeutic options available to patients, the authors of the third edition counsel 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 more than evidence is needed if such treatment is to be effective.' Personalised medicine and individualised care — in part necessitated by genetic differences in drug metabolism and action, as discussed in the third edition — require such a balanced approach. Cochrane himself voiced disdain for 'the considerable pressure…to provide physicians with a simple rule to tell them what it all meant' [Cochrane AL: Effectiveness and Efficiency: Random Reflections on Health Services. Cambridge (UK): Cambridge University Press, 1989, p. 41].

The first edition of *Acute Pain: Scientific Evidence* (led by MJC) and its counterpart US federal guideline over a decade ago (led by DBC) noted the clinical impression that undertreated acute pain may have damaging long-term consequences. Subsequent epidemiologic evidence now affirms this clinical insight and indicates that for some patients debilitating persistent pain can be averted by minimisation of acute pain after surgery or trauma. Even if it is not possible to prevent the transition from acute to chronic pain in every case, early recognition and treatment of incipient chronic pain by a vigilant healthcare system is necessary for cost-effective intervention. The National Pain Strategy document that underpins the 2010 Australian Pain Summit summarises the emerging literature on social, human and economic costs of undertreated acute and chronic pain — establishing pain as a major disease burden (www.painsummit.org.au) and proposing an integrated new framework for management of acute, chronic and cancer pain. This historic summit also reiterated that apart from considerations of reduced cost and increased efficiency, ethical medical practice mandates prevention of unnecessary pain and suffering. Further the Summit Strategy draws heavily

upon the scientific evidence and clinical practice of acute pain management that is the subject of this volume. The dedicated efforts of Dr Macintyre and colleagues to summarise the scientific evidence on acute pain management play an important role in shaping pain-related practice and policy worldwide. All those who care for patients or family members in pain, or who may one day suffer pain themselves, are in their debt.

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INTRODUCTION

This is the third 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) of Australia in 1999. The second edition was written by multiple contributors and a working party chaired by Assoc 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 a number of major organisations — the International Association for the Study of Pain (IASP), the Royal College of Anaesthetists (United Kingdom), the Australasian Faculty of Rehabilitation Medicine, the Royal Australasian College of Physicians, the Royal Australasian College of Surgeons, the Royal Australian and New Zealand College of Psychiatrists and the Australian Pain Society — and recommended to its members by the American Academy of Pain Medicine.

After publication, a companion document for consumers — *Managing Acute Pain: a Guide for Patients* — was prepared and approved by the NHMRC (ANZCA & FPM 2005).

In accord with NHMRC requirements that documents such as these be revised as further evidence accumulates, and as there had been an ongoing 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. ANZCA and the FPM therefore again took responsibility for revising and updating the document — this third edition. As with the second edition, this third edition has been endorsed by a number of key professional organisations (see list on the title page). It was also approved by the NHMRC on 4th February 2010, under section 14A of the *National Health and Medical Research Council Act 1992*.

A working party was convened to coordinate and oversee the development process. An editorial subgroup of the working party (Assoc Prof Pam Macintyre, Prof Stephan Schug, Assoc Prof David Scott, Dr Eric Visser and Dr Suellen Walker) coordinated the development process and edited and/or wrote the sections. The working party also included Dr Douglas Justins, Dean of the Faculty of Pain Medicine, Royal College of Anaesthetists in the United Kingdom, and Prof Karen Grimmer-Somers from the University of South Australia, who was the NHMRC-appointed Guidelines Assessment Register representative for the second edition and provided expert advice on 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 early drafts of the document and contribute more broadly as required. To ensure general applicability and inclusiveness, there was a very wide range of experts on the contributor and multidisciplinary committee, including medical, nursing, allied health and complementary medicine clinicians and a consumer. Comments on the document were also invited during a public consultation period. Details of the processes involved are outline in Appendix B, *Process Report*.

Acute Pain Management: Scientific Evidence covers a wide range of clinical topics. The purpose of the document is, as with the first two 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 the substantial amount of evidence currently available for the management of acute pain in a concise and easily readable form to assist the practising clinician. New and

updated content has been incorporated with the content of the previous version of the document.

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 more than evidence is needed 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 it must 'integrate research evidence, clinical expertise and patient values' (Sackett et al, 1996). 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 healthcare professionals. There is no substitute for the skilled assessment of each individual patient's health status, circumstances and perspectives, which healthcare professionals will then use to help select the treatments that are relevant and appropriate to that patient.

Review of the evidence

This document is a revision of the second edition of *Acute Pain Management: Scientific Evidence*, published in 2005. Therefore, most of the new evidence included in the third edition has been published from January 2005 onwards. Evidence-based guidelines have been published in the areas of acute back and musculoskeletal pain, and recommendations relevant to the management of the acute phase of these conditions were drawn directly from these.

For more details on the review of the evidence see Appendix B, *Process Report*.

Levels of evidence

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

Levels of evidence	
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised 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 pre-test and post-test
Clinical practice points	
☑	Recommended best practice based on clinical experience and expert opinion

Key messages

Key messages for each topic are given with the highest level of evidence available to support them, or with a symbol indicating that they are based on clinical experience or expert opinion. In the key messages, Level I evidence from the Cochrane Database is identified. Levels of evidence were documented according to the NHMRC designation and, as for the second edition of this document, clinical practice points have been added.

It was felt that there should be an indication of how the key messages in this third edition related to those in the second edition. The system used by Johnston et al (Johnston et al, 2003) to reflect the implications of new evidence on clinical recommendations was therefore

reviewed and adapted. 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 original report remains unchanged.
Strengthened	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged or expanded. The level of evidence and/or content of the key message in the original report 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 original report 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 original document.
NB	Clinical and scientific judgment informed the choices made by the Working Party 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 last edition of this document.

Management of retracted publications

In May 2009, two editorials (Shafer et al, 2009; White et al, 2009) were published in *Anesthesia and Analgesia* giving details of 21 publications that had been retracted by a number of journals because of allegations of scientific fraud. The editorial by Shafer (Shafer et al, 2009) contains a list of the retracted articles. This list can also be found at http://www.aaeditor.org/HWP/Retraction.Notice.pdf.

The position of the journal was that unretracted articles 'remain part of the unimpeached literature, at least for now'. In a companion editorial White et al (White et al, 2009) reviewed both the retracted and unimpeached literature, 'distinguishing our understandings that remain fully supported from those that are no longer supported by the unimpeached literature.' Also in May 2009, Eisenach (Eisenach, 2009), the editor of *Anesthesiology*, presented a graph of numbers of citations of retracted and unretracted articles affected by this issue and called for research re-examining the conclusions of the retracted articles.

A July 2009 editorial by Neal (Neal, 2009) described contact with 'the lead or high ranking authors' of six original articles and one review article in that editor's journal and which had not been retracted. These articles are listed in this editorial. He concluded that 'Based on the attestations of the involved coauthors and the investigations of the Chief Academic Officer of Baystate Medical Center, the Editorial Board of *Regional Anesthesia and Pain Medicine* is comfortable recommending that practitioners continue to make clinical decisions based on the information contained within the seven below cited articles.'

Of the references listed in the May 2009 retraction notice (Shafer, 2009), four were included in the second edition of *Acute Pain Management: Scientific Evidence* along with a further two publications that were not included in this list of retractions.

There are no precedents for how best to manage a problem such as this. However, the editors responsible for the development of this third edition of *Acute Pain Management: Scientific Evidence* decided against including any publications by the individuals affected by these retractions when listed as first author on the papers. An assessment was made of each of the meta-analyses that cited affected articles. This was based upon the other papers included in these meta-analyses, other supporting evidence and independent consideration by an expert in biostatistics. In some cases, although cited, the affected references were not actually included in the meta-analysis performed. In other cases, assessment indicated that the strength of the evidence may be reduced because of the inclusion of affected publications.

Following the consensus that appeared to rapidly emerge among editors of the leading peer-reviewed journals in anaesthesiology and pain medicine despite initial concerns about meta-analyses that included this work (White et al, 2009), the editors of the third edition of *Acute Pain Management: Scientific Evidence* felt that indiscriminately omitting all meta-analyses purely on the basis of inclusion of one or two of those papers would be to deny inclusion of some important credible information in the document. Indeed, the purpose of meta-analysis is to aggregate results from the literature as a whole, thereby diluting the impact of any one specific study.

Just prior to finalisation of this third edition of *Acute Pain Management: Scientific Evidence*, an article was published in *Anesthesiology* in December 2009 (Marret et al, 2009) which examined in detail the effect that excluding data obtained from the retracted articles would have on the results of 14 systematic reviews (six quantitative and eight qualitative) in which they were cited. Marret et al (2009) reanalysed the data after excluding results from affected articles and concluded that withdrawal of these articles did not alter the conclusions of five out of the six quantitative reviews (meta-analyses): the sixth meta-analysis has not been included in *Acute Pain Management: Scientific Evidence*. Thus there was agreement with the assessments that had already made about the validity of these meta-analyses which included the retracted articles. Marret et al (2009) concluded that meta-analyses were 'vulnerable' if data from retracted studies made up more than 30% of the total.

A footnote has been added to the relevant sections indicating the systematic reviews (quantitative and qualitative) that included affected articles along with a summary of the effect, if any, on the results obtained. Also, specific note has been made in the text of the third edition of *Acute Pain Management: Scientific Evidence* where retraction of the affected papers involved key messages that were published in the second edition. Should additional information become available it will be added as needed before publication of this document. Information that comes to light after publication will be posted as appropriate on the *Acute Pain Management: Scientific Evidence* website.

INN drug names

This document uses the generic names of drugs that apply in Australia and New Zealand. Where this differs from the International Nonproprietary Name (INN), the INN is given in brackets on first use within each of the major sections.

Pam Macintyre
On behalf of the Working Group of the Australian and New Zealand College of Anaesthetists and 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 vii to viii).

1. PHYSIOLOGY AND PSYCHOLOGY OF ACUTE PAIN

Psychological aspects of acute pain

1. Preoperative anxiety, catastrophising, neuroticism and depression are associated with higher postoperative pain intensity (**U**) (**Level IV**).
2. 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**).

Progression of acute to chronic pain

1. Some specific early anaesthetic and/or analgesic interventions reduce the incidence of chronic pain after surgery (**S**) (**Level II**).
2. Chronic postsurgical pain is common and may lead to significant disability (**U**) (**Level IV**).
3. Risk factors that predispose to the development of chronic postsurgical pain include the severity of pre- and postoperative pain, intraoperative nerve injury and psychosocial factors (**U**) (**Level IV**).
4. All patients with chronic postherniorrhaphy pain had features of neuropathic pain (**N**) (**Level IV**).

5 Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean section (**N**) (**Level IV**).

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 with epidural analgesia (**R**) (**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 drug, defined as preventive analgesia (**U**) (**Level I**).
3. NMDA receptor antagonist drugs in particular show preventive analgesic effects (**U**) (**Level I**).
4. Perioperative epidural analgesia combined with ketamine intravenously decreases hyperalgesia and long-term pain up to 1 year after colonic surgery compared with intravenous analgesia alone (**N**) (**Level II**).

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 (**N**) (**Level II**).

☑ 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**).

Pharmacogenomics and acute pain

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine and tramadol (**N**) (**Level II).**

☑ Genetic polymorphisms explain the wide inter-individual variability in plasma concentrations of a given dose of methadone (**N**).

2. ASSESSMENT AND MEASUREMENT OF PAIN AND ITS TREATMENT

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 numerical rating scales (**U**) (**Level III-2**).

☑ 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; developmental, cognitive, emotional, language and cultural factors should be considered (**U**).

☑ 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. Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief (**U**) (**Level II**).
2. Video education of patients with a whiplash injury reduces the incidence of persistent pain (**N**) (**Level II**).
3. Written information given to patients prior to seeing an anaesthetist is better than verbal information given at the time of the interview (**N**) (**Level III-2**).

4. 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, and information presented in video format may be better still (**N**) (**Level III-2**).
5. Implementation of an acute pain service may improve pain relief and reduce the incidence of side effects (**U**) (**Level III-3**).
6. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**U**) (**Level III-3**).
7. 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**).

☑ Successful management of acute pain requires close liaison with 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**).

4. SYSTEMICALLY ADMINISTERED ANALGESIC DRUGS

Opioids

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. Gabapentin, non-steroidal NSAIDs and ketamine are opioid-sparing medications and reduce opioid-related side effects (**N**) (**Level I**).
4. In appropriate doses, droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron are effective in the prevention of postoperative nausea and vomiting (**N**) (**Level I** [Cochrane Review]).
5. Alvimopan and methylnaltrexone are effective in reversing opioid-induced slowing of gastrointestinal transit time and constipation (**N**) (**Level I** [Cochrane Review]).
6. Droperidol, dexamethasone and ondansetron are equally effective in the prevention of postoperative nausea and vomiting (**U**) (**Level I**).
7. Paired combinations of 5HT3 antagonist, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**N**) (**Level I**).
8. Naloxone, naltrexone, nalbuphine, droperidol and 5HT3 antagonists are effective treatments for opioid-induced pruritus (**N**) (**Level I**).
9. Opioids in high doses can induce hyperalgesia (**N**) (**Level I**).
10. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
11. Pethidine is not superior to morphine in treatment of pain of renal or biliary colic (**U**) (**Level II**).
12. Morphine-6-glucuronide is an effective analgesic (**N**) (**Level II**).
13. In the management of acute pain, one opioid is not superior over others but some opioids are better in some patients (**U**) (**Level II**).

14. The incidence of clinically meaningful adverse effects of opioids is dose-related (**U**) (**Level II**).
15. High doses of methadone can lead to prolonged QT interval (**N**) (**Level II**).
16. Haloperidol is effective in the prevention of postoperative nausea and vomiting (**N**) (**Level II**).
17. Opioid antagonists are effective treatments for opioid-induced urinary retention (**N**) (**Level II**).
18. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**N**) (**Level III-2**).
19. Assessment of sedation is a more reliable way of detecting early opioid-induced respiratory depression than a decreased respiratory rate (**S**) (**Level III-3**).
20. The evidence for risk of cardiac arrhythmias following low-dose droperidol is poor (**N**) (**Level III-3**).
21. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).
22. 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**).

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

Paracetamol, non-selective non-steroidal anti-inflammatory drugs and coxibs

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects comparable to placebo (**S**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs are effective in the treatment of acute postoperative and low back pain, renal colic and primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
3. Coxibs are effective in the treatment of acute postoperative pain (**N**) (**Level I** [Cochrane Review]).
4. With careful patient selection and monitoring, the incidence of nsNSAID-induced perioperative renal impairment is low (**U**) (**Level I** [Cochrane Review]).
5. Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**Q**) (**Level I** [Cochrane Review]).
6. Coxibs do not appear to produce bronchospasm in individuals known to have aspirin-exacerbated respiratory disease (**U**) (**Level I**).
7. In general, aspirin increases bleeding after tonsillectomy (**N**) (**Level I**).
8. Non-selective NSAIDs given in addition to paracetamol improve analgesia compared with paracetamol alone (**U**) (**Level I**).
9. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related side effects (**N**) (**Level I**).
10. Non-selective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea, vomiting and sedation (**N**) (**Level I**).

11. Non-selective NSAIDs and coxibs are effective analgesics of similar efficacy for acute pain (**U**) (**Level I**).
12. Preoperative coxibs reduce postoperative pain and opioid consumption, and increase patient satisfaction (**N**) (**Level I**).
13. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related side effects (**N**) (**Level I**).
14. Coxibs and non-selective NSAIDs have similar adverse effects on renal function (**U**) (**Level I**).
15. Non-selective NSAIDs do not significantly increase blood loss after tonsillectomy but do increase the need for reoperation due to bleeding (**N**) (**Level I**).
16. Parecoxib and/or valdecoxib compared with placebo do not increase the risk of cardiovascular adverse events after non-cardiac surgery (**N**) (**Level I**).
17. Coxibs and non-selective NSAIDs are associated with similar rates of adverse cardiovascular effects, in particular myocardial infarction; naproxen may be associated with a lower risk than other non-selective NSAIDs and celecoxib may be associated with a lower risk than other coxibs and non-selective NSAIDs overall (**N**) (**Level I**).
18. Perioperative non-selective NSAIDs increase the risk of severe bleeding after a variety of other operations compared with placebo (**N**) (**Level II**).
19. Coxibs do not impair platelet function; this leads to reduced perioperative blood loss in comparison with non-selective NSAIDs (**S**) (**Level II**).
20. Short-term use of coxibs results in gastric ulceration rates similar to placebo (**U**) (**Level II**).
21. Use of parecoxib followed by valdecoxib after coronary artery bypass surgery increases the incidence of cardiovascular events and is therefore contraindicated (**S**) (**Level II**).

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

☑ The risk of adverse renal effects of non-selective NSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents and ACE inhibitors (**U**).

Adjuvant drugs

Inhalational agents

1. Nitrous oxide has some analgesic efficacy and is safe during labour (**U**) (**Level I**).
2. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations (**U**) (**Level II**).
3. Methoxyflurane, in low concentrations, may be an effective analgesia in the hospital and prehospital setting (**N**) (**Level IV**).

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

☑ The information about the complications of nitrous oxide 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 duration of exposure and supplementation with vitamin B12, 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

1. Perioperative low-dose ketamine used in conjunction with patient-controlled analgesia morphine is opioid-sparing and reduces the incidence of nausea and vomiting (**N**) (**Level I** [Cochrane Review]).
2. In general, a perioperative low-dose ketamine infusion is opioid-sparing, but does not produce a clinically significant reduction in pain scores or opioid-related adverse effects (**S**) (**Level I**).
3. Ketamine is a safe and effective analgesic for painful procedures in children (**N**) (**Level I**).
4. Ketamine and dextromethorphan have preventive (**U**) but not pre-emptive analgesic effects (**N**) (**Level I**).
5. Magnesium does not reduce postoperative pain scores or opioid consumption and has no preventive analgesic effect (**N**) (**Level I**).
6. Ketamine may improve analgesia in patients with severe acute pain that is poorly responsive to opioids, although evidence is conflicting (**W**) (**Level II**).
7. Ketamine reduces postoperative pain in opioid-tolerant patients (**N**) (**Level II**).

☑ The primary role of low dose ketamine is as an 'antihyperalgesic', 'antiallodynic', 'tolerance-protective' and preventive analgesic, rather than as an analgesic *per se* (**N**).

Antidepressant drugs

1. In neuropathic pain, tricyclic antidepressants are more effective than selective serotonergic re-uptake inhibitors (**S**) (**Level I** [Cochrane Review]).
2. Duloxetine is effective in painful diabetic neuropathy and fibromyalgia (**N**) (**Level I** [Cochrane Review]).
3. There is no good evidence that antidepressants are effective in the treatment of chronic low back pain (**R**) (**Level I** [Cochrane Review]).
4. Tricyclic antidepressants are effective in the treatment of chronic headaches (**U**) and fibromyalgia (**N**) (**Level I**).
5. Antidepressants reduce the incidence of chronic neuropathic pain after herpes zoster (**U**) (**Level II**).

   Note: withdrawal of previous key message:

   Antidepressants reduce the incidence of chronic neuropathic pain after breast surgery

   This has been deleted as the information and evidence supporting it has been withdrawn.

- ☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use tricyclic antidepressants and selective serotonin re-uptake inhibitors in the management of acute neuropathic pain (**S**).
- ☑ To minimise adverse effects, particularly in elderly people, it is advisable to initiate treatment with low doses (**U**).

Anticonvulsant drugs

1. Gabapentin is effective in the treatment of chronic neuropathic pain (**Q**); lamotrigine is most likely ineffective (**N**) (**Level I** [Cochrane Review]).
2. Carbamazepine is effective in the treatment of trigeminal neuralgia (**N**) (**Level I** [Cochrane Review]).
3. Pregabalin is effective in the treatment of chronic neuropathic pain related to diabetic neuropathy (**N**) (**Level I**).
4. Perioperative gabapentinoids (gabapentin/ pregabalin) reduce postoperative pain and opioid requirements (**U**) and reduce the incidence of vomiting, pruritus and urinary retention, but increase the risk of sedation (**N**) (**Level I**).

- ☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use anticonvulsants in the management of acute neuropathic pain (**U**).

Membrane stabilisers

1. Both lignocaine (lidocaine) and mexiletine are effective in the treatment of chronic neuropathic pain (**S**); there is no difference in efficacy or adverse effects compared with carbamazepine, amantadine, or morphine (**N**) (**Level I** [Cochrane Review]).
2. Perioperative intravenous lignocaine reduces pain and opioid requirements following abdominal surgery (**S**) as well as nausea, vomiting, duration of ileus and length of hospital stay (**N**) (**Level I**).

- ☑ Based on the experience in chronic neuropathic pain states, it would seem reasonable to use membrane stabilisers in the management of acute neuropathic pain (**U**).
- ☑ Lignocaine (intravenous or subcutaneous) may be a useful agent to treat acute neuropathic pain (**U**).

Alpha-2 agonists

1. The use of systemic alpha-2-agonists consistently improves perioperative opioid analgesia but the frequency and severity of side effects may limit their clinical usefulness (**U**) (**Level II**).

Salmon calcitonin and bisphosphonates

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

Cannabinoids

1. Current evidence does not support the use of cannabinoids in acute pain management (**S**) but these drugs appear to be mildly effective when used in the treatment of chronic neuropathic pain, including multiple sclerosis-related pain (**N**) (**Level I**).

Glucocorticoids

1. Dexamethasone, compared with placebo, reduces postoperative pain, nausea and vomiting, and fatigue (**Level II**).

Complementary and alternative medicines

☑ 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 (**N**).

5. REGIONALLY AND LOCALLY ADMINISTERED ANALGESIC DRUGS

Local anaesthetics

1. Lignocaine is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**N**) (**Level I** [Cochrane Review]).
2. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level 1**).
3. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blockade (**N**) (**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 when given in low doses for regional analgesia (epidural and peripheral nerve blockade) in terms of quality of analgesia or motor blockade (**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. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity, however uncertainties relating to dosage, efficacy and side effects still remain and therefore it is appropriate to administer lipid emulsion once advanced cardiac life support has begun and convulsions are controlled (**N**) (**Level IV**).

☑ Case reports following accidental overdose with ropivacaine and bupivacaine suggest that resuscitation is likely to be more successful with ropivacaine (**U**).

Opioids

1. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl after Caesarean section (**U**) (**Level I**).
2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
3. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo when administered after surgery (**R**) (**Level I**).

4. Evidence for a clinically relevant peripheral opioid effect at non-articular sites, including perineural, is inconclusive (**U**) (**Level I**).
5. Epidural pethidine produces better pain relief and less sedation than IV pethidine after Caesarean section (**U**) (**Level II**).
6. Extended release epidural morphine provides analgesia for up to 48 hours, however central depressant effects, including respiratory depression, may also be increased and prolonged (**N**) (**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**).

Adjuvant Drugs

1. Intrathecal clonidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics (**N**) (**Level I**).
2. Clonidine improves duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for peribulbar, peripheral nerve and plexus blocks (**N**) (**Level I**).
3. Intrathecal neostigmine marginally improves perioperative and peripartum analgesia in combination with other spinal medications but is associated with significant side effects (**S**) (**Level I**).
4. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).
5. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing side effects (**U**) (**Level I**).
6. Intrathecal midazolam combined with a local anaesthetic prolongs the time to first analgesia and reduces postoperative nausea and vomiting (**N**) (**Level I**).
7. Following Caesarean section, intrathecal morphine provides improved analgesia compared with placebo (**N**) (**Level I**) and more prolonged analgesia compared with more lipophilic opioids (**N**) (**Level II**).
8. Intrathecal clonidine added to intrathecal morphine improves and prolongs analgesia (**N**) (**Level II**).
9. Epidural clonidine reduces postoperative systemic opioid requirements (**N**) (**Level II**).
10. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).
11. In obstetrics, epidural neostigmine improves postoperative analgesia without increasing the incidence of adverse events (**N**) (**Level II**).
12. Addition of either clonidine or dexmedetomidine to intrathecal bupivacaine increases the speed of onset and duration of motor and sensory block without additional side effects (**N**) (**Level II**).

Anti-inflammatory drugs

Corticosteroids

1. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**N**) (**Level I**).
2. Lumbar epidural steroid administration is effective for short -term relief of acute radicular pain (**N**) (**Level I**).
3. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**N**) (**Level II**).
4. Intravenous regional anaesthesia combining dexamethasone with lignocaine improves analgesia for up to 24 hours (**N**) (**Level II**).
5. There is a risk of septic arthritis with intra-articular steroids (**N**) (**Level IV**).

Non-steroidal anti-inflammatory drugs

1. Topical NSAIDs are of limited efficacy in lateral elbow pain and provide short-term functional improvement; they result in fewer gastrointestinal side effects compared with oral NSAIDs (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs added to local anaesthetic solutions for IVRA improve postoperative analgesia (**N**) (**Level I**).
3. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries for up to 1 week with ketoprofen being significantly better than all other topical NSAIDs, and indomethacin similar to placebo (**N**) (**Level I**).
4. Topical diclofenac significantly reduces pain and inflammation in a range of sports, traumatic and inflammatory conditions and in acute musculoskeletal injuries is at least comparable to oral naproxen (**N**) (**Level I**).
5. Topical NSAIDs are effective analgesics for traumatic corneal abrasions (**N**) (**Level I**).

6. ADMINISTRATION OF SYSTEMIC ANALGESIC DRUGS

1. Paracetamol combined with codeine is more effective than either drug alone and shows a dose-response effect (**N**) (**Level I** [Cochrane Review]).
2. NSAIDs (both nsNSAIDs and coxibs) given parenterally or rectally are not more effective and do not result in fewer side effects than the same drug given orally (**U**) (**Level I** [Cochrane Review]).
3. Paracetamol combined with tramadol is more effective than either drug alone and shows a dose-response effect (**N**) (**Level I**).
4. Early postoperative oral administration of paracetamol results in highly variable plasma concentrations that may remain subtherapeutic in some patients (**N**) (**Level II**).
5. Rectal administration of single doses of paracetamol results in highly variable plasma concentrations that often remain subtherapeutic (**N**) (**Level II**).
6. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance (**U**) (**Level II**).
7. Intranasal opioids, in particular the more lipid-soluble drugs such as fentanyl, are effective for the management of acute pain (**N**) (**Level II**).

8. 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**).
9. Transdermal fentanyl should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration; furthermore, in most countries, it lacks regulatory approval for use in other than opioid-tolerant patients (**S**) (**Level IV**).

☑ 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 drugs (**U**).

☑ 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 drug absorption by other routes (**U**).

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

☑ Immediate-release 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**).

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

7. PCA, REGIONAL AND OTHER LOCAL ANALGESIA TECHNIQUES

Patient-controlled analgesia

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**S**) (**Level I** [Cochrane review]).
2. Opioid administration by intravenous PCA leads to higher opioid consumption (**R**), a higher incidence of pruritus (**R**), and no difference in other opioid-related adverse effects (**S**) or hospital stay (**S**) compared with traditional methods of intermittent parenteral opioid administration (**Level I** [Cochrane review]).
3. 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**).
4. Patient preference for intravenous PCA is higher when compared with conventional regimens (**U**) (**Level I**).
5. The addition of ketamine to PCA morphine does not improve analgesia or reduce the incidence of opioid-related side effects (**U**) (**Level I**).
6. Iontophoretic fentanyl PCA may not be as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**Level I**).
7. 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**).

8. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however in ultra-low doses the incidence of nausea and pruritus may be decreased (**U**) (**Level II**).
9. The addition of a background infusion to intravenous PCA does not improve pain relief or sleep, or reduce the number of PCA demands (**U**) (**Level II**).
10. Subcutaneous PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
11. Intranasal PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
12. The risk of respiratory depression with PCA is increased when a background infusion is used (**U**) (**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 antisyphon valves and in non-dedicated lines, antireflux valves (**U**).

☑ Drug concentrations should be standardised within institutions to reduce the chance of programming errors (**U**).

☑ Operator error remains a common safety problem (**N**).

Epidural analgesia

1. 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 (**N**) (**Level I** [Cochrane]).
2. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**S**) (**Level I** [Cochrane review]); except epidural analgesia using a hydrophilic opioid only (**N**) (**Level I**).
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 IV opioid analgesia (**N**) (**Level I**).
4. Epidural local anaesthetics improve oxygenation and reduce pulmonary infections and other pulmonary complications compared with parenteral opioids (**S**) (**Level I**).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery (**S**) (**Level I**).
6. Thoracic epidural analgesia extended for more than 24 hours reduces the incidence of postoperative myocardial infarction (**U**) (**Level I**).
7. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**U**) (**Level I**).
8. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**N**) (**Level I**).

9. The use of continuous background epidural infusion combined with PCEA results in improved maternal analgesia and reduced unscheduled clinician interventions (**N**) (**Level I**).
10. Thoracic epidural analgesia reduces need for ventilation in patients with multiple rib fractures (**S**) (**Level I**) and reduces incidence of pneumonia (**U**) (**Level II**).
11. 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**).
12. The risk of permanent neurological damage in association with epidural analgesia is very low; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV**).
13. Immediate decompression (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 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 (**N**).

Intrathecal analgesia

1. Intrathecal morphine offers improved analgesia and opioid-sparing for up to 24 hours especially following abdominal surgery (**S**) (**Level I**).
2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
3. After major surgery, the incidence of respiratory depression and pruritus is higher with intrathecal morphine compared with IV PCA opioids, but there is no difference in the incidence of nausea and vomiting (**N**) (**Level I**).

☑ Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**).

☑ The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids or the adverse event rate, suggests that the lowest effective dose should be used in all circumstances (**N**).

Regional analgesia and concurrent anticoagulant medications

1. Anticoagulation is the most important risk factor for the development of epidural haematoma after neuraxial blockade (**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**).

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. Compared with opioid analgesia, continuous peripheral nerve blockade (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**N**) (**Level I**).
3. Femoral nerve block provides better analgesia compared with parenteral opioid-based techniques after total knee arthroplasty (**S**) (**Level I**).
4. Compared with thoracic epidural analgesia, continuous thoracic paravertebral analgesia results in comparable analgesia but has a better side effect profile (less urinary retention, hypotension, nausea, and vomiting) than epidural analgesia and leads to a lower incidence of postoperative pulmonary complications (**N**) (**Level I**).
5. 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 (**N**) (**Level I**).
6. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**R**) (**Level I**).
7. Intra-articular local anaesthetics reduce postoperative pain to a limited extent only (**U**) (**Level I**).
8. Continuous local anaesthetic wound infusions lead to reductions in pain scores (at rest and with activity), opioid consumption, postoperative nausea and vomiting, and length of hospital stay; patient satisfaction is higher and there is no difference in the incidence of wound infections (**S**) (**Level I**).
9. Intraperitonal local anaesthetic after laparoscopic cholecystectomy improves early postoperative pain relief (**N**) (**Level I**).
10. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**N**) (**Level I**).
11. Continuous interscalene analgesia provides better analgesia, reduced opioid-related side effects and improved patient satisfaction compared with IV PCA after open shoulder surgery (**U**) (**Level II**).
12. Continuous femoral nerve blockade provides postoperative analgesia that is as effective as epidural analgesia but with fewer side effects following total knee joint replacement surgery (**U**) (**Level II**).
13. Continuous posterior lumbar plexus analgesia is as effective as continuous femoral analgesia following total knee joint replacement surgery (**U**) (**Level II**).
14. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**N**) (**Level IV**).

8. NON-PHARMACOLOGICAL TECHNIQUES

Psychological interventions

1. Listening to music produces a small reduction in postoperative pain and opioid requirement (**N**) (**Level I** [Cochrane Review]).
2. The evidence that information is effective in reducing procedure-related pain is tentatively supportive and not sufficient to make recommendations (**Q**) (**Level I**).
3. Distraction is effective in procedure-related pain in children (**N**) (**Level I**).
4. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative affect and analgesic use (**U**) (**Level I**).
5. Evidence of benefit of hypnosis in the management of acute pain is inconsistent (**W**) (**Level I**).
6. Immersive virtual reality distraction is effective in reducing pain in some clinical situations (**N**) (**Level III-2**).
7. Evidence for any benefit of relaxation techniques in the treatment of acute pain is weak and inconsistent (**N**) (**Level IV**).

Transcutaneous electrical nerve stimulation

1. Overall, there is no evidence that TENS is effective for the treatment of pain during labour (**N**) (**Level I** [Cochrane Review]).
2. Certain stimulation patterns of TENS are effective in some acute pain settings (**S**) (**Level I**).

Acupuncture

1. Acupuncture reduces postoperative pain as well as opioid-related adverse effects (**N**) (**Level I**).
2. Acupuncture may be effective in some other acute pain settings (**U**) (**Level I**).

9. SPECIFIC CLINICAL SITUATIONS

Postoperative pain

Risks of acute postoperative neuropathic pain

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

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

Acute postamputation pain syndromes

1. Continuous regional blockade via nerve sheath catheters provides effective postoperative analgesia after amputation, but has no preventive effect on phantom limb pain (**U**) (**Level II**).
2. Calcitonin, morphine, ketamine, gabapentin, amitriptyline and tramadol reduce phantom limb pain (**S**) (**Level II**).
3. Sensory discrimination training and motor imagery reduce chronic phantom limb pain (**S**) (**Level II**).

4. Ketamine, lignocaine (lidocaine), tramadol and amitriptyline reduce stump 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. Perioperative epidural analgesia reduces the incidence of post-thoracotomy pain syndrome (**N**) (**Level II**).
2. Cryoanalgesia for thoracotomy relieves postoperative pain but increases the risk of post-thoracotomy pain syndrome (**N**) (**Level II**).
3. Preincisional paravertebral block and perioperative use of gabapentin, mexiletine and/or eutectic mixture of local anaesthetic reduce the incidence of postmastectomy pain (**N**) (**Level II**).
4. Post-thoracotomy, postmastectomy, postherniotomy and posthysterectomy pain syndromes occur frequently (**N**) (**Level IV**).

Day-stay or short-stay surgery

1. Infiltration of the wound with local anaesthetic agents provides good and long-lasting analgesia after ambulatory surgery (**U**) (**Level II**).
2. Peripheral nerve blocks with long-acting local anaesthetic agents provide long-lasting postoperative analgesia after ambulatory surgery (**U**) (**Level II**).
3. Single shot infraclavicular blocks provide effective analgesia and less nausea following hand and wrist surgery and earlier ambulation and hospital discharge compared with general anaesthesia (N) (**Level II**).
4. Continuous peripheral nerve blocks provide extended analgesia after ambulatory surgery (**U**) (**Level II**), leading to reduced opioid requirements, less sleep disturbance, earlier achievement of discharge criteria and improved rehabilitation (**N**) (**Level II**).
5. Continuous peripheral nerve blocks have been shown to be safe at home, if adequate resources and patient education are provided (**U**) (**Level IV**).
6. Pain relief after ambulatory surgery remains poor (**N**) (**Level IV**) and is a common cause of unplanned readmissions (**N**) (**Level III-3**).

Cranial neurosurgery

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

Acute pain following spinal cord injury

1. Gabapentinoids (gabapentin/pregabalin) (**S**), intravenous opioids, ketamine or lignocaine (lidocaine) (**U**) tramadol, self-hypnosis and electromyelograph biofeedback (**N**) are effective in the treatment of neuropathic pain following spinal cord injury (**Level II**).

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

Acute burn injury pain

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during burn dressings changes (**N**) (**Level I** [Cochrane Review]).
2. Opioids, particularly via PCA, are effective in burn pain, including procedural pain (**S**) (**Level II**).
3. Augmented reality techniques (**N**) (**Level II**), virtual reality or distraction techniques (**N**) (**Level III-3**) reduce pain during burn dressings.
4. Gabapentin reduces pain and opioid consumption following acute burn injury (**N**) (**Level III-3**).
5. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burn dressings (**N**) (**Level IV**).

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

☑ Acute pain following burn injury requires aggressive multimodal and multidisciplinary treatment.

Acute back pain

1. Acute low back pain is non-specific 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, 'activity-focused' printed and verbal information, and behavioural therapy interventions are beneficial in acute low back pain (**U**) (**Level I**).
3. Advice to stay active, exercises, multimodal therapy and pulsed electromagnetic therapy (in the short term) are 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, 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 plan (**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 (**S**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**N**) (**Level I** [Cochrane Review]).
3. Non-selective 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. High frequency TENS is effective in primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
5. The onset of analgesia is faster when non-selective NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
6. Antispasmodics and peppermint oil are effective for the treatment of acute pain in irritable bowel syndrome (**U**) and gastrointestinal spasm (**N**) (**Level I**).
7. Non-selective NSAIDs and vitamin B1 are effective in the treatment of primary dysmenorrhoea (**U**) (**Level I**).
8. There is no difference between pethidine and morphine in the treatment of renal colic (**U**) (**Level II**).
9. Parenteral non-selective NSAIDs are as effective as parenteral opioids in the treatment of biliary colic (**U**) (**Level II**).

Herpes zoster-associated pain

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 of postherpetic neuralgia (**R**) (**Level I**) [Cochrane Review]).
2. Immunisation of persons aged 60 years or older with varicella-zoster virus vaccine reduces the incidence of herpes zoster and postherpetic neuralgia (**N**) (**Level II**).
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 oxycodone controlled release, provide analgesia in herpes zoster (**N**) (**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.

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, including the use of supplemental oxygen, nitroglycerine, beta blockers and strategies to improve coronary vascular perfusion (**U**).

Acute pain associated with haematological disorders

1. Parenteral corticosteroids appear to reduce the duration of analgesia requirements and length of hospital stay, without major side effects, during sickle cell crises (**S**) (**Level I** [Cochrane Review]).
2. There is insufficient evidence to suggest that fluid replacement therapy reduces pain associated with sickle cell crises (**N**) (**Level I** [Cochrane Review]).
3. Hydroxyurea is effective in decreasing the frequency of acute crises, life-threatening complications and transfusion requirements in sickle cell disease (**U**) (**Level I**).
4. 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 (**U**) (**Level II**).
5. Oxygen supplementation does not decrease pain during a sickle cell crisis (**U**) (**Level II**).

☑ 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 effective in the treatment of tension-type heachache (**N**) (**Level I** [Cochrane Review]).
2. The addition of caffeine to aspirin or paracetamol improves analgesia in the treatment of episodic tension-type heachache (**U**) (**Level I**).
3. Simple analgesics such as aspirin, paracetamol or NSAIDs, either alone or in combination, are effective in the treatment of episodic tension-type heachache (**U**) (**Level II**).

Migraine

4. Triptans are effective in the treatment of severe migraine (**U**) (**Level I**).
5. Aspirin-metoclopramide is effective in the treatment of mild-to-moderate migraine (**U**) (**Level I**).
6. Parenteral metoclopramide is effective in the treatment of migraine (**U**) (**Level I**).
7. Over-the-counter medications, including combined paracetamol-aspirin-caffeine preparations, are effective in the treatment of migraine with mild-to-moderate symptoms and disability (**N**) (**Level I**).
8. Effervescent aspirin, ibuprofen or dipyrone are effective in the treatment of migraine (**N**) (**Level I**).
9. In children or adolescents with migraine, ibuprofen or intranasal sumatriptan (over 12 years of age) are effective treatments (**N**) (**Level I**).
10. Pethidine is less effective than most other migraine treatments and should not be used (**N**) (**Level I**).
11. Parenteral prochlorperazine, chlorpromazine or droperidol are effective in the treatment of migraine, especially in the emergency department (**N**) (**Level II**).
12. Paracetamol is effective in the treatment of mild-to-moderate migraine (**U**) (**Level II**).
13. A 'stratified care strategy' is effective in treating migraine (**U**) (**Level II**).

Cluster headache

14. Parenteral triptans (sumatriptan or zolmitriptan) (**S**) or oxygen therapy (**U**), are effective treatments for cluster headache attacks (**Level II**).

Postdural puncture headache

15. There is no evidence that bed rest is beneficial in the treatment and prevention of postdural puncture headache (**U**) (**Level I** [Cochrane Review]).
16. The incidence of postdural puncture headache is reduced by using small-gauge spinal needles and/or a non-cutting bevel (**U**) (**Level I**).
17. Further high quality trials are required to determine the efficacy of epidural blood patch administration in the treatment of postdural puncture headache (**U**) (**Level I**), however benefit is likely (**N**) (**Level II**).

☑ Opioids should be used with extreme caution in the treatment of headache (**U**).

☑ Frequent use 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

☑ 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

Dental extraction

1. Paracetamol 1000 mg provides safe and effective analgesia with minimal adverse effects, following dental extraction (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs, coxibs, paracetamol, opioids or tramadol provide effective analgesia after dental extraction (**U**) (**Level I**).
3. Non-selective NSAIDs or coxibs provide better analgesia with fewer adverse effects, than paracetamol, paracetamol/opioid, paracetamol/tramadol, tramadol or weaker opioids, following dental extraction (**U**) (**Level I**).
4. Perioperative steroid administration reduces swelling (**S**) but not pain (**R**) (**Level I**) and reduces postoperative nausea (**U**) (**Level II**), following third molar extraction.
5. The combination of paracetamol with a non-selective NSAID provides analgesia that is superior to each drug given alone following third molar extraction (**N**) (**Level II**).

Tonsillectomy

6. Aspirin and some NSAIDs increase the risk of perioperative bleeding after tonsillectomy (**U**) except in children (**N**) (**Level I** [Cochrane Review]).
7. Peritonsillar infiltration or topical application of local anaesthetics produces a modest reduction in acute post-tonsillectomy pain (**R**) with topical application and infiltration being equally effective (**N**) (**Level I**).
8. Intraoperative dexamethasone administration reduces acute pain (**S**) (**Level I**), nausea and vomiting (**U**) (**Level I**) post-tonsillectomy, although there may be an increased bleeding risk (**N**) (**Level II**).
9. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements, but was no more effective than equivalent doses administered parenterally (**N**) (**Level II**).

Mucositis

10. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis, however PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
11. Topical treatments, including oral cooling or povidone-iodine solution, provide effective analgesia in mucositis (**N**) (**Level I**).
12. Oral laser light therapy reduces mucositis pain and progression (**N**) (**Level II**).

Pharyngitis

13. Steroids improve analgesia in sore throat, in particular in severe and exudative conditions (**N**) (**Level I**).
14. Paracetamol, nsNSAIDs or coxibs and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**N**) (**Level I**).

15. Steroids may reduce acute pain associated with severe pharyngitis or peritonsillar abscess (following drainage and antibiotics) (**N**) (**Level II**).

☑ Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches. Neuropathic orofacial pain (atypical odontalgia, phantom pain) may be exacerbated by repeated dental procedures, incorrect drug therapy or psychological factors (**U**).

Acute pain in patients with HIV infection

1. High concentration capsaicin patches, smoking cannabis and lamotrigine are effective in treating neuropathic pain in patients with HIV/AIDS (**N**) (**Level II**).
2. Nucleoside reverse transcriptase inhibitor (NRTIs)-induced neuropathic pain in HIV/AIDS patients is treatable with acetyl-L-carnitine (ALCAR) (**N**) (**Level II**).
3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use, but also more intense pain (**N**) (**Level III-2**).

☑ Neuropathic pain is common in patients with HIV/AIDS (**U**).

☑ In the absence of specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of cancer and chronic pain (**U**).

☑ Interaction between antiretroviral and antibiotic medications and opioids should be considered in this population (**U**).

Acute cancer pain

1. Oral transmucosal fentanyl is effective in treating acute breakthrough pain in cancer patients (**S**) (**Level I** [Cochrane Review]).
2. Radiotherapy and bisphosphonates are effective treatments of acute cancer pain due to bone metastases (**N**) (**Level I** [Cochrane Review]).
3. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects (**S**) (**Level II**).
4. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity (**U**) (**Level III**).

☑ 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**).

☑ Cancer patients receiving controlled-release opioids need access to immediate-release opioids for breakthrough pain; if the response is insufficient after 30 to 60 minutes, administration should be repeated (**U**).

☑ Breakthrough analgesia should be one-sixth of the total regular daily opioid dose in patients with cancer pain (except when methadone is used, because of its long and variable half life) (**U**).

☑ If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed (**U**).

Acute pain management in intensive care

1. 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 (**N**) (**Level III-1**).
2. Gabapentin is more effective than carbamazepine in reducing the pain associated with Guillain-Barre syndrome (**S**) (**Level II**).
3. Remifentanil or remifentanil with morphine provides better analgesia than morphine alone in ventilated intensive care unit patients (**N**) (**Level II**).
4. The use of formal pain and agitation assessment and subsequent treatment in ventilated intensive care unit patients decreases the incidence of pain and duration of ventilation (**N**) (**Level III-1**).

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

☑ Patients should be provided with appropriate sedation and analgesia during potentially painful procedures (**U**).

Acute pain management in emergency departments

Migraine

1. Triptans or phenothiazines (prochlorperazine, chlorpromazine) are effective in at least 75% of patients presenting to the emergency department with migraine (**U**) (**Level II**).

Local anaesthesia

2. Topical local anaesthetic agents (including those in liposomal formulations) (**N**) (**Level I**) or topical local anaesthetic-adrenaline agents (**N**) (**Level II**) provide effective analgesia for wound care in the emergency department.
3. 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 (**S**) (**Level II**).

☑ To ensure optimal management of acute pain, emergency departments should adopt systems to ensure adequate assessment of pain, provision of timely 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 (**N**) (**Level IV**).
3. Methoxyflurane, in low concentrations, may be an effective analgesia in the hospital and prehospital setting (**N**) (**Level IV**).
4. Ketamine provides effective analgesia in the prehospital setting (**N**) (**Level IV**)**.**
5. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**N**) (**Level IV**).

- ☑ The ideal prehospital analgesic agent should be simple to use, safe, 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. Consideration should be given to both choice of analgesic drug and route of administration (N).
- ☑ Non-pharmacological measures are effective in providing pain relief and should always be considered and used if practical (N).

10. THE PAEDIATRIC PATIENT

Long-term consequences of early pain and injury

- ☑ Following birth, even the most premature neonate responds to nociceptive stimuli (**U**).
- ☑ In early development more generalised reflex nociceptive responses occur in response to lower intensity stimuli (**U**).
- ☑ Due to the increased plasticity of the developing nervous system, pain and injury in early life may have adverse long-term consequences (**U**).

Paediatric pain assessment

- ☑ Pain assessment and measurement are important components of paediatric pain management (**U**).
- ☑ Pain measurement tools are available for children of all ages (**U**).
- ☑ Pain measurement tools must be matched to the age and development of the child, be appropriate for the clinical context and be explained and used consistently (**U**).

Management of procedural pain

1. Sucrose reduces the behavioural response to heel-stick blood sampling in neonates (**U**) (**Level I** [Cochrane Review]).
2. Breastfeeding or breast milk reduces measures of distress in neonates undergoing a single painful procedure compared to positioning or no intervention (**U**) (**Level I** [Cochrane Review]).
3. Distraction, hypnosis, and combined cognitive-behavioural interventions reduce pain and distress associated with needle-related procedures in children and adolescents (**S**) (**Level I** [Cochrane Review]).
4. EMLA® is an effective topical anaesthetic for children, but amethocaine is superior for reducing needle insertion pain (**N**) (**Level I** [Cochrane Review]).
5. Topical local anaesthetic application, inhalation of nitrous oxide (50%) or the combination of both provides effective and safe analgesia for minor procedures (**U**) (**Level I**).
6. Combinations of hypnotic and analgesic agents are effective for procedures of moderate severity (**U**) (**Level II**).

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

Analgesic agents

1. Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**R**) (**Level I** [Cochrane Review]).
2. Dexamethasone reduces post-tonsillectomy pain and postoperative nausea and vomiting (**N**) (**Level I**) but high doses may increase the risk of bleeding (**N**) (**Level II**).
3. Paracetamol and non-selective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major surgery (**U**) (**Level II**).
4. The efficacy of oral codeine in children is variable, individual differences in the ability to generate active metabolites may reduce efficacy (**U**) (**Level II**) or increase side effects (**N**) (**Level IV**).

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

☑ Aspirin should be avoided in children, but serious adverse events after non-selective NSAIDs are rare in children over 6 months of age (**U**).

Opioid infusions and PCA

1. Routine morphine infusion does not improve neurological outcome in ventilated preterm neonates (**N**) (**Level I** [Cochrane Review]).
2. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**N**) (**Level II**).
3. 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 (**U**) (**Level II**).
4. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).

☑ Intravenous opioids can be used safely and effectively in children of all ages (**U**).

☑ 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**).

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 (**U**) (**Level I** [Cochrane Review]).
3. Clonidine prolongs analgesia when added to caudal local anaesthetic blocks (**U**) (**Level I**) and improves analgesia when added to epidural local anaesthetic infusions (**U**) (**Level II**).
4. Wound infiltration, peripheral nerve blocks, and caudal local anaesthetic provide effective analgesia after day-case inguinal surgery (**U**) (**Level II**).
5. Epidural infusions of local anaesthetic and systemic opioids provide similar levels of analgesia (**U**) (**Level II**).
6. Epidural opioids alone are less effective than local anaesthetic or combinations of local anaesthetic and opioid (**U**) (**Level II**).
7. Intrathecal opioids provide prolonged analgesia after surgery (**N**) (**Level II**) and reduce blood loss during spinal fusion (**N**) (**Level II**).

- ☑ Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery and have a low incidence of serious complications (**U**).
- ☑ Continuous epidural infusions provide effective postoperative analgesia in children of all ages and are safe if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**U**).

Acute pain in children with cancer

1. PCA and continuous opioid infusions are equally effective in the treatment of pain in mucositis, but opioid consumption is less with PCA (**U**) (**Level I**).
2. PCA morphine and hydromorphone are equally effective for the control of pain associated with oral mucositis (**U**) (**Level II**).

11. OTHER SPECIFIC PATIENT GROUPS

The pregnant patient

Management of acute pain during pregnancy

1. Exercises reduce back and pelvic pain during pregnancy. There is weak evidence for improvements with acupuncture and chiropractic care (**N**) (**Level I**).
2. Use of NSAIDs during pregnancy is associated with an increased risk of miscarriage (**U**) (**Level III-2**).

- ☑ For pain management in pregnancy non-pharmacological 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 obstetrician and the medical practitioner managing the pain (**U**).
- ☑ NSAIDs should be used with caution in the last trimester of pregnancy and should be avoided after the 32nd week (**U**).

Management of pain during delivery

1. Epidural and combined spinal-epidural analgesia provide superior pain relief for labour and delivery compared with systemic analgesics (**S**) (**Level I** [Cochrane Review]).
2. Combined spinal-epidural in comparison with epidural analgesia reduces time to effective analgesia and increases the incidence of pruritus (**U**), does not increase maternal satisfaction (**R**), but increases the risk of urinary retention (**N**) (**Level I** [Cochrane Review]).
3. Epidural analgesia does not increase the incidence of Caesarean section or long-term backache (**S**) (**Level I** [Cochrane Review]).
4. Epidural analgesia is associated with increased duration of labour and increased rate of instrumental vaginal delivery (**S**) (**Level I** [Cochrane Review]).
5. Hypnosis used in labour reduces analgesic requirements (**S**) and improves satisfaction (**N**) (**Level I** [Cochrane Review]).
6. Acupuncture reduces analgesic requirements in labour (**U**) (**Level I** [Cochrane Review]).
7. TENS may reduce severe pain in labour but does not reliably reduce pain scores (**U**) or analgesic requirements (**N**) (**Level I** [Cochrane Review]).

8. Local anaesthetic wound infiltration and abdominal nerve blocks reduce opioid consumption following Caesarean section (**N**) (**Level I** [Cochrane Review]).
9. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, operative delivery and dissatisfaction (**U**) (**Level I**).
10. There is no significant difference in any outcome between use of bupivacaine and ropivacaine for epidural labour analgesia (**U**) (**Level I**).
11. Patient-controlled epidural analgesia provides effective analgesia but optimal settings are not clear (**N**) (**Level I**).
12. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics with increased pruritus (**U**) (**Level I**).
13. Systemic opioids in labour increase the need for neonatal resuscitation and worsen acid-base status compared with regional analgesia (**U**) (**Level I**).
14. Nitrous oxide has some analgesic efficacy and is safe during labour (**U**) (**Level I**).

Pain management during lactation

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

☑ Local anaesthetics, paracetamol and several non-selective NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (**U**).

☑ Morphine and fentanyl are considered safe in the lactating patient and are preferred over pethidine (**U**).

Pain management in the puerperium

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I**).
2. Paracetamol and non-selective NSAIDs are effective in treating perineal pain after childbirth (**U**) (**Level I**).
3. Paracetamol and non-selective NSAIDs are equally but only modestly effective in treating uterine pain (**U**) (**Level II**).
4. Topical agents may improve nipple pain, but no one treatment is superior (**N**) (**Level I**).
5. There is only limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**Q**) (**Level I**).
6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**N**) (**Level I**).

☑ 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. Experimental pain thresholds to a variety of noxious stimuli are altered in older people; there is also a reduction in tolerance to pain (**Q**) (**Level I**).
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).

3. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
4. 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 may be preferred (**S**) (**Level III-2**).
5. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**N**) (**Level III-2**).
6. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
7. The use of nsNSAIDs and coxibs in older people requires extreme caution; paracetamol is the preferred non-opioid analgesic (**U**) (**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, 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**).

☑ The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany aging than to the changes in pharmacokinetics (**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 (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander peoples and New Zealand Maoris, and may influence the choice of analgesic agent (**U**) (**Level IV**).
3. Clinicians should be aware that pain may be under-reported by this group of patients (**U**) (**Level IV**).

☑ Communication may be hindered by social, language and cultural factors (**U**).

☑ Provision of quality analgesia requires sensitivity to cultural practices and beliefs, and behavioural expressions of pain (**N**).

Different ethnic and cultural groups

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

☑ Ethnic and cultural background 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**).

☑ Differences between different ethnic and cultural groups should not be used to stereotype patients and lead to assumptions about responses to pain or pain therapies; pain assessment and management should be done on an individual patient basis (**N**).

The patient with obstructive sleep apnoea

1. Patients with obstructive sleep apnoea may at higher risk of complications after some types of surgery (**Q**).
2. Patients with obstructive sleep apnoea have an including an increased risk of obstructive episodes and desaturations (**N**) (**Level III-2**).
3. Morbidly obese patients undergoing bariatric surgery may be at increased risk of postoperative hypoxaemia independent of a diagnosis of obstructive sleep apnoea (**N**) (**Level III-2**).
4. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**U**) (**Level III-2**).

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

The patient with concurrent hepatic or renal 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. Opioid-tolerant patients report higher pain scores and have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
2. Ketamine improves pain relief after surgery in opioid-tolerant patients (**N**) (**Level II**).
3. Opioid-tolerant patients may have significantly higher opioid requirements than opioid-naive patients and interpatient variation in the doses needed may be even greater (**N**) (**Level III-2**).
4. Ketamine may reduce opioid requirements in opioid-tolerant patients (**U**) (**Level IV**).

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

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

☑ 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 (**U**).

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

☑ In patients with escalating opioid requirements the possibility of the development of both tolerance and opioid-induced hyperalgesia should be considered (**N**).

The patient with an addiction disorder

- ☑ Naltrexone should be stopped at least 24 hours prior to elective surgery (**U**).
- ☑ Patients who have completed naltrexone therapy should be regarded as opioid naive; in the immediate post-treatment phase they may be opioid-sensitive (**U**).
- ☑ Maintenance methadone regimens should be continued where possible (**U**).
- ☑ Buprenorphine maintenance may be continued; if buprenorphine is ceased prior to surgery conversion to an alternative opioid is required (**U**).
- ☑ There is no cross-tolerance between central nervous system stimulants and opioids (**U**).

1. PHYSIOLOGY AND PSYCHOLOGY OF ACUTE PAIN

1.1 APPLIED PHYSIOLOGY OF PAIN

1.1.1 Definition of acute pain

Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (Merskey & Bogduk, 1994). However, the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of suitable pain-relieving treatment. This emphasises the need for appropriate assessment and management of pain when caring for unconscious patients, preverbal or developmentally delayed children, and individuals with impaired communication skills due to disease or language barriers, as well as those who do not possess a command of the caregiver's language (Craig, 2006). Even individuals with native command of language and cultural skills can face difficulty in communicating the complexities of the pain experience (Craig, 2009).

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

It is increasingly recognised that acute and chronic pain may represent a continuum rather than distinct entities. Increased understanding of the mechanisms of acute pain 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.

Section 1.1 focuses on the physiology and pathophysiology of the transmission and modulation of painful stimuli (ie nociception). Psychological factors that impact on the experience of pain are outlined in Section 1.2. However, in individual patients, biological, psychological and environmental or social factors will all interact. An integrated biopsychosocial approach to management that also considers patient preferences and prior experiences is encouraged.

1.1.2 Pain perception and nociceptive pathways

The ability of the somatosensory system to detect noxious and potentially tissue-damaging stimuli is an important protective mechanism that involves multiple interacting peripheral and central mechanisms. The neural processes underlying the encoding and processing of noxious stimuli are defined as 'nociception' (Loeser & Treede, 2008). In addition to these sensory effects, the perception and subjective experience of 'pain' is multifactorial and will be influenced by psychological and environmental factors in every individual.

Peripheral nociceptors

The detection of noxious stimuli requires activation of peripheral sensory organs (nociceptors) and transduction into action potentials for conduction to the central nervous system. Nociceptive 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. The most numerous subclass of nociceptor

is the C-fibre polymodal nociceptor, which responds to a broad range of physical (heat, cold, pressure) and chemical stimuli. Thermal sensation is detected by a range of transient receptor potential (TRP) channels (Patapoutian et al, 2009). A number of receptors have been postulated to signal noxious mechanical stimuli, including acid-sensing ion channels (ASICs), TRPs and potassium channels (Woolf & Ma, 2007).

Tissue damage, such as that associated with infection, inflammation or ischaemia, produces disruption of cells, degranulation of mast cells, secretion by inflammatory cells, and induction of enzymes such as cyclo-oxygenase-2 (COX-2). Ranges of chemical mediators act either directly via ligand-gated ion channels or via metabotropic receptors to activate and/or sensitise nociceptors (see Table 1.1). Endogenous modulators of nociception, including proteinases (Russell & McDougall, 2009), pro-inflammatory cytokines (eg TNFα, IL-1β, IL-6) (Schafers & Sorkin, 2008), anti-inflammatory cytokines (eg IL-10) (Sloane et al, 2009) and chemokines (eg CCL3, CCL2, CX3CL1) (Woolf & Ma, 2007; White & Wilson, 2008), can also act as signalling molecules in pain pathways. Following activation, intracellular kinase cascades result in phosphorylation of channels (such as voltage-gated sodium and TRP channels), alterations in channel kinetics and threshold, and sensitisation of the nociceptor. Neuropeptides (substance P and calcitonin gene-related peptide) released from the peripheral terminals also contribute to the recruitment of serum factors and inflammatory cells at the site of injury (neurogenic oedema). This increase in sensitivity within the area of injury due to peripheral mechanisms is termed peripheral sensitisation, and is manifest as primary hyperalgesia (Woolf & Ma, 2007). Non-steroidal anti-inflammatory drugs (NSAIDs) modulate peripheral pain by reducing prostaglandin E2 (PGE_2) synthesis by locally induced COX-2. Inflammation also induces changes in protein synthesis in the cell body in the dorsal root ganglion and alters the expression and transport of ion channels and receptors, such as $TRPV_1$ and opioid receptors respectively, to the periphery (Woolf & Ma, 2007). The latter underlies the peripheral action of opioid agonists in inflamed tissue (Stein et al, 2009).

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

Ionotropic receptor	Subtype/subunits	Ligand
TRP	$TRPV_1$	heat (>42°C), capsaicin, H^+
	$TRPV_2$	heat (>53°C)
	$TRPV_3$, $TRPV_4$	warm (>32°C)
	$TRPM_8$	cool
	$TRPA_1$	noxious cold (<17°C)
acid sensing	DRASIC, ASIC	H^+
purine	P_2X_3	ATP
serotonin	$5HT_3$	5HT
NMDA	NR1, NR2A-D, NR3	glutamate
AMPA	iGluR1/iGluR2 and iGluR3/iGluR4	glutamate
kainate	iGluR5	glutamate

Metabotropic receptor	Subtype	Ligand
metabotropic glutamate	$mGluR_{1,2/3,5}$	glutamate
prostanoids	EP1-4	PGE_2
	IP	PGI_2

Metabotropic receptor	Subtype	Ligand
histamine	H_1	HA
serotonin	$5HT_{1A}$, $5HT_4$, $5HT_{2A}$	5HT
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
opioid	mu, delta, kappa	enkephalin, dynorphin, beta-endorphin

Notes: 5HT: serotonin; ASIC: acid sensing ion channel; ATP: adenosine triphosphate; BK: bradykinin; DRASIC: subtype of acid sensing ion channel; iGluR: ionotropic glutamate receptor; mGluP: metabotropic glutamate receptor; NK1: neurokinin-1; P2X3: purinergic receptor subtype; PAR: proteinase-activated receptor; PGE_2: prostaglandin E2; PGI_2: prostacyclin; TRP: transient receptor potential. Others (eg H1, EP1-4, $TRPV_2$) are designated subtypes of receptors rather than abbreviations.

Sodium channels are important modulators of neuronal excitability, signalling and conduction of neuronal action potentials to the central nervous system (CNS) (Cummins et al, 2007; Momin & Wood, 2008; Dib-Hajj et al, 2009). 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 contribute to hyperexcitability, and specific alterations in the expression of sodium channels (upregulation or downregulation) occur 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 (Dib-Hajj et al, 2008). However, subtype-selective drugs are not yet available (Momin & Wood, 2008).

The cell bodies of nociceptive afferents that innervate the trunk, limbs and viscera are found in the dorsal root ganglia (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 neurons within laminae I and II of the superficial dorsal horn and also 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 deep laminae III and IV.

Pain transmission in the spinal cord

Primary afferent terminals contain excitatory amino acids (eg glutamate, aspartate), peptides (eg substance P, calcitonin gene-related peptide [CGRP]) and neurotrophic factors (eg brain-derived neurotrophic factor [BDNF]), which act as neurotransmitters and are released by different intensity stimuli (Sandkuhler, 2009). Depolarisation of the primary afferent terminal results in glutamate release, which activates postsynaptic ionotropic alpha-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 (Woolf & Salter, 2000).

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 (NK_1) 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, and this mechanism has been implicated in learning and memory in the hippocampus and pain sensitisation in the spinal cord (Sandkuhler, 2009). Behavioural correlates of these electrophysiological phenomena have been seen in human volunteers, as repeated stimuli elicit progressive increases in reported pain (Hansen et al, 2007).

Intense and ongoing stimuli further increase the excitability of dorsal horn neurons. Electrophysiological studies have identified two patterns of increased postsynaptic response: 'windup' is evoked by low frequency C-fibre (but not A-beta fibre) stimuli and is manifest as an enhanced postsynaptic response during a train of stimuli; and 'LPT' is generated by higher frequency stimuli and outlasts the conditioning stimulus. 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. Centrally mediated changes in dorsal horn sensitivity and/or functional connectivity of A-beta mechanosensitive fibres and increased descending facilitation contribute to 'secondary hyperalgesia' (ie sensitivity is increased beyond the area of tissue injury). Windup, LTP and secondary hyperalgesia may share some of the same intracellular mechanisms but are independent phenomena. All may contribute to 'central sensitisation', which encompasses the increased sensitivity to both C and A-beta fibre inputs resulting in hyperalgesia (increased response following noxious inputs) and allodynia (pain in response to low intensity previously non-painful stimuli) (Sandkuhler, 2009).

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 et al, 2009). Unique patterns of either upregulation or downregulation of neuropeptides, G-protein coupled receptors, growth factors and their receptors, and many other messenger 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 the excitatory processes outlined above, inhibitory modulation also occurs within the dorsal horn and can be mediated by non-nociceptive peripheral inputs, local inhibitory GABAergic and glycinergic interneurons, descending bulbospinal projections, and higher order brain function (eg distraction, cognitive input). These inhibitory mechanisms are activated endogenously to reduce the excitatory responses to persistent C-fibre activity through neurotransmitters such as endorphins, enkephalins, noradrenaline (norepinephrine) and serotonin, and are also targets for many exogenous analgesic agents.

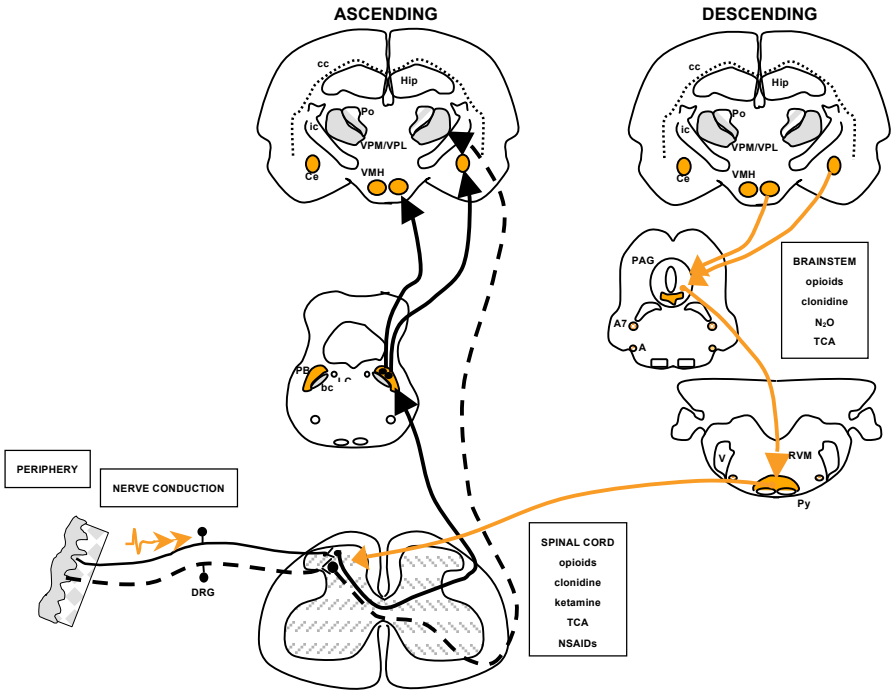
Thus, analgesia may be achieved by either enhancing inhibition (eg opioids, clonidine, antidepressants) or by reducing excitatory transmission (eg local anaesthetics, ketamine).

Central projections of pain pathways

Different qualities of the overall pain experience are subserved by projections of multiple parallel ascending pathways from the spinal cord to the midbrain, forebrain and cortex. 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. This pathway provides information on the sensory-discriminative aspects of pain

(ie the site and type of painful stimulus). The spinoreticular (spinoparabrachial) and spinomesencephalic tracts project to the medulla and brainstem 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. The spinoparabrachial pathway originates from superficial dorsal horn lamina I neurons that express the NK_1 receptor and projects to the ventromedial hypothalamus and central nucleus of the amygdala. Multiple further connections include those with 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, which are important for the regulation of descending pathways to the spinal cord (see Figure 1.1) (Hunt & Mantyh, 2001; Tracey & Mantyh, 2007; Tracey, 2008).

Figure 1.1 The main ascending and descending spinal pain pathways



Notes: (a) There are 2 primary ascending nociceptive pathways. The spinoparabrachial pathway (red) originates from the superficial dorsal horn and feeds areas of the brain concerned with affect. The spinothalamic pathway (blue) originates from deeper in the 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.
(b) The descending pathway highlighted originates from the amygdala and hypothalamus and terminates in the PAG. Neurons project from here to the lower brainstem and control many of the antinociceptive and autonomic responses that follow noxious stimulation.
Other less prominent pathways are not illustrated.
The site of action of some commonly utilised analgesics are included.

Legend A: adrenergic nucleus; bc: brachium conjunctivum; cc: corpus collosum; 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: rostroventrmedial 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 (Hunt & Mantyh, 2001).

Descending modulatory pain pathways

Descending pathways contribute to the modulation of pain transmission in the spinal cord via presynaptic actions on primary afferent fibres, postsynaptic actions on projection neurons, or via effects on intrinsic interneurons within the dorsal horn. Sources include direct corticofugal and indirect (via modulatory structures such as the PAG) pathways from the cortex, and 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 (Millan, 2002). The relative balance between descending inhibition and facilitation varies with the type and intensity of the stimulus and also with time following injury (Vanegas & Schaible, 2004; Heinricher et al, 2009; Tracey & Mantyh, 2007). Serotonergic and noradrenergic pathways in the dorsolateral funiculus (DLF) contribute to descending inhibitory effects (Millan, 2002) and serotonergic pathways have been implicated in facilitatory effects (Suzuki et al, 2004).

1.1.3 Neuropathic pain

Neuropathic pain has been defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' (Merskey & Bogduk, 1994; Loeser & Treede, 2008). Although commonly 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 patients and often it produces persistent symptoms (Hayes et al, 2002). Similarly, acute medical conditions may present with neuropathic pain (Gray, 2008) as discussed further in Section 9.

Nerve injury and associated alterations in afferent input can induce structural and functional changes at multiple points in nociceptive pathways. Damage to peripheral axons results in loss of target-derived growth factors and marked transcriptional changes in DRG of injured neurons (including downregulation of TRP and sodium channels) and a differing pattern in non-injured neighbouring neurons that contributes to spontaneous pain (Woolf & Ma, 2007). In the spinal cord, activation of the same signal transduction pathways as seen following inflammation can result in central sensitisation, with additional effects due to loss of inhibition (Sandkuhler, 2009). Central neurons in the RVM were sensitised after peripheral nerve injury (Carlson et al, 2007) and structural reorganisation in the cortex after spinal cord injury (Wrigley et al, 2009), and changes in cerebral activation have been noted in imaging studies of patients with neuropathic pain (Tracey & Mantyh, 2007).

1.2 PSYCHOLOGICAL ASPECTS OF ACUTE PAIN

Pain is an individual, multifactorial experience influenced, among other things, by culture, previous pain experience, belief, 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. The degree of disability experienced in relation to the experience of pain varies; similarly there is individual variation in response to methods to alleviate pain (Eccleston, 2001).

The IASP's definition of pain (Merskey & Bogduk, 1994) emphasises that pain is not a directly observable or measurable phenomenon, but rather a subjective experience that bears a variable relationship with tissue damage. The task of researchers and clinicians is to identify any factors that might contribute to the individual's pain experience. These could 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, vocalizations, and avoidance behaviour, partially represents the complexity of the psychological experience, but is not equivalent to it (Crombez & Eccleston, 2002; Kunz et al, 2004; Vervoot et al, 2009). Engel's enunciation (Engel, 1977) of a biopsychosocial model of illness has provided a framework for considering pain phenomena. A dynamic engagement between the clinician and the patient was recommended in order to explore possible relevant biological, psychological, and socio-cultural contributions to the clinical problem at hand.

The biopsychosocial model of pain (Turk & Monarch, 1995) proposed that biological factors can influence physiological changes and that 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 (eg Flor et al, 2002). 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 & Hermann, 2004). Other concepts and models of pain which challenge traditional reductionist, mind-body or biomedical paradigms have also been promulgated (Quintner et al, 2008).

1.2.1 Psychological factors

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

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 & Crombez, 1999).

The degree to which pain may interrupt attention depends on factors such as intensity, novelty, unpredictability, degree of awareness of bodily information, threat value of pain, catastrophic thinking, presence of emotional arousal, environmental demands (such as task difficulty), and emotional significance. Evidence from experimental studies has demonstrated that anxiety sensitivity (Keogh & Cochrane, 2002 **Level III-2**) and pain catastrophising (Vancleef & Peters, 2006 **Level III-2**) may also influence the interruptive qualities of pain on attention.

Learning and memory

The role of learning or memory 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 operantly conditioned by their consequences and this effect can be reflected in measures of associated skin conductance responses, facial activity and cortical responses (Flor et al, 2002; Jolliffe & Nicholas, 2004). Taken together, these studies provide support for the thesis that the experience of pain is not solely due to noxious input, but that environmental contingencies can also contribute.

Learning processes may also be involved in the development and maintenance of chronic pain (Birbaumer et al, 1995). Evidence of both classical and instrumental (operant) learning responses were reflected in stereotypy, or repetitive movements, of certain muscle groups to personally relevant stressful situations, as well as conditioning of muscle and pain responses to previously neutral tones and images.

Beliefs, 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 et al, 2007). Negative appraisals of internal and external stimuli (eg catastrophising), negative affectivity and anxiety sensitivity could 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.

1.2.2 Acute pain settings

The contribution of psychosocial factors to the pain experience is important in acute and chronic pain settings as well as in the transition from acute to chronic pain (Linton, 2000 **Level IV**; Pincus et al, 2002 **Level IV**).

Preoperative anxiety has been shown to be associated with higher pain intensities in the first hour after a variety of different operations (Kalkman et al, 2003 **Level IV**), including abdominal (Caumo et al, 2002 **Level IV**; Granot & Ferber, 2005 **Level IV**), coronary artery bypass (Nelson et al, 1998 **Level IV**), gynaecological (Hsu et al, 2005 **Level IV**; Carr et al, 2006 **Level IV**) and varicose vein (Terry et al, 2007 **Level IV**) surgery, and after laparoscopic tubal ligation (Rudin et al, 2008 **Level IV**). Preoperative anxiety was also associated with increased pain and reduced function 1 year after total knee replacement (Brander et al, 2003 **Level IV**), but not 5 years after the surgery (Brander et al, 2007 **Level IV**). Similarly, preoperative psychological distress was shown to predict pain up to 2 years after knee arthroplasty (Lingard & Riddle, 2007 **Level IV**). Pain from 2 to 30 days after breast surgery was also predicted by preoperative anxiety (Katz et al, 2005 **Level IV**). After elective Caesarean section, preoperative anxiety did not predict analgesic use, but was negatively associated with maternal satisfaction and speed of recovery (Hobson et al, 2006 **Level IV**).

In patients who underwent repair of their anterior cruciate ligament, those with high Pain Catastrophising Scale (PCS) scores, assessed prior to surgery, reported more pain immediately after surgery and when walking at 24 hours compared with those with low scores, but there was no difference in analgesic consumption (Pavlin et al, 2005 **Level IV**). After breast surgery, catastrophising was associated with increased pain intensity and analgesic use (Jacobsen & Butler, 1996 **Level IV**) and with higher pain scores after abdominal surgery (Granot & Ferber, 2005 **Level IV**) and Caesarean section (Strulov et al, 2007 **Level IV**). Preoperative PCS scores also predicted pain after knee arthroplasty on the second postoperative day (Roth et al, 2007 **Level IV**) and at 6 weeks (Sullivan et al, 2009 **Level IV**) and 2 years after surgery (Forsythe et al, 2008 **Level IV**).

Preoperative depression (Caumo et al, 2002 **Level IV**; Kudoh et al, 2002 **Level III-2**; Katz et al, 2005 **Level IV**; Rudin et al, 2008 **Level IV**) and neuroticism (Bisgaard et al, 2001 **Level IV**) were predictors of postoperative pain early after surgery; preoperative depression was also associated with pain 1 year after total knee replacement (Brander et al, 2003 **Level IV**) and reduced function at both 1 year (Brander et al, 2003 **Level IV**) and 5 years later (Brander et al, 2007 **Level IV**). Strong information-seeking behaviour was associated with a reduction in the incidence of severe pain (Kalkman et al, 2003 **Level IV**).

Preoperative anxiety and moderate to severe postoperative pain are, in turn, predictors of postoperative anxiety (Caumo et al, 2001 **Level IV**; Carr et al, 2006 **Level IV**).

In opioid-tolerant patients, the anxiety and autonomic arousal associated with withdrawal (Tetrault & O'Connor, 2008) may also impact on acute pain experience and report (see Section 11.7 for further details). Behavioural problems were more common in methadone-maintained patients who required inpatient acute pain management (Hines et al, 2008 **Level III-2**).

Patient-controlled analgesia

A number of studies have looked specifically at the relationship between pain relief and psychological factors in patients using patient-controlled analgesia (PCA) in the postoperative period.

In general, anxiety seems to be the most important psychological variable that affects PCA use. Preoperative anxiety correlated with increased postoperative pain intensity, the number of PCA demands made by the patient (often 'unsuccessful', that is, during the lockout interval), degree of dissatisfaction with PCA and lower self-reports of quality of analgesia (Jamison et al, 1993 **Level IV**; Perry et al, 1994 **Level IV**; Thomas et al, 1995 **Level III-1**; Brandner et al, 2002 **Level IV**; Ozalp et al, 2003 **Level IV**; Hsu et al, 2005 **Level IV**; De Cosmo et al, 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 PCA lockout interval demands and postoperative pain, as did preoperative intrusive thoughts and avoidant behaviours about the impending surgery (Katz et al, 2008 **Level IV**).

Evidence regarding PCA opioid consumption is contradictory; both no change (Gil et al, 1990 **Level IV**; Gil et al, 1992 **Level IV**; Jamison et al, 1993 **Level IV**) and an increase (Ozalp et al, 2003 **Level IV**; De Cosmo et al, 2008 **Level IV**; Katz et al, 2008 **Level IV**) have been reported.

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 weeks after surgery, preoperative self-distraction 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 weeks after surgery (Cohen et al, 2005 **Level IV**).

There was no relationship between locus of control and postoperative pain intensity, satisfaction with PCA or PCA dose-demand ratio (Brandner et al, 2002 **Level IV**). However, preoperative depression was associated with increased pain intensity, opioid requirements, PCA demands and degree of dissatisfaction (Ozalp et al, 2003 **Level IV**; De Cosmo et al, 2008 **Level IV**).

Key messages

1. Preoperative anxiety, catastrophising, neuroticism and depression are associated with higher postoperative pain intensity (**U**) (**Level IV**).
2. 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 PROGRESSION OF ACUTE TO CHRONIC PAIN

The importance of addressing the link between acute and chronic pain has been emphasised by recent studies. To highlight this link, chronic pain is increasingly referred to as persistent pain. A survey of the incidence of chronic pain-related disability in the community concluded

that patients often relate the onset of their pain to an acute injury, drawing attention to the need to prevent the progression from acute to chronic pain (Blyth et al, 2003 **Level IV**).

The association between acute and chronic pain is well-defined, but few randomised controlled studies have addressed the aetiology, time course, prevention or therapy of the transition between the two pain states. Acute pain states that may progress to chronic pain include postoperative and post-traumatic pain (see below and Section 9.1), acute back pain (see Section 9.4) and herpes zoster (see Section 9.6.2).

Chronic pain is common after surgery (see Table 1.2) (Kehlet et al, 2006; Macrae, 2008) and represents a significant source of ongoing disability, often with considerable economic consequences. Such pain frequently has a neuropathic element. For example, all patients with chronic postherniorrhaphy pain had features of neuropathic pain (Aasvang et al, 2008 **Level IV**). Neuropathic pain may be seen early in the postoperative period (see Section 9.1.1).

There is some evidence that specific early analgesic interventions may reduce the incidence of chronic pain after surgery. Epidural analgesia initiated prior to thoracotomy and continued into the postoperative period resulted in significantly fewer patients reporting pain 6 months later compared with patients who had received intravenous (IV) PCA opioids for postoperative analgesia (45% vs 78% respectively) (Senturk et al, 2002 **Level II**). There was no statistically significant difference in the incidence of chronic pain between patients given pre-emptive epidural analgesia (initiated prior to surgery) and patients in whom epidural analgesia was commenced after surgery – 39.6% vs 48.6% (Bong et al, 2005 **Level I**). In patients undergoing colonic resection, continuous perioperative epidural analgesia led to a lower risk of developing persistent pain up to 1 year after surgery compared with IV analgesia (Lavand'homme et al, 2005 **Level II**).

Spinal anaesthesia in comparison to general anaesthesia reduced the risk of chronic postsurgical pain after Caesarean section (Nikolajsen et al, 2004 **Level IV**) and hysterectomy (OR: 0.42; CI 0.21 to 0.85) (Brandsborg et al, 2007 **Level IV**). The latter study found no difference in risk between abdominal and vaginal hysterectomy.

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 months (Blumenthal et al, 2005 **Level II**).

Local anaesthetic wound infiltration reduced the proportion of patients with persistent pain and neuropathic pain 2 months following intracranial tumour resection (Batoz et al, 2009 **Level II**).

Preincisional paravertebral block reduced prevalence and intensity of pain 12 months after breast surgery (Kairaluoma et al, 2006 **Level II**). Perioperative use of gabapentin or mexiletine after mastectomy reduced the incidence of neuropathic pain at 6 months postoperatively, from 25% in the placebo to 5% in both treatment groups (Fassoulaki et al, 2002 **Level II**). Similar protective results were achieved by the same group by the use of a eutectic mixture of local anaesthetics alone (Fassoulaki et al, 2000 **Level II**) or in combination with gabapentin (Fassoulaki et al, 2005 **Level II**).

Deliberate neurectomy (of the ilioinguinal nerve) for inguinal hernia repair reduced the incidence of chronic postsurgical pain (from 21% to 6%) (Malekpour et al, 2008 **Level II**), although this was not seen in an earlier study (Picchio et al, 2004 **Level II**).

See Section 1.5 below for more examples of the use of pre-emptive and preventive analgesic interventions in attempts to reduce the risk of persistent pain after surgery, and Sections 9.1.2 to 9.1.3 for more details on prevention of phantom pain after limb amputation and other postoperative pain syndromes.

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 section	6–55	4
Cholecystectomy	3–50	Not estimated
Vasectomy	0–37	Not estimated
Dental surgery	5–13	Not estimated

Sources: Adapted from Kehlet et al (Kehlet et al, 2006) and Macrae (Macrae, 2008)

1.3.1 Predictive factors for chronic postsurgical pain

A number of risk factors for the development of chronic postsurgical pain have been identified (Kehlet et al, 2006; Macrae, 2008). A systematic review of psychosocial factors identified depression, psychological vulnerability, stress and late return to work as having a correlation to chronic postsurgical pain (Hinrichs-Rocker et al, 2009 **Level III-3**). Very young age may be a protective factor as hernia repair in children under 3 months age did not lead to chronic pain in adulthood (Aasvang & Kehlet, 2007 **Level IV**).

Table 1.3 Risk factors for chronic postsurgical pain

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

Sources: Adapted from Kehlet et al (Kehlet et al, 2006) and Macrae (Macrae, 2008)

1.3.2 Mechanisms for the progression from acute to chronic pain

The pathophysiological processes that occur after tissue or nerve injury mean that acute pain may become persistent (Cousins et al, 2000). Such processes include inflammation at the site of tissue damage with a barrage of afferent nociceptor activity that produces changes in the peripheral nerves, spinal cord, higher central pain pathways and the sympathetic nervous system (see Section 1.1).

After limb amputation, reorganisation or remapping of the somatosensory cortex and other cortical structures may be a contributory mechanism in the development of phantom limb pain (Flor et al, 1995; Grusser et al, 2004). There is preclinical and clinical evidence of a genetic predisposition for chronic pain (Mogil, 1999), although one study found that an inherited component did not feature in the development of phantom pain in members of the same family who all had a limb amputation (Schott, 1986).

Descending pathways of pain control may be another relevant factor as patients with efficient diffuse noxious inhibitory control (DNIC) had a reduced risk of developing chronic postsurgical pain (Yarnitsky et al, 2008 **Level III-2**).

Key messages

1. Some specific early anaesthetic and/or analgesic interventions reduce the incidence of chronic pain after surgery (**S**) (**Level II**).
2. Chronic postsurgical pain is common and may lead to significant disability (**U**) (**Level IV**).
3. Risk factors that predispose to the development of chronic postsurgical pain include the severity of pre- and postoperative pain, intraoperative nerve injury and psychosocial factors (**U**) (**Level IV**).
4. All patients with chronic postherniorrhaphy pain had features of neuropathic pain (**N**) (**Level IV**).
5 Spinal anaesthesia in comparison to general anaesthesia reduces the risk of chronic postsurgical pain after hysterectomy and Caesarean section (**N**) (**Level IV**).

1.4 Pre-emptive and preventive analgesia

In laboratory studies, administration of an analgesic prior to an acute pain stimulus more effectively minimises dorsal horn changes associated with central sensitisation than the same analgesic given after the pain state is established (see Section 1.1) (Woolf, 1983). This led to the hypothesis that pain relief prior to surgery may enhance postoperative pain management – that is, 'pre-emptive preoperative analgesia' (Wall, 1988). 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; Katz & McCartney, 2002).

As the process of central sensitisation relates not only to skin incision but also to the extent of intraoperative tissue injury and postoperative inflammation, the focus has shifted from the timing of a single intervention to the concept of 'protective' and therefore 'preventive' analgesia (Kissin, 1994) (see Table 1.4). The differences in these terms relates to the outcomes being described, because all rely on minimising sensitisation. *Pre-emptive* analgesia has been described above and is measured in terms of pain intensity or related outcomes. *Protective* analgesia describes a technique that reduces measures of sensitisation such as hyperalgesia.

Preventive analgesia is the persistence of analgesic treatment efficacy beyond its expected duration. In clinical practice, preventive analgesia appears to be the most relevant and holds the most hope for minimising chronic pain after surgery or trauma, possibly because it decreases central sensitisation and 'windup'. An important consideration to maximise the benefit of any preventive strategy is that the active intervention should be continued for as long as the sensitising stimulus persists, that is well into the postoperative period (Dahl & Moiniche, 2004; Pogatzki-Zahn & Zahn, 2006).

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 surgery. The only difference is the timing of administration.
Preventive analgesia	Postoperative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment, or no treatment as long as the effect is observed at a point in time that exceeds the expected duration of action of the intervention. The intervention may or may not be initiated before surgery.

Sources: Moiniche et al (Moiniche et al, 2002) and Katz & McCartney (Katz & McCartney, 2002).

The benefits of pre-emptive analgesia have been questioned by two systematic reviews (Dahl & Moiniche, 2004; Moiniche et al, 2002). However a more recent meta-analysis provided support for pre-emptive epidural analgesia (Ong et al, 2005 **Level I**[1]). 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 was most marked for epidural analgesia (0.38; CI 0.28 to 0.47) and improvements were found in all outcomes. Pre-emptive effects of local anaesthetic wound infiltration and NSAID administration were also found, but results were equivocal for systemic NMDA antagonists and there was no clear evidence for a pre-emptive effect of opioids.

Note: reversal of conclusions

This reverses the Level 1 conclusion in the previous edition of this document as pre-emptive effects have been shown with epidural analgesia; earlier meta-analyses using more simple outcomes had reported no pre-emptive effects.

Pre-emptive thoracic epidural analgesia (local anaesthetic +/– opioid) reduced the severity of acute pain only on coughing following thoracotomy. There was a marginal effect on pain at rest and, although acute pain was a predictor of chronic pain at 6 months in two studies, there was no statistically significant difference in the incidence of chronic pain in the pre-emptive (epidural analgesia initiated prior to surgery) versus control (epidural analgesia initiated after surgery) — 39.6% vs 48.6% (Bong et al, 2005 **Level I**).

[1] This meta-analysis includes studies that have since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. After excluding results obtained from the retracted publications, Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data relating to possible pre-emptive effects of local anaesthetic wound infiltration and NSAID administration. They concluded that removal of this information did not significantly alter the results of the meta-analysis.

A systematic review (Katz & Clarke, 2008 **Level I**[2]) reported preventive effects following the use of a number of different drugs, but equivocal or no benefit from pre-emptive treatment (Table 1.5). The methodology was unable to identify specific therapeutic techniques that may be of benefit.

Table 1.5 Summary of studies according to target agent administered

		Pre-emptive effects		Preventive effects			
Agent(s)	**No. of studies**	**Positive**	**Negative**	**Positive**	**Negative**	**Opposite effects**	**Total no. effects**
Gabapentin	6	0 (0)	1 (16.7)	4 (66.6)	1 (16.7)	0 (0)	**6 (100)**
Local anaesthetics	13	3 (20)	3 (20)	6 (40)	1 (6.7)	2 (13.3)	15 (100)
Opioids	5 [-1]	3 (60) [-1]	1 (20)	0 (0)	1 (20)	0 (0)	**5 (100)** **[-1]**
NSAIDs	14 [-2]	7 (43.8) [-1]	3 (18.8)	4 (25) [-1]	2 (12.4)	0 (0)	**16 (100)** **[-2]**
NMDA antagonists	14	2 (11.8)	1 (5.9)	9 (53)	4 (23.4)	1 (5.9)	**17 (100)**
Multimodal	5	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	0 (0)	**6 (100)**
Other	4 [-1]	1 (25)	0 (0)	3 (75) [-1]	0 (0)	0 (0)	**4 (100)** **[-1]**
Total[a]	**61**	**17**[b] **(24.6)**	**10 (14.5)**	**28**[c] **(40.6)**	**11 (15.9)**	**3 (4.4)**	**69 (100)**

Notes: Table shows the total number of studies and number (%) with positive and negative pre-emptive and preventive effects. Also shown is the number (%) of studies reporting effects opposite to those predicted and the total number of effects (positive, negative and opposite). The total number of effects exceeds the number of studies because some studies were designed to evaluate both pre-emptive and preventive effects. See text for definition of pre-emptive and preventive effects.

a p = 0.02 for z-test comparison of proportion of total positive pre-emptive plus preventive effects (0.64) versus proportion of total negative pre-emptive plus preventive effects (0.31).

b p = 0. 36 for z-test comparison of proportion of total positive pre-emptive effects (17/27 = 0.63) versus proportion of total negative pre-emptive effects (10/27 = 0.37)

c p = 0.03 for z-test comparison of proportion of total positive preventive effects (28/39 = 0.72) versus proportion of total negative preventive effects (11/39 = 0.28)

Legend: NSAIDs: non-steroidal anti-inflammatory drugs; NMDA: N-methyl-D-aspartate

Source: Reproduced with kind permission from Katz and Clark, Preventive analgesia and beyond: current status, evidence, and future directions, Table 9.4 p 165 *Clinical Pain Management: Acute Pain 2e*, Hodder Arnold.

[2] This meta-analysis includes studies that have since been withdrawn from publication and which are shown as subtractions in Table 1.5. These were four positive reports: pre-emptive effects of opioids, pre-emptive effects of venlafaxine (listed under 'Other'), and both pre-emptive and preventive effects of NSAIDs. Reanalysis of the data would be required to determine the overall strength of the evidence. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles.

As activation of the NMDA receptor plays an important role in central sensitisation, many studies have focussed on the ability of NMDA receptor antagonists to produce pre-emptive or preventive analgesic effects. A qualitative systematic review of NMDA receptor antagonists showed that ketamine and dextromethorphan produced a significant preventive analgesic benefit; in all positive preventive studies, a direct analgesic benefit of the drug also occurred in the early postoperative period; no positive effect was seen in four studies using magnesium (McCartney et al, 2004 **Level I**). The addition of low-dose IV ketamine to thoracic epidural analgesia reduced the severity and need for treatment of post-thoracotomy pain at 1 and 3 months postoperatively (Suzuki et al, 2006 **Level II**). However, in a later study of thoracic surgery patients, when single dose intrapleural ropivacaine and intravenous analgesia was combined with either perioperative ketamine or saline, no difference in chronic pain up to 4 months was noted (Duale et al, 2009 **Level II**).

In a study of multimodal 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 year after surgery was demonstrated with continuous perioperative epidural analgesia; residual pain at 1 year was lowest in patients who received intraoperative versus postoperative epidural analgesia (Lavand'homme et al, 2005 **Level II**).

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 with epidural analgesia (**R**) (**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 drug, defined as preventive analgesia (**U**) (**Level I**).
3. NMDA receptor antagonist drugs in particular show preventive analgesic effects (**U**) (**Level I**).
4. Perioperative epidural analgesia combined with ketamine intravenously decreases hyperalgesia and long-term pain up to 1 year after colonic surgery compared with intravenous analgesia alone (**N**) (**Level II**).

1.5 Adverse physiological and psychological effects of acute pain

1.5.1 Acute pain and the injury response

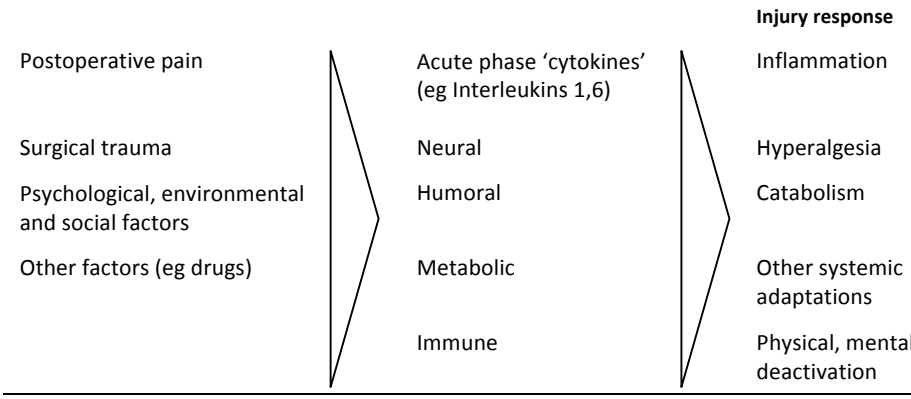
Acute pain is one of the activators of the complex neurohumoral and immune response to injury (Figure 1.2), and both peripheral and central injury responses have a major influence on acute pain mechanisms. Thus acute pain and injury of various types are inevitably interrelated and if severe and prolonged, the injury response becomes counterproductive and can have adverse effects on outcome (Kehlet & Dahl, 2003; Chapman et al, 2008).

Although published data relate to the *combination* of surgery or trauma and the associated acute pain, some data have been obtained with experimental pain in the absence of injury. 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 cortisol, catecholamines and glucagon, and a decrease in insulin sensitivity (Greisen et al, 2001). Although acute pain is only one of the important triggers of the 'injury response' (Figure 1.2),

as the magnitude and duration of the response is related to the magnitude and duration of the stimulus, effective pain relief can have a significant impact on the injury response (Liu & Wu, 2008; Carli & Schricker, 2009).

Release of proinflammatory cytokines may contribute to postoperative ileus, but the impact of modulating this response on overall patient outcome requires further evaluation. Intravenous lignocaine infusion attenuated postoperative increases in pro-inflammatory cytokines, such as IL-6 (interleukin-6), IL-8 and IL-1RA (a competitive inhibitor of IL-1β) and was associated with more rapid return of bowel function following abdominal surgery (Kuo et al, 2006 **Level II**; Herroeder et al, 2007 **Level II**). Reductions in pain scores and opioid consumption were found in only one study (Kuo et al, 2006 **Level II**). Benefits of lignocaine were more marked when administered via the thoracic epidural route than by intravenous infusion (Kuo et al, 2006 **Level II**).

Figure 1.2 The injury response



Note: Pain is only one of the factors, including psychological and environmental factors, that trigger complex intermediates (neural, humoral etc) leading to the 'injury response'. Thus acute pain and the injury response are inevitably inter-related. The end result is physical and mental deactivation.

Source: *Acute Pain Management: the Scientific Evidence* (NHMRC 1999); © Commonwealth of Australia, reproduced with permission.

1.5.2 Adverse physiological effects

Clinically significant injury responses can be broadly classified as inflammation, hyperalgesia, hyperglycaemia, protein catabolism, increased free fatty acid levels (lipolysis) and changes in water and electrolyte flux (Liu & Wu, 2008; Carli & Schricker, 2009) (Figure 1.3). In addition, there are cardiovascular effects of increased sympathetic activity and diverse effects on respiration, coagulation and immune function (Liu & Wu, 2008).

Table 1.6 Metabolic and endocrine responses to injury

Endocrine	↑ Catabolic hormones	↑ ACTH, cortisol, ADH, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons, IL-1, TNF, IL-6
	↓ Anabolic hormones	↓ Insulin, testosterone
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, IL-6, 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; ECF: extracellular fluid; ICF: intracellular fluid; IL: interleukin; TNF: tumour necrosis factor.

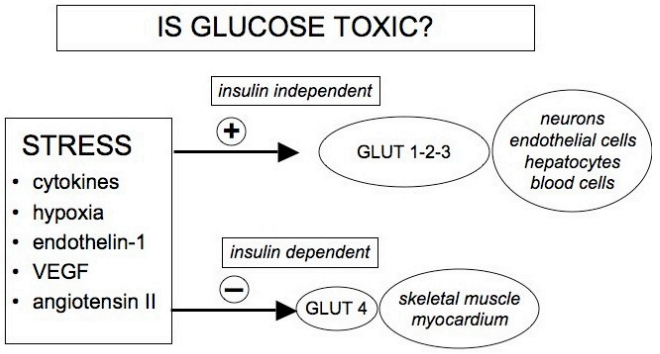
Source: *Acute Pain Management: the Scientific Evidence* (NHMRC 1999); copyright Commonwealth of Australia, reproduced with permission.

Hyperglycaemia

Hyperglycaemia is broadly proportional to the extent of the injury response. Injury response mediators stimulate insulin-independent membrane glucose transporters glut-1, 2 and 3, which are located diversely in brain, vascular endothelium, liver and some blood cells. Circulating glucose enters cells that do not require insulin for uptake, resulting in cellular glucose overload and diverse toxic effects. Excess intracellular glucose non-enzymatically glycosylates proteins such as immunoglobulins, rendering them dysfunctional. Alternatively, excess glucose enters glycolysis and oxidative phosphorylation pathways, leading to excess superoxide molecules that bind to nitric oxide (NO), with formation of peroxynitrate, ultimately resulting in mitochondrial dysfunction and death of cells served by glut-1, 2 and 3. Myocardium and skeletal muscle are protected from this toxicity because these two tissues are served by glut-4, the expression of which is inhibited by injury response mediators (Figure 1.3) (Carli & Schricker, 2009).

Even modest increases in blood glucose can be associated with poor outcome particularly in metabolically challenged patients such as people with diabetes (Lugli et al, 2008 **Level II**). Fasting glucose levels over 7 mmol/L or random levels of greater than 11.1 mmol/L were associated with increased inhospital mortality, a longer length of stay and higher risk of infection in intensive care patients (Van den Berghe, 2004). Tight glycaemic control has been associated with improved outcomes following coronary artery bypass graft (CABG) in patients with diabetes (Lazar et al, 2004 **Level II**), but the risks and benefits of tight glycaemic control in intensive care patients (Wiener et al, 2008 **Level I**) continues to be debated (Fahy et al, 2009 **Level IV**).

Figure 1.3 Proposed pathways of glucose-induced cellular toxicity



Source: Reproduced with kind permission from Carli and Schricker, Modification of Metabolic Response to Surgery by Neural Blockade, Figure 6.3 page 134 *Neural Blockade in Clinical Anesthesia and Pain Medicine 4th Ed,* Wolters Kluwer, Lippincott Williams & Wilkins.

Lipotoxicity

Free fatty acid (FFA) levels are increased due to several factors associated with the injury response and its treatment (see Table 1.6) and can have detrimental effects on cardiac function. High levels of FFA can depress myocardial contractility (Korvald et al, 2000), increase myocardial oxygen consumption (without increased work) (Oliver & Opie, 1994; Liu et al, 2002), and impair calcium homeostasis and increase free radical production leading to electrical instability and ventricular arrhythmias (Oliver & Opie, 1994).

Protein catabolism

The injury response is associated with an accelerated protein breakdown and amino acid oxidation, in the face of insufficient increase in protein synthesis. Following abdominal surgery, amino acid oxidation and release from muscle increased by 90% and 30% respectively, while whole body protein synthesis increased only 10% (Harrison et al, 1989 **Level IV**). After cholecystectomy 50 g of nitrogen may be lost (1 g nitrogen = 30 g lean tissue) which is equivalent to 1500 g of lean tissue. Importantly, the length of time for return of normal physical function after hospital discharge has been related to the total loss of lean tissue during hospital stay (Chandra, 1983).

Protein represents both structural and functional body components, thus loss of lean tissue may lead to delayed wound healing (Windsor & Hill, 1988 **Level III-3**), reduced immune function (Chandra, 1983) and diminished muscle strength (Watters et al, 1993 **Level III-3**) — all of which may contribute to prolonged recovery and increased morbidity (Watters et al, 1993; Christensen et al, 1982).

An overall reduced ability to carry out activities of daily living (ADLs) results from muscle fatigue and muscle weakness. Impaired nutritional intake, inflammatory–metabolic responses, immobilisation, and a subjective feeling of fatigue may all contribute to muscle weakness (Christensen et al, 1990). Such effects are broadly proportional to the extent of injury but there are major variations across populations, with durations also varying up to 3 to 4 weeks.

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

Pain from injury sites can activate sympathetic efferent nerves and increase heart rate, inotropy, 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 (GI) 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. 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 & Wu, 2008).

All relevant studies address the combination of injury and pain. The majority involve use of epidural neural blockade, which in addition to effects on pain *per se* can influence the injury response (eg via reduced sympathetic activity). As a result, the site of epidural placement and extent of block can influence results. The impact of analgesic technique on outcome is more fully discussed in Section 7. Epidural analgesia has been reported to improve pain and decrease arrhythmias following cardiac surgery (Liu et al, 2004 **Level I**), but early reports of reduced postoperative myocardial infarction (Beattie et al, 2001 **Level I**) and impact on mortality have not been replicated (Rigg et al, 2002 **Level II**; Liu et al, 2004 **Level I**). Regional versus systemic analgesia decreased postoperative pulmonary complications (Rodgers et al, 2000 **Level I**; Ballantyne et al, 1998 **Level I**; Jorgensen et al, 2000 **Level I**) but the impact was greater following abdominal (Nishimori et al, 2006 **Level I**) than hip or knee surgery (Choi et al, 2003 **Level I**). Intraoperative epidural analgesia/anaesthesia (versus general anaesthesia) decreased the odds ratio for deep vein thrombosis (DVT) and postoperative confusion, but did not reduce mortality following hip fracture (Parker et al, 2004 **Level I**). Epidural local anaesthetic, when compared to epidural or systemic opioid, enhanced return of GI function (Jorgensen et al, 2000 **Level I**). Compared with systemic opioid administration, intraoperative thoracic epidural anaesthesia also led to lower plasma concentrations of adrenaline (epinephrine) and cortisol, and prevented perioperative impairment of proinflammatory lymphocyte function (Ahlers et al, 2008 **Level II**). The advantages of epidural analgesia were greatest when used as part of a multimodal, accelerated rehabilitation care pathway, since other factors may influence GI recovery (Joshi, 2005).

There is also some evidence that regional anaesthetic and analgesic techniques might have a beneficial effect on rates of cancer recurrence after tumour resection. Paravertebral anaesthesia/analgesia reduced the risk of recurrence or metastases following mastectomy from 23% to 6% compared with general anaesthesia and systemic morphine analgesia (Exadaktylos et al, 2006 **Level IV**). Similarly, after prostatectomy under general anaesthesia, epidural analgesia compared with systemic morphine reduced the risk of recurrence by 57% (Biki et al, 2008 **Level IV**).

1.5.4 Acute rehabilitation and 'fast-track' surgery

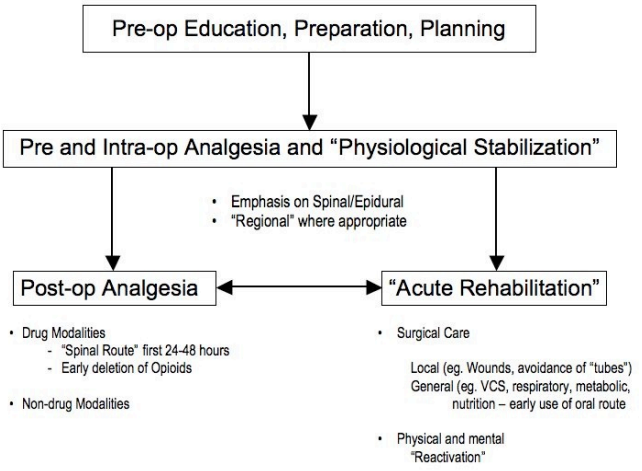
In view of the numerous triggers of the injury response, including acute nociception and pain, it is not surprising that early attempts to modify the catabolism of the injury response, with *pain relief alone*, were not successful. Following abdominal surgery, epidural analgesia without nutritional support had no effect on protein catabolism and related outcomes (Hjortso et al, 1985 **Level II**). Minimising the impact of perioperative fasting with IV amino acid infusions decreased postoperative protein catabolism following colorectal surgery (Schricker et al, 2008 **Level III-2**; Donatelli et al, 2006 **Level III-2**).

Epidural analgesia, aimed at the operative area spinal segments and comprising low doses of local anaesthetic and opioid, facilitated mobilisation and accelerated food intake. Such a program permitted a more rapid postoperative return of normal cardiopulmonary response to treadmill exercise and facilitated return of overall exercise capacity 6 weeks after surgery (Basse et al, 2002 **Level III-2**; Carli et al, 2002 **Level II**).

It can be seen from the foregoing that a multi-interventional and rehabilitation strategy is required, including very effective pain relief, if optimal outcomes are to be achieved, as outlined in procedure-specific recommendations from the PROSPECT group (Kehlet et al, 2007). Postoperative rehabilitation should include pharmacological, physical, psychological and nutritional components (Figure 1.4).

Recognition of the importance of the above factors has led to the concept of 'fast-track' surgery (Wilmore & Kehlet, 2001; White et al, 2007). This has provided enhanced recovery leading to decreased hospital stay with an apparent reduction in medical morbidity (Kehlet & Wilmore, 2008). For example, 'fast-track' colorectal programs have led to a reduction in length of hospital stay (Delaney et al, 2003 **Level II**; Jakobsen et al, 2006 **Level III-2**; Wind et al, 2006 **Level III-1**; Khoo et al, 2007 **Level II**); readmission rates may (Khoo et al, 2007 **Level II**; Jakobsen et al, 2006 **Level III-2**) or may not (Wind et al, 2006 **Level III-1**) be higher. A fast-track system also enabled early discharge (less than 3 days) after total hip and knee arthroplasty, although after total knee arthroplasty, pain at 10 days after discharge was still significant (52% of patients with moderate pain and 16% with severe pain) indicating a need for improved postdischarge analgesia (Andersen et al, 2009 **Level III-3**).

Figure 1.4 Acute pain management and rehabilitation



Source: Reproduced with kind permission from Carli and Schricker, Modification of Metabolic Response to Surgery by Neural Blockade, Figure 6.12 page 134 *Neural Blockade in Clinical Anesthesia and Pain Medicine,4th Ed,* Wolters Kluwer, Lippincott Williams & Wilkins .

1.5.5 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 et al, 2004). In some forms of acute pain (eg low back pain), psychological and environmental responses in the acute phase may be major determinants of progression to a persistent phase (Young Casey et al, 2008).

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 et al, 2007; Monk et al, 2008), surgical procedures (eg coronary artery bypass) and perioperative drug therapy (Flacker & Lipsitz, 1999). Elderly patients have an increased incidence of POCD and are more likely to have prolonged symptoms (see Section 11.2.3). Neurotransmitters involved may include acetylcholine and serotonin and inflammatory mediators (eg cytokines) may also contribute, especially in the elderly (Caza et al, 2008). 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 & Lipsitz, 1999; Gao et al, 2005).

Key messages

1. Recognition of the importance of postoperative rehabilitation including pharmacological, physical, psychological and nutritional components has led to enhanced recovery (**N**) (**Level II**).

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 Pharmacogenomics and acute pain

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

Pharmacogenomics deals with the influence of genetic variation on drug response in patients. By correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity, the aim is to develop rational means to optimise drug 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 inter-patient variability in postoperative opioid requirements (Anderson & Palmer, 2006). Information from genotyping may help in selecting the analgesic drug and the dosing regimen for an individual patient (Lotsch & Geisslinger, 2006). Although there is currently limited information, often from small numbers of subjects, for translation into clinical practice (Stamer & Stuber,

2007; Anderson & Palmer, 2006), some preliminary estimates for dose adaptations are possible (Lotsch & Geisslinger, 2006). However, genetic factors must be considered within the context of the multiple interacting physiological, psychological and environmental factors that influence responses to pain and analgesia (Kim et al, 2009; Searle & Hopkins, 2009).

1.6.1 Loss of pain sensation

Recognised hereditary syndromes associated with loss of pain sensation include the 'channelopathy-associated insensitivity to pain' caused by variants in the SCN9A gene, which codes for the alpha-subunit of the voltage-gated sodium channel Na(v)1.7. Na(v)1.7 is located in peripheral neurons and plays an important role in action potential production in these cells. Mutations result in loss of Na(v)1.7 function and affected individuals are unable to feel physical pain (Drenth & Waxman, 2007).

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 (Oertel & Lotsch, 2008). Hereditary sensory neuropathy type I (HSN-I) is a dominantly transmitted sensorimotor axonal neuropathy accompanied by painless injuries. Hereditary sensory neuropathy type II (HSN-2) variants result in loss of sensitivity to touch, pain and temperature (Drenth & Waxman, 2007). Familial dysautonomia is a congenital sensory and autonomic neuropathy (HSN-3) that affects the development and survival of sensory, sympathetic, and some parasympathetic neurons and results in an indifference to pain and temperature. Hereditary sensory and autonomic neuropathy type IV (HSAN-4) is a severe autosomal recessive disorder characterised by childhood onset of insensitivity to pain and anhidrosis. HSAN-4 is caused by mutations in the NTRK1 gene coding for the tyrosine kinase receptor A (Wieczorek et al, 2008). HSAN type V is a very rare disorder. It is characterised by the absence of thermal and mechanical pain perception caused by a decreased number of small diameter neurons in peripheral nerves (de Andrade et al, 2008).

1.6.2 Reduced sensitivity to pain

Reduced pain sensitivity has been associated with variants in genes encoding the mu-opioid receptor (OPRM1), catechol-O-methyltransferase (COMT), guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia (GCH1), transient receptor potential ($TRPV_1$), and the melanocortin-1 receptor (MC1R) (Lotsch et al, 2006).

The mu-opioid receptor variant N40D which is coded by the single nucleotide polymorphism (SNP) 118A > G of the OPRM1 gene has been associated with reduced acute pain responsiveness (Fillingim et al, 2005 **Level III-3**; Lotsch et al, 2006 **Level IV**) but increased exogenous opioid analgesic requirements (Klepstad et al, 2004 **Level III-3**). Intrathecal fentanyl requirements in labour were reduced in women with the 304G allele but increased in those with the 304A allele of OPRM1 (Landau et al, 2008 **Level III-3**). For additional detail related to individual opioids see Section 4.1.2.

COMT metabolises noradrenaline, adrenaline, and dopamine, and has recently been implicated in the modulation of pain. COMT inhibition may lead to increased pain sensitivity via beta-adrenergic receptor dependent mechanisms (Nackley et al, 2007). Haplotypes with high COMT activity are associated with low pain sensitivity to mechanical and thermal stimuli (Diatchenko et al, 2005). The Val158Met polymorphism influences the activity of the COMT enzyme. In cancer pain, carriers of COMT Val/Val and Val/Met genotypes had higher morphine requirements than carriers of the Met/Met genotype (Reyes-Gibby et al, 2007 **Level III-3**).

GCH1 is the rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis, an essential cofactor in the biosynthesis of biogenic amines and nitric oxide. It is a key modulator of peripheral

neuropathic and inflammatory pain (Montagna, 2007). A haplotype of the GCH1 gene present in 15.4% of humans has been associated with reduced sensitivity to pain following discectomy (Tegeder et al, 2006 **Level III-2**) and homozygotes have reduced sensitivity to experimental pain (Tegeder et al, 2008 **Level III-2**).

Point mutations affecting $TRPV_1$ were found in a person with total insensitivity to capsaicin (Park et al, 2007). Polymorphisms in the human $TRPV_1$ gene have been identified, but there has been no systematic investigation of their functional consequences (Xu et al, 2007).

Kappa-opioid agonists such as nalbuphine and pentazocine have greater analgesic efficacy in women than in men (Gear et al, 1996 **Level III-3**; Gear et al, 1999 **Level II**). Subjects carrying loss-of-function melanocortin-1 receptor gene (MC1R) variants possess a red-hair fair-skin phenotype (Oertel & Lotsch, 2008). There was a significantly greater analgesic effect from a kappa-opioid agonist in female subjects with two variant (non-functional) alleles of the MC1R gene compared with those with zero or one allele (Mogil et al, 2003 **Level III-3**). Subject with non-functional alleles also had reduced sensitivity to noxious stimuli and an increased analgesic response to morphine-6-glucuronide (Mogil et al, 2005 **Level III-3**).

1.6.3 Drug metabolism

Drug-metabolising enzymes represent a major target for identifying associations between an individual's genetic profile and drug response (pharmacogenetics) (Stamer & Stuber, 2007). The polymorphic cytochrome P450 enzymes metabolise numerous drugs and show inter-individual variability in their catalytic activity. The CYP2D6 gene is highly polymorphic (Stamer & Stuber, 2007) and is of clinical interest as it influences the metabolism of codeine, dihydrocodeine, oxycodone and tramadol to the more potent hydroxyl metabolites, which have a higher affinity for the mu-opioid receptor (Anderson & Palmer, 2006; Mikus & Weiss, 2005).

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 two variant alleles known to decrease enzymatic capacity; and poor metabolisers have no functionally active alleles and have minimal or no enzyme activity (Stamer et al, 2007; Stamer & Stuber, 2007). In Caucasian populations, 8% to 10% of people are poor metabolisers; however 3% to 5% are ultrarapid metabolisers (Stamer & Stuber, 2007).

For additional detail related to individual opioids see Section 4.1.2.

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 (Williams et al, 2002 **Level II**; Poulsen et al, 1998 **Level IV**; Persson et al, 1995 **Level IV**).

CYP2D6 genotypes predicting ultrarapid metabolism (CYP2D6 gene duplication) resulted in about 50% higher plasma concentrations of morphine and its glucuronides following oral codeine compared with the extensive metabolisers (Kirchheiner et al, 2007 **Level IV**). Both the impaired renal clearance of metabolites and genetic background (CYP2D6 ultrarapid metaboliser status) have been implicated in reports of respiratory depression due to codeine (Stamer & Stuber, 2007 **Level IV**). Morphine toxicity and death has been reported in a breastfed neonate whose mother was an ultrarapid metaboliser of codeine (Madadi et al, 2007). 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 et al, 2009 **Level III-2**).

Tramadol

O-demethylation of tramadol by CYP2D6 produces the active metabolite (+)-*O*-desmethyltramadol or M1, which has an affinity for mu-opioid receptors that is approximately 200 times more than the parent drug (Shipton, 2000). Poor metabolisers have significantly lower plasma concentrations of M1 compared with both homozygous and heterozygous extensive metabolisers (Stamer et al, 2003 **Level III-3**; Fliegert et al, 2005 **Level II**) and experience less analgesia (Poulsen et al, 1998 **Level IV**; Stamer et al, 2003 **Level III-3**). The selective serotonin reuptake inhibitor (SSRI) paroxetine (a CYP2D6 inhibitor) significantly inhibited (+) and (–) tramadol metabolism by about a third (Laugesen et al, 2005 **Level II**). As with codeine, impaired renal clearance of metabolites and genetic background (CYP26 ultrarapid metaboliser status) have been implicated in cases of respiratory depression after tramadol (Desmeules et al, 1996 **Level II**).

Methadone

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

Cytochrome P450 (CYP) 2B6 and 3A4 have been identified as the main CYP isoforms involved in methadone metabolism, but CYP2D6 has also been reported to have an effect (Li et al, 2008). Differing effects for isomers of methadone have also been reported. Genetic variability in CYP2B6 influenced (S)-, and to a lesser extent, plasma (R)-methadone concentrations; fluoxetine (CYP2D6 inhibitor) only increased (R)-methadone (Kharasch et al, 2004 **Level III-1**); and paroxetine (CYP2D6 inhibitor) increased steady-state (R)-, (S)-, and (R, S)-methadone in extensive metabolisers, but only increased (S)-methadone in poor metaboliser genotypes (Anderson & Palmer, 2006).

NSAIDs

Wide variability in gene expression and functional polymorphisms in the COX-2 gene (PTGS2) may explain part of the inter-individual variations in acute pain and the analgesic efficacy of non-selective NSAIDs (nsNSAIDs) and coxibs; this may be useful to predict patient risk and benefit to drugs based on individual genetic variations (Somogyi et al, 2007; Lee et al, 2006 **Level III-2**).

NsNSAIDs like ibuprofen, naproxen and piroxicam are metabolised by CYP2C9 (Rollason et al, 2008). Between 1% and 3% of Caucasians are poor metabolisers. Homozygous carriers of the CYP2D9* 3 allele may accumulate celecoxib and ibuprofen in blood and tissues and be at risk of increased adverse effects (Kirchheiner et al, 2003 **Level III-3**; Kirchheiner et al, 2002 **Level IV**; Stamer & Stuber, 2007).

Key messages

1. CYP2D6 polymorphisms affect plasma concentrations of active metabolites of codeine and tramadol (**N**) (**Level II**)**.**

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

☑ Genetic polymorphisms explain the wide inter-individual variability in plasma concentrations of a given dose of methadone (**N**).

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2. ASSESSMENT AND MEASUREMENT OF PAIN AND ITS TREATMENT

2.1 ASSESSMENT

Reliable and accurate assessment of acute pain is necessary to ensure patients experience safe, effective and individualised 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 a patient's response. Pain should be assessed within a biopsychosocial model that recognises that physiological, psychological and environmental factors influence the overall pain experience.

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 appropriately frequent intervals. At these times, evaluation of pain intensity, functional impact, and side effects of treatment must be undertaken and recorded using tools and scales that are consistent, valid and reliable (Scott & McDonald, 2008). 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 et al, 2005).

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 et al, 2008). 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 & McDonald, 2008).

While nociceptive pain typically predominates in the acute pain setting, patients may also experience neuropathic pain (see Section 1.3). Features in the pain history that may suggest a diagnosis of neuropathic pain include (Gray, 2008; Dworkin et al, 2007):

- 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.

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 & Max, 2001) 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).

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 et al, 2008)
	b McGill Pain Questionnaire: includes sensory and affective descriptors (Melzack, 1987)
	c neuropathic pain characteristics (eg Neuropathic Pain Questionnaire) (Backonja & Krause, 2003)
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, side 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

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 et al, 2003). Self-report measures may be influenced by mood, sleep disturbance and medications (Scott & McDonald, 2008).

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 10.3), elderly patients (see Section 11.2.3), 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 et al, 2003).

Recording pain intensity as 'the fifth vital sign' aims to increase awareness and utilisation of pain assessment (JCAHO & NPC, 2001) and may lead to improved acute pain management (Gould et al, 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 drug or intervention (Gordon et al, 2005). 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 et al, 2008).

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 acute pain service 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 et al, 2003; Breivik et al, 2008).

Categorical scales

Categorical scales use words to describe the magnitude of pain or the degree of pain relief (Moore et al, 2003). 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 (Banos et al, 1989 **Level III-2**), but the VDS is a less sensitive measure of pain treatment outcome than the VAS (Jensen et al, 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 et al, 2000 **Level II**). Other limitations include personal, cultural or linguistic differences in interpretation of the specific words chosen as descriptors both between patients and also between patients and their clinicians.

Numerical rating scales

Numerical rating scales (NRS) have both written and verbal forms. Patients rate their pain intensity on the scale of 0 to 10 where 0 represents 'no pain' and 10 represents 'worst pain imaginable'. The Verbal NRS (VNRS) is typically administered using a phrase such as: 'On a scale of 0 to 10, with 0 being no pain at all and 10 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 (0) rather than 1 (Scott & McDonald, 2008). Pain *relief* may be measured in the reverse direction with 0 representing 'no relief' to 10 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 et al, 2008). This is widely used, but some patients have difficulty representing their pain in numerical terms and are better suited to a categorical scale. A value of 4 or more is often used as a threshold to guide clinical intervention (Hartrick et al, 2003).

Visual analogue scales (VAS) 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, side 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 et al, 2009 **Level III-2**).

VAS ratings of greater than 70 mm are indicative of 'severe pain' (Aubrun et al, 2003 **Level IV**; Jensen et al, 2003 **Level IV**) and 0 to 5 mm 'no pain', 5 to 44 mm 'mild pain' and 45 to 74 'moderate pain' (Aubrun et al, 2003 **Level IV**). A reduction in pain intensity by 30% to 35% has been rated as clinically meaningful by patients with postoperative pain (Cepeda et al, 2003 **Level IV**; Jensen et al, 2003 **Level IV**), acute pain in the emergency department (Lee et al, 2003 **Level IV**), breakthrough cancer pain (Farrar et al, 2000 **Level IV**) and chronic pain (Farrar et al, 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 & McDonald, 2008). However, the scales require more concentration and coordination, need physical devices, are unsuitable for children under 5 years and may also be unsuitable in up to 26% of adult patients (Cook et al, 1999).

The VAS has been shown to be a linear scale for patients with postoperative pain of mild–moderate intensity (Myles et al, 1999 **Level IV**) and severe pain (Myles & Urquhart, 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 (VNRS) are often preferred because they are simpler to administer, give consistent results and correlate well with the VAS (Murphy et al, 1988 **Level IV**; DeLoach et al, 1998 **Level IV**; Breivik et al, 2000 **Level IV**). Recall of pain intensity using the VNRS

over the previous 24 hours was a reasonable indicator of average pain experienced by the patient during that time (Jensen et al, 2008 **Level III-2**).

Patients asked to rate their pain using a VNRS prior to and after morphine administration were also asked to rate their pain relief on a 5-point standard Likert scale as 0 = no pain relief, 1 = a little pain relief, 2 = moderate pain relief, 3 = a lot of pain relief and 4 = complete pain relief. The VNRS reductions associated with these pain relief ratings were 9.0, 7.5, 3.9, 2.1 and –0.1 respectively (Bernstein et al, 2006 **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 et al, 2008). 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 score (FAS score) is a simple three-level ranked categorical score designed to be applied at the point of care (Scott & McDonald, 2008). 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 0 to 3);
B — mild limitation	the patient is able to undertake the activity but experiences moderate to severe pain (pain intensity score is typically 4 to 10); and
C — significant limitation	the patient is unable to complete the activity due to pain, or pain treatment-related side 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 et al, 1983) and the McGill Pain Questionnaire, which assesses the sensory, affective and evaluative dimensions of pain (Melzack, 1987).

Unidimensional tools such as the VAS are inadequate when it comes to quantifying neuropathic pain. Specific scales have been developed that identify (and/or quantify) descriptive factors specific for neuropathic pain (Bouhassira et al, 2004 **Level IV**; Cruccu et al, 2004 **Level IV**; Bouhassira et al, 2005 **Level IV**; Dworkin et al, 2007 **Level III-2**) and that may also include

sensory examination (Cruccu et al, 2004; Bouhassira et al, 2005) and allow evaluation of response to treatment (Bouhassira et al, 2004).

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 et al, 2003). 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 et al, 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 side effects (Svensson et al, 2001 **Level IV**; Carlson et al, 2003 **Level IV**; Jensen et al, 2004 **Level IV**). Although complete absence of pain is not required for patients to report high levels of satisfaction, moderate pain (VAS greater than 50, scale 0 to 100) has been associated with dissatisfaction (Jensen et al, 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 10.3). 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 emergency department or intensive care) require special attention as do patients whose language or cultural background differs significantly from that of their health care team (see Sections 9.8, 9.9, 11.2.3, 11.3 and 11.4). Communication aids and behavioural scales such as the modified Faces, Legs, Activity, Cry and Consolability (FLACC) scale (Erdek & Pronovost, 2004) can be particularly useful in these situations (see Section 11.2.3).

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 numerical rating scales (**U**) (**Level III-2**).

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; developmental, cognitive, emotional, language and cultural factors should be considered (**U**).

☑ 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 et al, 2008).

2.3.1 Outcome measures

Pain

The aim of many clinical trials is to determine whether a drug or intervention provides adequate pain relief for the majority of participants or is equivalent or non-inferior 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 et al, 2001). 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 visual analogue scales of pain intensity or relief produce a range of summary outcomes that can be used to assess (Moore et al, 2003):

- the degree of analgesic effect:
  - difference between the baseline and postintervention 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;
  - mean 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;
  - time to remedication/rescue analgesia.

A widely used method of describing the effectiveness of an analgesic intervention is the number-needed-to-treat (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 to 6 hour treatment period (Moore et al, 2003). Analysis at other cut-off points (30% to 70% max TOTPAR) has shown the same relative efficacy of different treatments (McQuay et al, 2003).

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 et al, 2004 **Level I**).

The use of supplemental analgesic consumption as an outcome measure has been questioned in situations where pain scores are not similar (McQuay et al, 2008).

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). 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). These scales have been used in some studies of acute spinal pain and cancer-related pain:

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

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 section) (Garratt et al, 2001). Generic measures facilitate comparisons among the functional limitations of different conditions and treatments, and may have advantages for audit of an acute pain service that includes patients with a range of conditions (Patrick & Deyo, 1989).

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 consequences (lost confidence or self-efficacy or post-traumatic stress disorder) for the individual's emotional functioning.

Adverse symptoms and events

In trials of efficacy, adverse events are usually considered to be of secondary importance and inadequate reporting has been found in as many as half of randomised trials reviewed (Edwards et al, 1999; Ioannidis & Lau, 2001). If adverse events 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 events and therefore they are also absent from systematic reviews. Large clinical trials specifically designed to detect adverse events are required (eg the VIGOR study investigated GI toxicity and NSAIDs) (Bombardier et al, 2000). Case reports and postmarketing epidemiological research and surveillance (eg the Australian Adverse Drug Reactions Advisory Committee) remain important for detection of delayed events 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 outcomes in acute pain management (Cameron et al, 2007 **Level IV**; Wijeysundera et al, 2008 **Level IV**; Wijeysundera & Feldman, 2008).

Besides the adverse outcomes attributed to acute pain management interventions, another area of interest is whether the adverse outcomes of trauma and surgery might be prevented by effective acute pain management. Outcomes such as mortality, morbidity due to derangements of the cardiovascular, respiratory, GI and coagulation systems and progression to chronic pain have also been reported (see Section 1.3).

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 drug prescription, monitoring of patients and recognition and treatment of any adverse effects of pain relief, and in some situations, the provision of an acute pain service (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.

Equally, if not more importantly, patient participation (ie including the patient as part of the treating and 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 and up-to-date information, including risks and likely outcomes of treatment, and be partners in discussions relating to choice of care. They should also have access to other evidence-informed information that explains current treatment recommendations as well as have access to treatment consistent with those recommendations (Duckett, 2009).

3.1 EDUCATION

3.1.1 Patients

Patients and their carers who learn about assessment of pain as well as risks and side effects of treatment, and who are made aware that they should communicate both effectiveness (or otherwise) and the onset of any side effects, will have some control over the delivery and success of their pain relief, regardless of the technique used. There should also be information on treatment options, goals, and likely benefits and probability of success (Macintyre & Schug, 2007; Counsell et al, 2008).

Patient or carer education may take a number of forms — the most common methods are the use of booklets or short videos and specialist one-on-one education. A review of the evidence for any benefit from preoperative education or the best educational technique concluded that it is varied and inconsistent (Oshodi, 2007).

Patients may find that preoperative education is helpful (Shuldham, 1999) and it may increase patient or carer knowledge about pain and positive attitudes towards pain relief (Chambers et al, 1997 **Level II**; Greenberg et al, 1999 **Level II**; Watkins, 2001 **Level II**; Cheung et al, 2007 **Level II**). Patient knowledge about pain relief was lower in those given verbal (non-standardised) information at the time of seeing the anaesthetist prior to surgery compared with those given written information before they attended the interview; more patients in the latter group felt that the information was thorough and understandable and helped in discussion about postoperative pain management options (Binhas et al, 2008 **Level III-2**).

Others have suggested that in general, structured preoperative patient education may improve patient outcome including pain relief (Devine, 1992 **Level III-2**; Guruge & Sidani, 2002 **Level III-2**; Giraudet-Le Quintrec et al, 2003 **Level II**). Compared with routine and also structured patient information, education using a video about patient-controlled analgesia (PCA) improved both patient knowledge and pain relief (Chen et al, 2005 **Level III-2**).

Some studies have shown no effect of education on postoperative pain or analgesic requirements (Griffin et al, 1998 **Level II**; Greenberg et al, 1999 **Level II**), including PCA (Chumbley et al, 2004 **Level III-1**), although there may be an increase in patient satisfaction (Knoerl et al, 1999 **Level III-1**; Watkins, 2001 **Level II**; Sjoling et al, 2003 **Level III-2**) and less preoperative anxiety (Sjoling et al, 2003 **Level III-2**).

In studies looking at specific types of surgery, there was no evidence that preoperative patient education has any effect on postoperative pain after:

- hip or knee replacement (McDonald et al, 2004 **Level I**);
- cardiac surgery in adults (Shuldham et al, 2002 **Level II**; Watt-Watson et al, 2004 **Level II**) or children (Huth et al, 2003 **Level II**);
- gynaecological surgery (Lam et al, 2001 **Level II**);
- laparoscopic cholecystectomy (Blay & Donoghue, 2005 **Level II**);
- gastric banding (Horchner & Tuinebreijer, 1999 **Level III-1**); or
- spinal fusion in children and adolescents (Kotzer et al, 1998 **Level III-3**).

A systematic review of studies, looking at the benefits or otherwise of preoperative education for orthopaedic patients, highlighted the difficulties of comparing studies of variable methodological quality; while some individual studies may show benefits of preoperative education, the lack of a consistent pattern with regard to effect was confirmed (Johansson et al, 2005 **Level III-2**).

The effect of patient education has also been studied in patients with non-surgical pain. Antenatal teaching about postnatal nipple pain and trauma resulted in reduced nipple pain and improved breastfeeding (Duffy et al, 1997 **Level II**). After an acute whiplash injury, fewer patients shown an educational video in addition to 'usual care' had persistent pain at 3 and 6 months; opioid use and use of health care resources was also lower (Oliveira et al, 2006 **Level II**). Education and counseling regarding pain management, physical activity, and exercise reduced the number of days off work in patients with acute low back pain (Godges et al, 2008 **Level III-1**). In a study of patients with pain presenting to an emergency department, those shown educational videos or printed brochures had greater decreases in self-reported pain than those given no education (Marco et al, 2006 **Level III-1**). Compared with verbal advice, provision of an information sheet to patients with acute chest pain reduced anxiety and depression and improved mental health and perception of general health, but did not alter patient satisfaction with health care or other outcomes such as lifestyle changes or presentation with further chest pain (Arnold et al, 2009 **Level II**).

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 & Schug, 2007). Medical and nursing staff education may take a number of forms — the evidence for any benefit or the best educational technique is varied and inconsistent. Education may also include the provision of guidelines.

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 et al, 2004 **Level III-1**; Karlsten et al, 2005 **Level III-2**) and intensive care units (Arbour, 2003 **Level IV**; Erdek & Pronovost, 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 et al, 2006 **Level III-2**).

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 et al, 1992 **Level III-2**; Harmer & Davies, 1998 **Level III-3**). In emergency departments, 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 et al, 2007 **Level III-2**). Personalised feedback forms given to anaesthetists have been shown to increase the use of PCA, non-steroidal anti-inflammatory drugs (NSAIDs), epidural morphine and nerve blocks (Rose et al, 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 et al, 1997 **Level III-3**; Ury et al, 2002 **Level III-3**) and specifically for NSAIDs (May et al, 1999 **Level III-3**; Figueiras et al, 2001 **Level I**; Ray et al, 2001 **Level II**), paracetamol (acetaminophen) (Ripouteau et al, 2000 **Level III-3**) and pethidine (meperidine) (Gordon et al, 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 et al, 2008 **Level III-3**).

However, education programs may not always be successful in improving nursing staff knowledge or attitudes (Dahlman et al, 1999 **Level III-3**) or pain relief (Knoblauch & Wilson, 1999 **Level IV**). In rural and remote settings, distance and professional isolation could impact on the ability of health care 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 et al, 1996) 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 et al, 2007 **Level III-2**).

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

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 & FPM, 2008). However, effective acute pain management will, to a large extent, depend not on the drugs and techniques available but on the systems involved in their delivery (Macintyre & Schug, 2007). Even simple methods of pain relief can be more effective if proper attention is given to education (see Section 3.1), analgesic drug orders, documentation, monitoring of patients and the provision of appropriate policies, protocols and guidelines (Gould et al, 1992 **Level III-3**). In

some institutions, the APS will assume responsibility for managing more advanced methods of pain relief such as PCA and epidural analgesia.

3.2.1 General requirements

Guidelines that aim to enhance patient outcomes and standardise analgesic techniques (eg drug and drug concentrations, dose, dose intervals), monitoring requirements, equipment used, and responses to inadequate or excessive analgesic doses and other complications, may lead to consistency of practice and potentially improved patient safety and analgesic efficacy, regardless of technique used (Macintyre & Schug, 2007; Counsell et al, 2008; Macintyre & Scott, 2009).

Marked improvements in conventional methods of pain relief have followed the introduction of guidelines for intramuscular (IM) opioid administration (Gould et al, 1992 **Level III-3**; Humphries et al, 1997 **Level III-3**). However, implementation of guidelines and not their development remains the greatest obstacle to their use. Compliance with available guidelines is highly variable and may be better in larger institutions (Carr et al, 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 et al, 2001 **Level IV**).

Professional bodies in a number of countries have issued guidelines for the management of acute pain (Carr et al, 1992; ANZCA & FPM, 2003; ASA, 2004; RCA et al, 2004; ANZCA & FPM, 2007).

3.2.2 Acute pain services

Many institutions would now say that they have an APS. However, there is a very wide diversity of APS structures, no consensus as to the best model, and no agreed definition of what might constitute such a service (Counsell et al, 2008). Some are 'low-cost' nurse-based (Shapiro et al, 2004; Rawal, 2005), others are anaesthetist-led but rely primarily on APS nurses as there may not be daily clinical participation by an anaesthetist (Harmer, 2001; Nagi, 2004), and some are comprehensive and multidisciplinary services with APS nursing staff, sometimes pharmacists or other staff, and daily clinical input from, and 24-hour cover by, anaesthetists (Ready et al, 1988; Macintyre et al, 1990; Schug & Haridas, 1993).

The degree of medical input varies enormously. 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 a half day) varied from zero in 27%, just one or two a week in a further 22%, four to six per week in 22% and ten per week in 15% (Roberts, 2008). A survey in the United Kingdom 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 week in 40% and in only 4% were there five or more sessions (Nagi, 2004).

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 (Macintyre & Schug, 2007; Breivik, 2002; Counsell et al, 2008). Increasingly, APSs are also called on to deal with much more complex pain management issues (eg acute-on-chronic pain, acute pain after spinal cord injury and other major trauma, and acute pain resulting from a multitude of medical illnesses) and much more complex patients (eg opioid-tolerant patients, older patients) (Counsell et al, 2008).

Given the enormous heterogeneity of APS models and types of patients and pain treated, as well as variation in the quality of published studies, it is not surprising that it is difficult to come up with a meaningful analysis of the benefits or otherwise of an APS. Individual

publications have reported that the presence of an APS reduced pain scores (Gould et al, 1992 **Level III-3**; Harmer & Davies, 1998 **Level III-3**; Miaskowski et al, 1999 **Level IV**; Sartain & Barry, 1999 **Level III-3**; Salomaki et al, 2000 **Level III-3**; Bardiau et al, 2003 **Level III-3**; Stadler et al, 2004 **Level III-3**) and side effects (Schug & Torrie, 1993 **Level IV**; Stacey et al, 1997 **Level III-3**; Miaskowski et al, 1999 **Level IV**; Sartain & Barry, 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 PONV, but that it was not possible to determine which model was superior (Werner et al, 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.

Although systematic reviews have been attempted (McDonnell et al, 2003; NICS, 2002), the poor quality of the studies looking at the effectiveness or otherwise of APSs, and the many different types of APSs, means that a proper meta-analysis cannot be performed.

In addition, the above studies looked at outcome in terms of immediate pain and side 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 days after their return to a general ward, showed a significant improvement in postoperative outcome; the incidence of serious adverse events decreased from 23 events per 100 patients to 16 events per 100 patients, and the 30-day mortality fell from 9% to 3 % (Story et al, 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 et al, 2008).

Table 3.1 Possible benefits of an Acute Pain Service

Benefit	References
Better pain relief	Gould et al, 1992; Harmer & Davies, 1998; Miaskowski et al, 1999; Sartain & Barry, 1999; Salomaki et al, 2000; Werner et al, 2002; Bardiau et al, 2003; Stadler et al, 2004
Lower incidence of side effects	Schug & Torrie, 1993; Stacey et al, 1997; Miaskowski et al, 1999; Sartain & Barry, 1999; Werner et al, 2002
Lower postoperative morbidity/ mortality	Story et al, 2006
Management of analgesic techniques that may reduce the incidence of persistent pain after surgery	Obata et al, 1999; Senturk et al, 2002; Gehling & Tryba, 2003

Key messages

1. Preoperative education improves patient or carer knowledge of pain and encourages a more positive attitude towards pain relief (**U**) (**Level II**).
2. Video education of patients with a whiplash injury reduces the incidence of persistent pain (**N**) (**Level II**).
3. Written information given to patients prior to seeing an anaesthetist is better than verbal information given at the time of the interview (**N**) (**Level III-2**).
4. 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, and information presented in video format may be better still (**N**) (**Level III-2**).
5. Implementation of an acute pain service may improve pain relief and reduce the incidence of side effects (**U**) (**Level III-3**).
6. Staff education and the use of guidelines improve pain assessment, pain relief and prescribing practices (**U**) (**Level III-3**).
7. 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**).

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

☑ Successful management of acute pain requires close liaison with 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**).

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4. SYSTEMICALLY ADMINISTERED ANALGESIC DRUGS

4.1 OPIOIDS

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

4.1.1 Choice of opioid

All full opioid agonists given in appropriate doses produce the same analgesic effect and therapeutic index (McQuay, 1991), although accurate determination of equianalgesic doses is difficult due to interindividual variabilities in kinetics and dynamics (Gammaitoni et al, 2003). Equianalgesic conversion dose tables are often used to assist in the change from one opioid to another. However, such tables should be used as a guide only as they are based largely on single-dose studies in opioid-naive 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 (Weschules & Bain, 2008).

In general there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of side 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 et al, 1999 **Level II**). Comparisons of the different opioids are commonly done in patients using patient-controlled analgesia (PCA) (see Section 7.1.2 for these comparisons).

While the data to support the concept of opioid rotation originate from cancer pain (Quigley, 2004 **Level I**), it may be a useful strategy in the management of acute pain in patients with intolerable opioid-related side effects that are unresponsive to treatment, and in opioid-tolerant patients (see Section 11.7).

4.1.2 Specific opioids

The efficacy of various opioids administered by the different routes used in the management of acute pain is discussed in detail in Sections 6 and 7.1. The following section describes other relevant aspects of selected opioid agents including tramadol.

Buprenorphine

Buprenorphine is a semi-synthetic 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 et al, 2005). Mean terminal half-lives are 24 hours following sublingual administration and 2 to 3 hours after parenteral injection; two-thirds of the drug 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). Maximum onset of effect is slower than for other opioids making acute titration difficult. In a study using experimental pain stimuli, the time to maximal peak effect after administration of an IV bolus dose of buprenorphine was between 70 and 100 minutes (Yassen et al, 2006 **Level III-3**).

In clinically relevant doses, buprenorphine appears to behave like a full mu-opioid receptor agonist, and in animals as well as humans in low doses (ie transdermal buprenorphine), there also appears to be no antagonism of other concurrently administered mu-agonist drugs (Kress, 2009). Contrary to earlier concerns, there was a ceiling effect found for respiratory depression but not for analgesia (Dahan et al, 2005 **Level III-2**; Dahan et al, 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). Should buprenorphine-induced respiratory depression occur, reversal is possible although higher-than-usual doses and a longer duration infusion of naloxone may be required (van Dorp, Yassen et al, 2006 **Level III-2**).

In animal models of pain, buprenorphine appears to have good efficacy for neuropathic pain (Hans, 2007). In the clinical setting, case reports have suggested that buprenorphine is also effective (Kress, 2009). Using experimental pain stimuli in humans, and unlike pure mu-opioid agonists, buprenorphine has been shown to be antihyperalgesic (ie the area of hyperalgesia was reduced), which may be related in part to its kappa-opioid antagonist activity (Koppert et al, 2005).

Withdrawal symptoms, which may be seen if the drug is ceased after long-term treatment, are milder and more delayed in onset (72 hours or more) than other opioids (Kress, 2009).

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 given to morphine, via the CYP2D6 cytochrome P450 isoenzyme (Lotsch, 2005).

Over 100 allelic variants of CYP2D6 have been identified, resulting in wide variability in enzyme activity (Somogyi et al, 2007). 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 & Stuber, 2007). In Caucasian populations, 8% to 10% of people are poor metabolisers; however 3% to 5% are ultrarapid metabolisers (Stamer & Stuber, 2007; Madadi et al, 2009). 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 et al, 2007 **Level IV**).

There are large inter-ethnic 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 & Stuber, 2007); the proportion of poor metabolisers is lower in Asians and African Americans (Holmquist, 2009).

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 et al, 2009 **Level III-2**). A number of similar cases have been reported and health care workers and mothers of breastfeeding infants should be aware of this risk (Madadi et al, 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 et al, 2009 **Level III-2**).

The principal metabolite of codeine is codeine-6-glucuronide, which has a similar low potency to the parent drug and is renally excreted.

Dextropropoxyphene

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 & Zhang, 1997 **Level I**). A later study comparing this combination with paracetamol alone in the treatment of pain after third molar surgery confirmed the lack of analgesic benefit (Sorich et al, 2004 **Level II**).

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 et al, 2006). These include a euphorigenic component with risk of abuse and complex pharmacokinetics (particularly in the elderly), with the risk of accumulation and QT-interval prolongation and possibility of Torsades de Pointes (TdP) and cardiogenic death. For these reasons, it was announced that a phased withdrawal of dextropropoxyphene combination preparations would commence in the United Kingdom from January 2005 (Hawton et al, 2009). A marked decrease in prescribing of this combination was followed by a major reduction in deaths (accidental and suicide) related to its use, and while prescriptions of other analgesics increased significantly during this time, there was no evidence of a corresponding increase in deaths related to use of these other drugs (Hawton et al, 2009).

The major metabolite of dextropropoxyphene is nordextropropoxyphene, which has a mean half-life of 29 hours (compared with 16 hours for the parent drug) and is renally excreted (Brosen et al, 1985); accumulation of nordextropropoxyphene can lead to CNS, respiratory and cardiac depression (Davies et al, 1996).

Diamorphine

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to monoacetylmorphine (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 & Lackband, 2001).

There was no difference between parenteral diamorphine and morphine in terms of analgesia and side effects after hip surgery (Robinson et al, 1991 **Level II**). Epidurally administered diamorphine resulted in a longer time to first PCA use and lower total 24-hour morphine requirements compared with the same dose given as an IM injection (Green et al, 2007 **Level II**).

Dihydrocodeine

Dihydrocodeine is a semi-synthetic 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 drug (Lotsch, 2005).

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 (Peng & Sandler, 1999).

Mu-opioid receptor A304G polymorphisms can affect pain relief after fentanyl administration. Intrathecal fentanyl requirements in labour were reduced in women with the 304G allele but increased in those with the 304A allele of genes encoding the mu-opioid receptor (Landau et al, 2008 **Level III-3**).

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; Wright et al, 2001; Murray & Hagen, 2005).

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 et al, 2005; Fredheim et al, 2008).

It has good oral bioavailability (70% to 80%), high potency and long duration of action, and a lack of active metabolites, (Lugo et al, 2005). 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 hours; range 4 to 190 hours) leading to an increased risk of accumulation (Weschules et al, 2008). 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 including CYP2B6, CPY3A4 and, to a lesser extent, CYP2D6 (Weschules et al, 2008). Concurrent administration of other drugs that are cytochrome P450 inducers may increase methadone metabolism and lower methadone blood levels (eg carbamazepine, rifampicin, phenytoin, St John's Wort and some antiretroviral agents). Conversely, drugs that inhibit cytochrome P450 (eg other antiretroviral agents, some selective serotonin reuptake inhibitors, grapefruit juice, and antifungal agents) may lead to raised methadone levels and an increase in adverse effects (Fredheim et al, 2008). See Section 9.6.8 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 most widely used opioid for the management of pain and 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, contributes to morphine analgesia in patients with both normal and impaired renal function, and has other morphine-like effects including respiratory depression; 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; van Dorp, Romberg et al, 2006; Dahan, van Dorp et al, 2008).

Clinical trials have investigated M6G as an analgesic agent after a variety of different types of surgery. Two showed that M6G was as effective as morphine (Cann et al, 2002 **Level II**; Hanna et al, 2005 **Level II**). In another two, in higher doses, it was more effective than placebo (Romberg et al, 2007 **Level II**; Smith et al, 2009 **Level II**).

Excellent pain relief was also obtained after intrathecal 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 to 12 hours after the dose was given) requiring treatment with

naloxone, and a high incidence of nausea (76% to 88%, depending on dose) and vomiting (60% to 64%) (Grace & Fee, 1996 **Level II**).

Although it has been shown that M6G is more potent than morphine in various pain models and that the potency ratios also vary according to route of administration (Lotsch, 2005; van Dorp, Romberg et al, 2006), clinical studies suggest that the same amount of, or more, M6G is required to produce the same analgesic effect as a given dose of morphine (Dahan, van Dorp et al, 2008).

Most of the studies were not designed to look at side effects, but the incidence of nausea and vomiting may be less than with morphine (Cann et al, 2002 **Level II**). In healthy volunteers, morphine 0.15 mg/kg and M6G 0.2 mg/kg resulted in similar reductions in ventilatory response to carbon dioxide (Romberg et al, 2003 **Level III-1**).

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 et al, 1998 **Level IV**; Klepstad et al, 2003 **Level IV**) with the potential risk of severe long-lasting sedation and respiratory depression.

Genetic polymorphisms of the mu-opioid receptor may influence the efficacy of morphine. Several single nucleotide polymorphisms have been identified, A118G being the most common. Patients can be genotyped as A118 homozygous (AA), that is homozygous for the wild-type A allele, heterozygous (AG), or homozygous for the variant G allele (GG). Studies from Taiwan (Chou, Wang et al, 2006 **Level III-2**; Chou, Yang et al, 2006 **Level III-2**) and Singapore (Sia, 2008 **Level III-2**) showed that patients who were GG homozygotes had increased PCA morphine requirements in the postoperative period. However, no significant difference in morphine use was seen in two other studies (Coulbault et al, 2006 **Level III-2**; Janicki et al, 2006 **Level III-2**) looking at populations of predominantly white or mixed ethnicity patients respectively. In one of these studies (Coulbault et al, 2006), where a trend to higher morphine requirements was associated with the G allele, a low frequency of the G allelic variant was noted. The frequency of AG and GG variants is higher in Asian than Caucasian populations (Landau, 2006), which could influence results when small numbers of a mixed-ethnicity population are studied.

Other polymorphisms at genes encoding for morphine metabolism (UGT2B7 gene) and transport across the blood-brain barrier by p-glycoprotein (MDR1 gene) may also influence the clinical efficacy of morphine (Klepstad et al, 2005). Other substrates of p-glycoprotein, one of the main efflux transporters, include methadone and fentanyl (Sweeney, 2007). As well as morphine, UGT2B7 also mediates the metabolism and formation of glucuronides from other opioids including buprenorphine, codeine, dihydrocodeine and hydromorphone, but the clinical significance of UGT2B7 gene variants has not yet been well defined (Somogyi et al, 2007; Holmquist, 2009).

Oxycodone

Oxycodone is a potent opioid agonist derived from the opium alkaloid thebaine. It is metabolised in the liver primarily to noroxycodone and oxymorphone, but these metabolites have clinically negligible analgesic effects (Lalovic et al, 2006; Riley et al, 2008). Oxymorphone, the production of which relies on CYP2D6, is more potent than oxycodone, but plasma concentrations are low; noroxycodone, the major metabolite and the production of which relies on CYP3A4, is only weakly active (Coluzzi & Mattia, 2005; Lalovic et al, 2006; Holmquist, 2009). Unlike codeine, inhibition of CYP2D6 with quinine does not reduce the analgesic effect of oxycodone (Lalovic et al, 2006). Animal studies have shown that oxycodone is actively taken up into the brain, resulting in a brain concentration that is up to six times those of free plasma levels (Bostrom et al, 2008).

In an experimental pain model comparing oxycodone, morphine and placebo, and involving mechanical, thermal and electrical pain stimuli in skin, muscle and oesophagus, oxycodone was more effective than morphine for pain related to mechanical and thermal stimulation of the oesophagus, suggesting it could be better than morphine for visceral pain (Staahl et al, 2006 **Level II**). One explanation of this difference is that, in animal studies at least, oxycodone is thought to act as a kappa-receptor agonist (Nielsen et al, 2007) and these receptors may play an important role in the mediation of visceral pain (Staahl et al, 2006).

Pethidine

Pethidine (meperidine) is a synthetic opioid still widely used even though it has multiple disadvantages. 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 et al, 2000 **Level II**) or hydromorphone (Jasani et al, 1994 **Level II**). Similarly, pethidine and morphine 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 et al, 2002 **Level IV**).

Pethidine induced more nausea and vomiting than morphine when used parenterally in the emergency department (Silverman et al, 2004 **Level III-3**) and in the first 2 hours after gynaecological surgery (Ezri et al, 2002 **Level II**).

Accumulation of its active metabolite, norpethidine (normeperidine), is associated with neuroexcitatory effects that range from nervousness to tremors, twitches, multifocal myoclonus and seizures (Simopoulos et al, 2002 **Level IV**). As impaired renal function increases the half-life of norpethidine, 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 (Latta et al, 2002).

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 (Lotsch, 2005). 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 in the currently recommended doses (Thevenin et al, 2008 **Level II**). Tramadol is an effective treatment of neuropathic pain with an NNT of 3.8 (Hollingshead et al, 2006 **Level I**).

Tramadol given with morphine to patients immediately after surgery was shown to be morphine-sparing, but the combination was infra-additive (Marcou et al, 2005 **Level II**).

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 (or M1), is a more potent mu-opioid receptor agonist than the parent drug (Raffa et al, 1992; Lotsch, 2005). Patients who are poor metabolisers may get less analgesic effect from tramadol (Stamer et al, 2003). Conversely, carriers of a CYP2D6 gene duplication allele (ultrarapid metabolisers) may be more sensitive to the effects of tramadol (Kirchheiner et al, 2008).

Coadministration with other drugs 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 et al, 2005 **Level II**).

Inhibition of 5HT3 receptors by ondansetron also decreased the analgesic effect of tramadol (Arcioni et al, 2002 **Level II**; De Witte et al, 2001 **Level II**).

Tramadol's adverse effect profile is different from other opioids. The risk of respiratory depression is significantly lower at equianalgesic doses (Tarkkila et al, 1997 **Level II**; Tarkkila et al, 1998 **Level II**; Mildh et al, 1999 **Level II**) and it does not depress the hypoxic ventilatory response (Warren et al, 2000 **Level II**). Significant respiratory depression has only been described in patients with severe renal failure, most likely due to accumulation of the metabolite M1 (Barnung et al, 1997).

In addition, tramadol has less effect on gastrointestinal (GI) motor function than morphine (Wilder-Smith, Hill, Osler et al, 1999 **Level II**; Wilder-Smith, Hill, Wilkins et al, 1999 **Level II**; Lim & Schug, 2001 **Level II**). Nausea and vomiting are the most common adverse effects and occur at rates similar to other opioids (Radbruch et al, 1996 **Level IV**). Tramadol given within recommended dose limits does not increase the incidence of seizures compared with other analgesic agents (Jick et al, 1998 **Level III-2**; Gasse et al, 2000 **Level III-2**).

4.1.3 Determinants of opioid dose

Interpatient opioid requirements vary greatly (Macintyre & Jarvis, 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.

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 et al, 1989 **Level IV**; Macintyre & Jarvis, 1996 **Level IV**; Gagliese et al, 2000 **Level IV**; Coulbault et al, 2006 **Level IV**; Gagliese et al, 2008 **Level IV**). The decrease in opioid requirement is not associated with reports of increased pain (Burns et al, 1989 **Level IV**; Macintyre & Jarvis, 1996 **Level IV**).

This age-related decrease in opioid requirement is due mainly to differences in pharmacodynamics or brain penetration rather than systemic pharmacokinetic factors (Scott & Stanski, 1987; Minto et al, 1997; Macintyre & Upton, 2008) (see Section 11.2).

Gender

In general it has been found that females report more severe pain than males with similar disease processes or in response to experimental pain stimuli (Hurley & Adams, 2008; Fillingim et al, 2009). Response to opioids may also differ although both the degree and direction of variation depend on many variables (Dahan, Kest et al, 2008). There is no consistent evidence for any difference in mu-opioid agonist requirements (Fillingim et al, 2009). However, kappa-opioid agonists such as nalbuphine and pentazocine have greater analgesic efficacy in women than in men – see Section 1.6.2 .These variations as well as other known and unknown factors involved in the very large interpatient differences in opioid requirements seen clinically, mean that gender cannot be used as a basis for opioid dose alteration and confirms the need to titrate doses to effect for each patient.

Acute postsurgical pain shows a tendency towards greater intensity in females, although the evidence is inconsistent, as is the evidence for any difference in opioid requirements (Fillingim et al, 2009). For example, higher pain scores and higher morphine requirements in the immediate postoperative period have been reported for female patients (Cepeda &Carr, 2003 **Level III-2**; Aubrun et al, 2005 **Level III-2**). After knee ligament reconstruction, women reported higher pain scores than men on the first day after surgery but there was no difference in morphine consumption (Taenzer et al, 2000 **Level III-2**). Females also reported more pain after endoscopic inguinal hernia repair (Lau & Patil, 2004 **Level III-2**), laparoscopic cholecystectomy (De

Cosmo et al, 2008 **Level III-2**; Uchiyama et al, 2006 **Level III-2**), and arthroscopic knee surgery (Rosseland & Stubhaug, 2004 **Level III-2**). However, in adolescent patients using PCA morphine in the postoperative period, no difference was seen between male and female patients in average daily pain ratings (Logan & Rose, 2004 **Level III-2**). In a study of Chinese patients, females consumed significantly less morphine than males (Chia et al, 2002 **Level III-2**).

When pain is assessed at a longer time interval after surgery, there appears to be no differences between male and female patients (Fillingim et al, 2009). For example, there was no difference in pain after arthroscopic knee surgery at one year, although disability was greater in females (Rosseland et al, 2008 **Level III-2**), or in pain at 12 to 18 months after hip arthroplasty (Nikolajsen, Brandsborg et al, 2006 **Level III-2**).

Genetics

Genetic variability may also affect a patient's response to opioids (see Section 1.6).

Psychological factors

Evidence of any effect of psychological factors such as anxiety on opioid requirements is contradictory (see Section 1.2).

4.1.4 Adverse effects of opioids

Common adverse effects of opioids are sedation, pruritus, nausea, vomiting, slowing of GI function and urinary retention. Meta-analyses have shown that the risk of side 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 et al, 2005 **Level I**).

Results from a review of all trials (including cohort studies, case-controlled studies and audit reports as well as randomised-controlled trials) suggested that there may be differences in the clinical setting (Cashman & Dolin, 2004; Dolin & Cashman, 2005). The following incidences (means) were associated with the use of PCA opioids: respiratory depression 1.2% to 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% to 37% (using the same indicators), nausea 17%, vomiting 21.9%, pruritus 3.4%, and excessive sedation 5.2% (Cashman & Dolin, 2004 **Level IV**; Dolin & Cashman, 2005 **Level IV**).

Clinically meaningful adverse effects of opioids 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 et al, 2005 **Level I**[3]). In a later prospective evaluation of the incidence of nausea and vomiting in elderly surgical inpatients requiring a length of stay greater than 2 days and given no postoperative nausea and vomiting (PONV) prophylaxis, there was also a direct correlation between increasing opioid dose and the incidence of both nausea and vomiting (Roberts et al, 2005 **Level IV**). In patients after laparoscopic cholecystectomy performed on an ambulatory basis, once a threshold dose was reached, every 3 to 4 mg increase of morphine-equivalent dose per day was associated with one additional meaningful adverse event or patient-day with such an event (Zhao et al, 2004 **Level II**).

[3] This meta-analysis includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Expert advice suggested that withdrawal of the retracted articles would not influence the conclusions but that reanalysis would be required for this to be confirmed. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data included in this meta-analysis after excluding that obtained from the retracted publications. They concluded that removal of this information did not significantly alter the results.

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 et al, 2002; Oderda et al, 2007 **Level IV**).

Respiratory depression

Respiratory depression (decreased central CO_2 responsiveness resulting in hypoventilation and elevated $PaCO_2$ levels), the most feared side effect of opioids, can usually be avoided by careful titration of the dose against effect. However, a variety of clinical indicators have been used to indicate respiratory depression, and not all may be appropriate or accurate.

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 et al, 1985 **Level IV**; Jones et al, 1990; Wheatley et al, 1990 **Level IV**; Kluger et al, 1992 **Level IV**). As respiratory depression is almost always preceded by sedation, the best early clinical indicator is increasing sedation (Ready et al, 1988; Vila et al, 2005; Macintyre & Schug, 2007).

Introduction of a numerical pain treatment algorithm in a cancer setting was followed by a review of opioid-related adverse reactions. 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 et al, 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 et al, 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 were examined (Macintyre & Coldrey, 2008). It would appear that the development of respiratory depression may 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 11.5).

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 et al, 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.

Checking 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 et al, 2009). However, it was noted only that 'in cases with other concerning signs, it is acceptable to awaken a sleeping patient to assess level of consciousness'. In this situation it would be possible for increasing sedation and respiratory depression to be missed if no attempt is made to rouse the patient.

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, 2007). 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). In contrast, the ASA publication (Horlocker et al, 2009) stated that both the Task Force members and consultants 'disagree that pulse oximetry is more likely to detect respiratory depression than are clinical signs'.

Measuring haemoglobin 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 & Dolin, 2004 **Level IV**). However, the same authors showed that patients given IM opioids reported significantly more pain (moderate–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 et al, 2002 **Level IV**).

Increases in PCO_2 are the most reliable way of detecting respiratory depression. Continuous monitoring of transcutaneous CO_2 for 24 hours after major abdominal surgery showed that patients given IV PCA morphine had significantly higher CO_2 levels that those receiving epidural local anaesthetic/fentanyl infusions (Kopka et al, 2007 **Level III-2**; McCormack et al, 2008 **Level III-2**).

Cardiac effects

The use of methadone has been linked to the development of prolonged QT interval with a risk of TdP and cardiac arrest (Gupta et al, 2007). 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 et al, 2006; Fredheim et al, 2008). Risk factors include female sex, heart disease, other drugs with effects on QT interval (eg tricyclic antidepressants, antipsychotics, diuretics) or methadone metabolism, congenital or acquired prolonged QT syndromes, liver impairment and hypokalaemia (Fredheim et al, 2008).

Of patients receiving 60 to 100 mg methadone per day, 23% developed prolonged QT intervals during treatment compared with none of the buprenorphine patients taking 16 to 32 mg three times a week (Wedam et al, 2007 **Level II**). 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).

The use of dextropropoxyphene also carries a risk of TdP (Barkin et al, 2006).

Nausea and vomiting

PONV is common and related to opioid administration in a dose-dependent manner (Marret et al, 2005 **Level I**[4]; Roberts et al, 2005 **Level IV**), although many other risk factors for PONV have also been identified (Gan, 2006). Therefore, drugs used as components of multimodal analgesia and which are opioid-sparing may also reduce PONV. Opioid-sparing and a reduction in PONV has been shown with concurrent administration of gabapentin (Tiippana et al, 2007 **Level I**), non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) (Elia et al, 2005 **Level I**[4]; Marret et al, 2005 **Level I**[4]); and ketamine (Bell et al, 2006 **Level I**). Opioid-sparing with no decrease in PONV was reported for paracetamol and coxibs (Elia et al, 2005 **Level I**[4]; Remy et al, 2005 **Level I**).

The risk of PONV is significantly reduced by the use of droperidol, dexamethasone and ondansetron, which are equally effective (Tramer, 2001 **Level I**; Apfel et al, 2004 **Level II**); propofol and omission of nitrous oxide (N_2O) are less effective (Apfel et al, 2004 **Level II**).

A Cochrane review identified eight drugs that effectively prevented PONV compared with placebo: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron (Carlisle & Stevenson, 2006 **Level I**[4]). The authors concluded that evidence for differences between the drugs was unreliable due to publication bias. There were few data to compare side effects, but droperidol was more sedative and headache was more common after ondansetron.

Combinations of antiemetics may be more effective than one drug given alone. Prophylaxis with the combination of a 5HT3-receptor antagonist and dexamethasone was associated with lower use of rescue antiemetics than 5HT3-receptor antagonist or dexamethasone alone (Kovac, 2006 **Level I**). Similarly, the combination of droperidol and ondansetron was additive (Chan et al, 2006 **Level I**). Other combinations that were more effective than either drug given alone were cyclizine and granisteron (Johns et al, 2006 **Level II**), dexamethasone and haloperidol (Rusch et al, 2007 **Level II**; Chu CC et al, 2008 **Level II**), and dexamethasone and dolasetron (Rusch et al, 2007 **Level II**). 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 and not 10 mg (Wallenborn et al, 2006 **Level II**).

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 United States Food and Drug Administration (FDA) in 2001. Following this there has been a significant reduction in the use of this drug, even though the warning was felt by many to be unwarranted (Habib & Gan, 2008a).

In a study in healthy volunteers, QT prolongation with droperidol 1 mg IV was significantly greater than following ondansetron 4 mg IV, but the effect of combining both drugs was no worse than droperidol alone (Charbit et al, 2008 **Level II**). Significant but similar QT prolongation (compared with pretreatment values) was also noted in patients given droperidol 0.75 mg IV or ondansetron 4 mg IV after surgery (Charbit et al, 2005 **Level II**). However, QT interval was already prolonged in 21% of these patients prior to administration of any antiemetic drug. There was also a transient increase in QT interval after administration of ondansetron 4 mg IV, droperidol 1.25 mg IV, or their combination given prior to surgery, but there were also no

[4] This meta-analysis includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Expert advice suggested that withdrawal of the retracted articles would not influence the conclusions but that reanalysis would be required for this to be confirmed. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data included in this meta-analysis after excluding that obtained from the retracted publications. They concluded that removal of this information did not significantly alter the results.

differences between the groups (Chan et al, 2006 **Level II**). Another study showed that QT prolongation occurred after 0.625 and 1.25 mg IV droperidol, but that this was not significantly different from that seen with saline, indicating that other causes of mild QT prolongation occur with anesthesia and surgery (White et al, 2005 **Level II**).

A large review (Nuttall et al, 2007 **Level III-3**) of surgical patients in the periods 3 years before (139 932 patients) and 3 years after (151 256 patients) 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 hours of their surgery. Despite a reduction in the use of droperidol from 12% to 0% of patients following the warning, there was no difference in the incidence of QT prolongation, ventricular tachycardia, or death within 48 hours of surgery and no clearly identified case of TdP related to use of droperidol (Nuttall et al, 2007 **Level III-3**). The authors concluded that for low-dose droperidol, the 'black box' warning was 'excessive and unnecessary'. Others have supported use of the warning but suggested it should be made clear that the doses commonly used in the prevention and treatment of PONV are 'off-label' and that the 'FDA has no position on the safety and efficacy of doses below 2.5 mg' (Ludwin & Shafer, 2008).

The authors of recent guidelines for the management of PONV also expressed concerns about the quality and validity of evidence that led to the FDA caution and concluded that without this warning, 'droperidol would have been the panel's overwhelming choice for PONV prophylaxis' (Gan, Meyer et al, 2007).

Haloperidol has also been associated with prolonged QT intervals and TdP (Habib & Gan, 2008b). Using data from studies published up until 1988, a meta-analysis showed that haloperidol was also an effective antiemetic (Buttner et al, 2004 **Level I**). More recent studies have confirmed its effectiveness compared with placebo (Aouad et al, 2007 **Level II**), ondansetron (no differences in efficacy, side effects or QT intervals) (Aouad et al, 2007 **Level II**; Lee Y et al, 2007 **Level II**; Rosow et al, 2008 **Level II**) and droperidol (as effective) (Wang et al, 2008 **Level II**). Combination of haloperidol with ondansetron was more effective than ondansetron alone (Grecu et al, 2008 **Level II**) and haloperidol and dexamethasone also more effective than either drug given alone (Chu CC et al, 2008 **Level II**), again with no difference in side effects or QT intervals. Compared with droperidol, the only advantage of haloperidol may be 'that there is no black box warning' (Ludwin & Shafer, 2008).

Dolasetron (IV and oral formulations) is contraindicated by the Canadian authorities for any therapeutic use in children and adolescents under 18 years of age and the prevention or treatment of PONV in adults because of the risk of QT prolongation (Health Canada, 2006). The age restriction is not limited to Canada, but valid in a number of countries including the United Kingdom; cases of prolonged QT interval have also been reported after overdose (Rochford et al, 2007).

NK1-receptor antagonists may also be effective in the treatment of PONV. Aprepitant was more effective than ondansetron for preventing vomiting at 24 and 48 hours after open abdominal surgery, and in reducing the severity of nausea in the first 48 hours (Diemunsch et al, 2007 **Level II**). In a similar study with a slightly smaller number of patients after open abdominal surgery, aprepitant was also found to be superior to ondansetron for prevention of vomiting in the first 24 and 48 hours, but no difference was seen in the incidence of nausea (Gan, Apfel et al, 2007 **Level II**).

P6 acupoint stimulation in patients with no antiemetic prophylaxis resulted in significant reductions in the risks of nausea, vomiting and the need for rescue antiemetics; compared

with antiemetic prophylaxis, P6 acupoint stimulation seems to reduce the risk of nausea but not vomiting (Lee & Done, 2004 **Level I**).

Supplemental oxygen (inspired oxygen concentration 80%) did not reduce PONV (Orhan-Sungur et al, 2008 **Level I**).

Impairment of gastrointestinal motility

Opioids impair return of bowel function after surgery. The peripheral acting opioid antagonists alvimopan and methylnaltrexone were effective in reversing opioid-induced slowing of GI transit time and constipation, and alvimopan was an effective treatment for postoperative ileus; insufficient evidence exists about the efficacy or safety of naloxone or nalbuphine (McNicol et al, 2008 **Level I**).

A combined formulation of controlled-release (CR) oxycodone and naloxone has been studied. Compared with CR oxycodone alone in patients with chronic non-malignant pain, the combination formulation resulted in similar analgesic efficacy but less bowel dysfunction (Vondrackova et al, 2008 **Level II**).

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 was effective in 42% of study participants (Rosow et al, 2007 **Level II**). These data suggest that at least part of the bladder dysfunction caused by opioids is peripherally mediated.

Premedication with gabapentin reduced urinary retention caused by opioids (NNT 7) (Tiippana et al, 2007 **Level I**). 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 & Maxwell, 2007). Naloxone, naltrexone, nalbuphine and droperidol are effective in the treatment of opioid-induced pruritus, although minimum effective doses remain unknown (Kjellberg & Tramer, 2001 **Level I**).

Prophylactic 5HT3 antagonists reduce the incidence of pruritus after neuraxial opioids (Bonnet et al, 2008 **Level I**); however the authors of this meta-analysis were concerned about possible publication bias.

Premedication with gabapentin (Sheen, Ho, Lee, Tsung & Chang, 2008 **Level II**) and mirtazepine (Sheen, Ho, Lee, Tsung, Chang et al, 2008 **Level II**) also reduced the incidence and severity of pruritus associated with intrathecal opioids. Evidence of any benefit with propofol is mixed (Ganesh & Maxwell, 2007). Promethazine was not effective for the treatment of spinal morphine-induced pruritus but was associated with more sedation; droperidol and, to a lesser extent propofol, were of use (Horta et al, 2006 **Level II**).

Cognitive function and confusion

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 but the rates were 4.3% for patients given fentanyl and 14.3% for those receiving morphine; there was less depression of cognitive function with fentanyl (Herrick et al, 1996 **Level II**). Compared with morphine, no differences in cognitive function were reported in patients receiving tramadol (Silvasti et al, 2000 **Level II**; Ng et al, 2006 **Level II**), but cognitive function was poorer in patients given hydromorphone (Rapp et al, 1996 **Level II**). Studies of lower quality reported a significantly greater incidence of delirium with

pethidine compared with morphine (Adunsky et al, 2002 **Level III-3**) and a variety of other opioids (Morrison et al, 2003 **Level III-2**). Pethidine use postoperatively was associated with an increased risk of delirium in the postoperative period; there was no difference between various other opioids (Fong et al, 2006 **Level I**).

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 opioid-induced hyperalgesia (OIH) (a sensitisation of pronociceptive pathways leading to pain hypersensitivity), and that both these phenomena can significantly reduce the analgesic effect of opioids (Angst & Clark, 2006; Chu LF et al, 2008). 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 (Angst & Clark, 2006; Mao, 2008).

Mao (Chang et al, 2007; Mao, 2008) distinguishes between 'pharmacological tolerance' (ie tolerance, as defined in Section 11.7 — 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. 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 (Angst & Clark, 2006). 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 et al, 2007; Mao, 2008; Chu LF et al, 2008).

It is probable that the degree of OIH varies between opioids. Morphine, in high doses, may be more likely to result in OIH than 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 & Clark, 2006). Similarly, it appears that opioids differ in their ability to induce tolerance and, at least in part, this may reflect their varying ability to promote receptor internalisation and recycling. While drugs such as methadone, fentanyl and sufentanil promote receptor internalisation and thereby recycling, activation of opioid receptors by morphine leads to little or no receptor internalisation and an increased risk of development of tolerance (Joo, 2007).

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 11.7.3).

Studies using experimental pain stimuli

Many animal studies have shown that opioid administration can lead to OIH (Angst & Clark, 2006). A number of 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 et al, 2000 **Level IV**; Doverty et al, 2001 **Level III-2**; Athanasos et al, 2006 **Level III-2**). Similarly, pain sensitivity to cold pressor but not heat stimuli was noted in patients 1 month after starting oral morphine therapy (Chu et al, 2006 **Level III-2**), and to cold pressor but not electrical pain stimuli in patients with chronic non-cancer pain taking either methadone or morphine (Hay et al, 2009 **Level III-2**). In a comparison of methadone-maintained and buprenorphine-maintained patients, pain sensitivity to cold pressor pain stimuli was increased in both groups and overall there was no

difference between the groups; in the few patients not also taking illicit opioids, subjects taking buprenorphine were less hyperalgesic than those taking methadone (Compton et al, 2001 **Level III-2**).

Angst and Clark (Angst & Clark, 2006 **Level I**) summarised studies that investigated the effects of a short-duration remifentanil infusion in volunteer subjects with pre-existing experimentally induced mechanical hyperalgesia; the use of remifentanil was shown to aggravate hyperalgesia, the magnitude of the effect was directly related to the dose given, and coadministration of ketamine abolished the effect of remifentanil. 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-naive patients; dose-dependent increases in cold pressor tolerance were found (Hay et al, 2009 **Level III-2**).

Clinical studies

It may be more difficult to distinguish between pharmacological tolerance and OIH in the clinical setting when subjective pain scores are used to assess adequacy of analgesia (Chang et al, 2007). Many of the studies to date provide only indirect evidence for the development of OIH (Angst & Clark, 2006; Chu LF et al, 2008). A formal diagnosis of hyperalgesia requires quantitative sensory testing (QST), that is, serial assessment of the responses to varying intensities of a nociceptive stimulus in order to determine pain thresholds (Mitra, 2008). QST before and after starting chronic opioid therapy, may assist in the differentiation between OIH and pharmacological tolerance (Chu LF et al, 2008) but this is unlikely to become common practice in the acute pain setting.

There have been a number of studies, summarised in reviews by Angst and Clark (Angst & Clark, 2006 **Level IV**) and Chu et al (Chu LF et al, 2008 **Level IV**), investigating the effects of intraoperative use of a potent opioid (commonly a remifentanil infusion) on pain and postoperative opioid requirements, but the results are conflicting. Some have shown that this leads to increased pain and postoperative opioid requirements, and attributed this to OIH, other studies have not been able to replicate these findings — leading to the suggestion that the outcome may be dose-dependent and more likely to occur when higher opioid doses are administered (Chu LF et al, 2008). For example, morphine requirements and hyperalgesia and allodynia adjacent to the surgical wound were greater following high-dose intraoperative remifentanil infusions compared with low-dose infusions (Joly et al, 2005 **Level II**). A study in volunteers given remifentanil infusions to obtain two different 'but clinically relevant' steady-state target concentrations of the drug, found that these were not associated with changes in response to thermal, electrical and cold pressor stimuli (Angst et al, 2009 **Level II**).

Also, it is not yet clear from many of these papers whether this acute 'apparent tolerance' is due to pharmacological tolerance or OIH (Angst & Clark, 2006; Mao, 2008). True differentiation between pharmacological tolerance and OIH requires direct assessment of pain sensitivity, as noted above (Mitra, 2008). However, if patients given a remifentanil infusion intraoperatively report higher levels of postoperative pain than matched controls who have not received any opioids, then OIH should be considered (Chang et al, 2007).

Severity of acute pain following a single subcutaneous (SC) injection of lignocaine was compared in patients taking opioids for chronic pain and opioid-naive controls; pain and unpleasantness scores were higher in those patients taking opioids and correlated with opioid dose and duration of treatment (Cohen et al, 2008 **Level III-2**).

There are case reports of patients with cancer and chronic non-cancer 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 & Clark, 2006; Chu LF et al, 2008), however there have been no similar reports from an acute pain setting.

Clinical implications and possible attenuation of tolerance and OIH

See Section 11.7.1.

Tolerance to adverse effects of opioids

Tolerance to the side 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 et al, 2007).

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. Gabapentin, non-steroidal NSAIDs and ketamine are opioid-sparing medications and reduce opioid-related side effects (**N**) (**Level I**).
4. In appropriate doses, droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron are effective in the prevention of postoperative nausea and vomiting (**N**) (**Level I** [Cochrane Review]).
5. Alvimopan and methylnaltrexone are effective in reversing opioid-induced slowing of gastrointestinal transit time and constipation (**N**) (**Level I** [Cochrane Review]).
6. Droperidol, dexamethasone and ondansetron are equally effective in the prevention of postoperative nausea and vomiting (**U**) (**Level I**).
7. Paired combinations of 5HT3 antagonist, droperidol or dexamethasone provide superior prophylaxis of postoperative nausea and vomiting than either compound alone (**N**) (**Level I**).
8. Naloxone, naltrexone, nalbuphine, droperidol and 5HT3 antagonists are effective treatments for opioid-induced pruritus (**N**) (**Level I**).
9. Opioids in high doses can induce hyperalgesia (**N**) (**Level I**).
10. Tramadol has a lower risk of respiratory depression and impairs gastrointestinal motor function less than other opioids at equianalgesic doses (**U**) (**Level II**).
11. Pethidine is not superior to morphine in treatment of pain of renal or biliary colic (**U**) (**Level II**).
12. Morphine-6-glucuronide is an effective analgesic (**N**) (**Level II**).
13. In the management of acute pain, one opioid is not superior over others but some opioids are better in some patients (**U**) (**Level II**).
14. The incidence of clinically meaningful adverse effects of opioids is dose-related (**U**) (**Level II**).
15. High doses of methadone can lead to prolonged QT interval (**N**) (**Level II**).
16. Haloperidol is effective in the prevention of postoperative nausea and vomiting (**N**) (**Level II**).
17. Opioid antagonists are effective treatments for opioid-induced urinary retention (**N**) (**Level II**).

18. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**N**) (**Level III-2**).
19. Assessment of sedation is a more reliable way of detecting early opioid-induced respiratory depression than a decreased respiratory rate (**S**) (**Level III-3**).
20. The evidence for risk of cardiac arrhythmias following low-dose droperidol is poor (**N**) (**Level III-3**).
21. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).
22. 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**).

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

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

4.2 Paracetamol, non-selective non-steroidal anti-inflammatory drugs and coxibs

4.2.1 Paracetamol

Paracetamol (acetaminophen) 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 & Milner, 2009). It can also be given rectally and intravenously (see below and Section 6).

The mechanism of action of paracetamol remains unclear. In contrast with opioids, paracetamol has no known endogenous binding sites, and unlike NSAIDs, apparently does not inhibit peripheral cyclo-oxygenase activity. There is increasing evidence of a central antinociceptive effect. Although the mechanism of analgesic efficacy of paracetamol remains elusive, it may involve direct and indirect inhibition of central cyclo-oxygenases, but the activation of the endocannabinoid system and spinal serotonergic pathways also appear to be essential (Bertolini et al, 2006; Botting, 2006; Pickering et al, 2006; Mallet et al, 2008; Pickering et al, 2008). Paracetamol has also been shown to prevent prostaglandin production at the cellular transcriptional level, independent of cyclo-oxygenase activity (Mancini et al, 2003).

As one of the mechanisms of action of paracetamol appears to be linked to the serotonergic system, it is possible that other drugs with serotonergic effects could affect pain relief. In volunteers, coadministration of tropisetron or granisetron blocked the analgesic effects of paracetamol (Pickering et al, 2006 **Level II**; Pickering et al, 2008 **Level II**). The significance of this in the clinical setting has not yet been elucidated.

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 drugs such as codeine are discussed and listed in Section 6 and Table 6.1.

Superiority of an oral dose of 1000 mg over doses below 1000 mg was shown after wisdom tooth extraction (Weil et al, 2007 **Level I**). In a meta-analysis designed to look at dose response,

1000 mg was superior to 500 mg (McQuay & Moore, 2007 **Level I**). However, in a broader meta-analysis, no dose-response was noted between doses of 500 mg, 600 to 650 mg and 975 to 1000 mg; the rate of adverse effects was comparable to placebo (Toms et al, 2008 **Level I**). A comparison of two high-dose regimens of oral paracetamol in young adults undergoing third molar extractions showed no difference between doses of 90 mg/kg and 60 mg/kg (Zacharias et al, 2007 **Level II**). Another comparison of single doses of IV doses of 2 g and 1 g showed better pain relief following third molar surgery with the 2 g dose (Juhl et al, 2006 **Level II**).

Paracetamol is also an effective adjunct to opioid analgesia, opioid requirements being reduced by 20% to 30% when combined with a regular regimen of oral or rectal paracetamol (Romsing et al, 2002 **Level I**). The use of oral paracetamol in higher daily doses (1 g every 4 hours) in addition to PCA morphine lowered pain scores, shortened the duration of PCA use and improved patient satisfaction (Schug et al, 1998 **Level II**). Meta-analyses looking at paracetamol as an adjunct to PCA opioids also showed that PCA morphine requirements were decreased but that there was no improvement in pain relief or decrease in opioid-related adverse effects (Elia et al, 2005 **Level I**; Remy et al, 2005 **Level I**).

In the same doses, orally administered paracetamol was less effective and of slower onset than paracetamol given by IV injection, but more effective and of faster onset than paracetamol administered by the rectal route, when subtherapeutic blood concentrations are common (see Section 6).

IV paracetamol was an effective analgesic after surgery (Sinatra et al, 2005 **Level II**). It was as effective as ketorolac (Varrassi et al, 1999 **Level II**; Zhou et al, 2001 **Level II**), diclofenac (Hynes et al, 2006 **Level II**) and metamizol (Landwehr et al, 2005 **Level II**) and was equivalent to morphine and better tolerated after dental surgery (Van Aken et al, 2004 **Level II**), although there was evidence of a ceiling effect (Hahn et al, 2003 **Level II**). Compared with parecoxib, propacetamol (the IV prodrug of paracetamol) led to the same degree of opioid-sparing after surgery, although patients receiving parecoxib were more likely to rate their pain relief as 'good' or 'excellent' (Beaussier et al, 2005 **Level II**).

The combination of paracetamol and NSAID was clearly more effective than paracetamol alone, but evidence for superiority relative to the NSAID alone was more limited and of uncertain clinical significance (Hyllested et al, 2002 **Level I**; Romsing et al, 2002 **Level I**).

Adverse effects

Paracetamol has fewer side effects than NSAIDs and can be used when the latter are contraindicated (eg patients with a history of asthma or peptic ulcers). 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, 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 (Benson et al, 2005; Graham et al, 2005; Oscier & Milner, 2009). There is no evidence that patients who have depleted glutathione stores (eg patients who are malnourished, or who have cirrhosis, hepatitis C or human immunodeficiency virus [HIV]) are at increased risk of liver dysfunction when exposed to therapeutic doses of paracetamol (Benson et al, 2005 Graham et al, 2005; Oscier & Milner, 2009).

Paracetamol interacts with warfarin to increase the International Normalised Ratio (INR) (Mahe et al, 2005 **Level II**; Parra et al, 2007 **Level II**).

4.2.2 Non-selective non-steroidal 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). 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 (PGH) synthase, which has both cyclo-oxygenase and hydroperoxidase sites. Two subtypes of cyclo-oxygenase enzyme have been identified – the 'constitutive' COX-1, the 'inducible' COX-2: a COX-3 is also being investigated (Simmons et al, 2004; Gajraj & Joshi, 2005; Botting, 2006; Kam & So, 2009).

Prostaglandins have many physiological functions including gastric mucosal protection, renal tubular function and intrarenal vasodilation, bronchodilatation, production of endothelial prostacyclin that leads to vasodilation and prevents platelet adhesion, and platelet thromboxane that results in platelet aggregation and vessel spasm. Such physiological roles are mainly regulated by COX-1 and are 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 pain and inflammation, and COX-2 induction within the spinal cord may play a role in central sensitisation. COX-2 may also be 'constitutive' in some tissues, including the kidney, cardiovascular system and brain (Kam & So, 2009). NsNSAIDs are 'non-selective' cyclo-oxygenase inhibitors that inhibit both COX-1 and COX-2. Aspirin acetylates and inhibits cyclo-oxygenase irreversibly but nsNSAIDs are reversible inhibitors of the enzymes. The coxibs have been developed to inhibit selectively the inducible form (Simmons et al, 2004; Gajraj & Joshi, 2005; Botting, 2006).

Efficacy

Single doses of nsNSAIDs are effective in the treatment of pain after surgery (Derry et al, 2009a **Level I**; Derry et al, 2009b **Level I**; Derry et al, 2009c **Level I**), low back pain (Roelofs et al, 2008 **Level I**), renal colic (Holdgate & Pollock, 2004 **Level I**) and primary dysmenorrhoea (Marjoribanks et al, 2003 **Level I**). For a list of NNTs for each drug see Table 6.1.

NsNSAIDs are integral components of multimodal analgesia (Kehlet, 1997; Brodner et al, 2001; Barratt et al, 2002). However, while useful analgesic adjuncts, they are inadequate as the sole analgesic agent in the treatment of severe postoperative pain. When given in combination with opioids after surgery, nsNSAIDs resulted in better analgesia, reduced opioid consumption and a lower incidence of PONV and sedation (Elia et al, 2005 **Level I**[5]; Marret et al, 2005 **Level I**[5]). There was no effect on pruritus, urinary retention and respiratory depression (Marret et al, 2005 **Level I**[5]). Similarly, in patients less than 70 years of age undergoing cardiothoracic surgery, the use of nsNSAIDs reduced pain scores and opioid requirements (Bainbridge et al, 2006 **Level I**) although the use of these drugs in patients following coronary artery bypass surgery is controversial (see below).

[5] This meta-analysis includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Expert advice suggested that withdrawal of the retracted articles would not influence the conclusions but that reanalysis would be required for this to be confirmed. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data included in this meta-analysis after excluding that obtained from the retracted publications. They concluded that removal of this information did not significantly alter the results.

The combination of paracetamol and nsNSAID was clearly more effective than paracetamol alone, but evidence for superiority relative to the nsNSAID alone was more limited and of uncertain clinical significance (Hyllested et al, 2002 **Level I**; Romsing et al, 2002 **Level I**).

Adverse effects

NsNSAID side effects are more common with long-term use — and there are concerns relating to prothrombotic effects. In the perioperative 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 haemodynamic disturbances, fluid shifts, activation of the neurohumoral stress response and deficient enteral feeding. In general, the risk and severity of nsNSAID-associated side effects is increased in elderly people (Pilotto et al, 2003; Juhlin et al, 2005).

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 to brief nsNSAID administration.

In patients with normal preoperative renal function, nsNSAIDs caused a clinically insignificant and transient decrease in creatinine clearance the first day after surgery, and there were no differences between patients given diclofenac, ketorolac, indomethacin (indometacin) or ketoprofen (Lee A et al, 2007 **Level I**). 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 and angiotensin-converting enzyme (ACE) inhibitors (RCA, 1998 **Level IV**).

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 A et al, 2007 **Level I**).

Platelet function

NsNSAIDs inhibit platelet function. In meta-analyses of tonsillectomy in both adult and paediatric patients, nsNSAIDs were found to increase the risk of reoperation for bleeding (NNH 29 to 60) (Marret et al, 2003 **Level I**; Moiniche et al, 2003 **Level I**) but surgical blood loss was not significantly increased (Moiniche et al, 2003 **Level I**) (see also Sections 9.6.7 and 10.5). Looking at studies in children only, there was no increase in the risk of reoperation for bleeding after tonsillectomy (Cardwell et al, 2005 **Level I**). Aspirin, which irreversibly inhibits platelet aggregation, increased the risk of post-tonsillectomy haemorrhage (Krishna et al, 2003 **Level I**).

After a variety of different operations, the use of nsNSAIDs showed a significant increase in risk of severe bleeding from 0 to 1.7% compared with placebo (NNH 59) (Elia et al, 2005 **Level I**). This was also found in the large HIPAID study after hip replacement, where the ibuprofen group had a significantly increased risk of major bleeding complications (OR 2.1) (Fransen et al, 2006 **Level II**). After gynaecological or breast surgery, use of diclofenac led to more blood loss than rofecoxib (Hegi et al, 2004 **Level II**). After otorhinolaryngological surgery in an outpatient setting, tenoxicam increased bleeding at the surgical site (Merry et al, 2004 **Level II**).

Peptic ulceration

A large case-controlled study using a general practice database identified 10 892 patients over 4 years with a 'first ever' diagnosis of an upper GI ulcer or bleeding and compared them with matched controls (Hippisley-Cox et al, 2005 **Level III-3**). Where individual drugs were specified in the results, the risks were shown to be significantly increased for patients using naproxen, diclofenac, ibuprofen, aspirin and rofecoxib, but not those taking celecoxib.

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 more than 5 days and in elderly people (Strom et al, 1996 **Level IV**). After 5 days of naproxen and ketorolac use in healthy elderly subjects, ulcers were found on gastroscopy in 20% and 31% of cases respectively (Harris et al, 2001 **Level II**; Stoltz et al, 2002 **Level II**; Goldstein et al, 2003 **Level II**).

The gastric and duodenal epithelia have various protective mechanisms against acid and enzyme attack and many of these involve prostaglandin production. Chronic nsNSAID use is associated with peptic ulceration and bleeding and the latter may be exacerbated by the antiplatelet effect. It has been estimated that the relative risk of perforations, ulcers and bleeds associated with nsNSAIDs is 2.7 compared with people not consuming nsNSAIDs (Ofman et al, 2002 **Level III-2**). Use of ketorolac and piroxicam carried the highest risk (Lanas et al, 2003 **Level III-3**). Concurrent use of a proton-pump inhibitor (PPI) significantly reduced the incidence of nsNSAID-related peptic ulcer disease (Targownik et al, 2008 **Level III-2**).

Aspirin-exacerbated respiratory disease

Precipitation of bronchospasm by aspirin is a recognised phenomenon in individuals with asthma, chronic rhinitis and nasal polyps. Aspirin-exacerbated respiratory disease (AERD) affects 10% to 15% of people with asthma, can be severe and there is a cross-sensitivity with nsNSAIDs but not coxibs (Simon & Namazy, 2003 **Level IV**; Szczeklik & Stevenson, 2003 **Level IV**; West & Fernandez, 2003 **Level I**). A history of AERD is a contraindication to nsNSAID use, although there is no reason to avoid nsNSAIDs in other people with asthma.

Bone healing

Evidence for an effect on bone healing is conflicting. In one study of 88 patients, 30 of whom were given ketorolac after spinal fusion, the incidence of incomplete union or non-union was higher in those given ketorolac; the relative risk was approximately six times higher than control group of patients who did not receive an NSAID and smoking was said to have had no effect on the spinal fusion outcome (Park et al, 2005 **Level III-2**). In another study of 405 patients, 228 of whom were given ketorolac after similar surgery, there was no significant difference in the non-union rates between the two groups; in this study there were no patients who smoked (Pradhan et al, 2008 **Level III-3**).

Cardiovascular

Most publications looking at the risk of cardiovascular side effects associated with nsNSAID use also include information relating to risks with coxibs. See discussion under Section 4.2.3 below.

4.2.3 Cyclo-oxygenase-2 selective inhibitors (coxibs)

Coxibs selectively inhibit the inducible cyclo-oxygenase enzyme, COX-2, and spare constitutive COX-1 (see above). The coxibs available at present include 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 side effects than nsNSAIDs.

Efficacy

Coxibs were as effective as nsNSAIDs in the management of postoperative pain (Romsing & Moiniche, 2004 **Level I**[6]). They were also as effective as nsNSAIDs for the treatment of low back pain (although effect sizes were small) but the incidence of side effects was lower with coxibs (Roelofs et al, 2008 **Level I**). NNTs are comparable with those for nsNSAIDs for the treatment of moderate to severe acute pain. For a list of NNTs for each drug see Table 6.1.

Preoperative coxibs reduced postoperative pain and opioid consumption and increased patient satisfaction (Straube et al, 2005 **Level I**[6]). When given in combination with opioids after surgery, coxibs were opioid-sparing (Hubbard et al, 2003 **Level II**; Malan et al, 2003 **Level II**; Ng et al, 2003 **Level II**; Reynolds et al, 2003 **Level II**; Gan et al, 2004 **Level II**; Celik et al, 2005 **Level II**; Nussmeier et al, 2006 **Level II**; Snabes et al, 2007 **Level II**; White PF et al, 2007 **Level II**), but both a decrease in the incidence of opioid-related side effects (Malan et al, 2003 **Level II**; Gan et al, 2004 **Level II**) and no difference (Hubbard et al, 2003 **Level II**; Ng et al, 2003 **Level II**; Celik et al, 2005 **Level II**; Snabes et al, 2007 **Level II**; White PF et al, 2007 **Level II**) has been reported. A meta-analysis concluded that there was no evidence for a decrease in adverse effects (Romsing et al, 2005 **Level I**) as did a meta-analysis that included trials of coxibs given to patients receiving PCA morphine; it showed reduced opioid consumption but no significant reductions in pain scores or opioid-related adverse effects (Elia et al, 2005 **Level I**[7]).

Timing of administration may not be critical. A comparison of celecoxib, started preoperatively or postoperatively and continued for 3 days after surgery, showed opioid-sparing and improved patient satisfaction in both patient groups compared with placebo, but there was no advantage for administration before surgery (Sun et al, 2008 **Level II**). 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 et al, 2007 **Level II**). 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 et al, 2008 **Level II**).

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 & Harris, 2004 **Level IV**; Kramer et al, 2004 **Level IV**).

Coxibs and nsNSAIDs have similar adverse effects on renal function (Curtis et al, 2004 **Level I**). A statistically significant increased risk of renal failure was reported following administration of

[6] This systematic review includes a study or studies that have since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. While reanalysis of the data would be required to confirm the conclusions, in this instance, expert advice suggested that withdrawal of the retracted articles would not influence the results. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) re-examined the data included in this review. While unable to reach a unanimous agreement as to whether exclusion of the retracted papers would have altered any of the conclusions, their disagreement did not concern the statement above to which this reference is attached but referred to specific comments about rofecoxib.

[7] This meta-analysis includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Expert advice suggested that withdrawal of the retracted articles would not influence the conclusions but that reanalysis would be required for this to be confirmed. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) reanalysed the data included in this meta-analysis after excluding that obtained from the retracted publications. They concluded that removal of this information did not significantly alter the results.

coxibs in cardiac surgery patients (NNH 73) (Elia et al, 2005 **Level I**). An analysis of the effects of different coxibs on renal function showed that a COX-2 inhibitor class effect was not evident as rofecoxib was associated with an increased risk of renal dysfunction while celecoxib was not (Zhang et al, 2006 **Level I**).

Platelet function

Platelets produce only COX-1, not COX-2, and as a corollary coxibs do not impair platelet function (Munsterhjelm et al, 2006 **Level II**). The use of rofecoxib reduced surgical blood loss in comparison with diclofenac (Hegi et al, 2004 **Level II**).

Cardiovascular effects

Information relating to the cardiovascular (CV) risks associated with the use of nsNSAIDs and coxibs is derived from long-term treatment data and may not reflect the risk of short-term use in the acute pain setting.

In a comparison of drug groups, there was no difference in the incidence of CV complications with nsNSAIDs compared with coxibs (Moore et al, 2007 **Level I**). However, there may be differences between different drugs in each class, although the evidence is conflicting.

One meta-analysis failed to show any difference in the risk of CV events between celecoxib and placebo or between celecoxib and nsNSAIDs (White WB et al, 2007 **Level I**) but another concluded that the risk was less with celecoxib and valdecoxib compared with nsNSAIDs as a group (Moore et al, 2007 **Level I**). Yet another study reported that coxibs were associated with a moderate increase in the risk of CV events, as were high dose regimens of ibuprofen and diclofenac, but not high doses of naproxen (Kearney et al, 2006 **Level I**). The American Heart Association has identified naproxen as the preferred NSAID for long-term use in patients with or at high risk for cardiovascular disease (Antman et al, 2007).

A large case-controlled study using a general practice database identified 9218 patients over 4 years with a 'first ever' diagnosis of myocardial infarction and compared them with matched controls (Hippisley-Cox & Coupland, 2005 **Level III-3**). Where individual drugs were specified in the results, the risks were significantly increased for patients using rofecoxib, diclofenac and ibuprofen but not those taking celecoxib. Systematic reviews of case-control and cohort studies also found that celecoxib in commonly used doses may not increase the CV risk but confirmed an increased risk with diclofenac and rofecoxib (Hernandez-Diaz et al, 2006 **Level I**; McGettigan & Henry, 2006 **Level I**).

An increase in the incidence of cerebrovascular and CV events in patients given parecoxib, then valdecoxib after coronary artery bypass graft (CABG) surgery has also been reported (Nussmeier et al, 2005 **Level II**). Therefore, their use is contraindicated after this type of surgery. However, short-term use of parecoxib and/or valdecoxib after non-cardiac surgery does not increase the risk of CV adverse events (Schug et al, 2009 **Level I**).

The FDA concluded that 'Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately postoperative from coronary artery bypass surgery)' (FDA, 2005).

It is possible that some nsNSAIDs may inhibit the protective effect of aspirin. Ibuprofen but not diclofenac may abolish the benefits of aspirin (MacDonald & Wei, 2003 **Level III-3**; Hudson et al, 2005 **Level III-3**). The FDA issued a caution about the concomitant use of ibuprofen and immediate-release preparations (not enteric coated) of aspirin saying that 'At least 8 hours should elapse after ibuprofen dosing, before giving aspirin, to avoid significant interference'; insufficient data were available to make any recommendations on the use of enteric coated aspirin (FDA, 2006).

Gastrointestinal

GI complications are less likely with use of coxibs compared with nsNSAIDs; the incidence was lowest with celecoxib and valdecoxib (Moore et al, 2007 **Level I**).

Short-term use of parecoxib as required to treat acute pain results in gastroscopic ulcer rates similar to placebo, even in elderly patients at increased risk, in contrast to increased rates of ulceration with nsNSAIDs in the same setting (Harris et al, 2001 **Level II**; Stoltz et al, 2002 **Level II**; Goldstein et al, 2003 **Level II**).

The best gastroprotective strategy was the combination of a coxib and a PPI (Targownik et al, 2008 **Level III-2**). In high-risk populations, ulcer recurrence can be avoided even in long-term therapy by combining a coxib (celecoxib) with a PPI (Chan et al, 2007 **Level II**).

Aspirin-exacerbated respiratory disease

Investigation of patients with AERD has provided encouraging evidence that coxibs, administered at analgesic doses, do not produce bronchospasm in these patients (Martin-Garcia et al, 2003 **Level II**; West & Fernandez, 2003 **Level I**).

Bone healing

At present, data on the effect of coxibs on bone healing are mainly limited to animal models. There is no good evidence of any clinically significant inhibitory effect of coxibs on bone healing (Gerstenfeld & Einhorn, 2004; Bandolier, 2004).

Key messages

1. Paracetamol is an effective analgesic for acute pain; the incidence of adverse effects comparable to placebo (**S**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs are effective in the treatment of acute postoperative and low back pain, renal colic and primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
3. Coxibs are effective in the treatment of acute postoperative pain (**N**) (**Level I** [Cochrane Review]).
4. With careful patient selection and monitoring, the incidence of nsNSAID-induced perioperative renal impairment is low (**U**) (**Level I** [Cochrane Review]).
5 Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**Q**) (**Level I** [Cochrane Review]).
6. Coxibs do not appear to produce bronchospasm in individuals known to have aspirin-exacerbated respiratory disease (**U**) (**Level I**).
7. In general, aspirin increases bleeding after tonsillectomy (**N**) (**Level I**).
8. Non-selective NSAIDs given in addition to paracetamol improve analgesia compared with paracetamol alone (**U**) (**Level I**).
9. Paracetamol given in addition to PCA opioids reduces opioid consumption but does not result in a decrease in opioid-related side effects (**N**) (**Level I**).
10. Non-selective NSAIDs given in addition to PCA opioids reduce opioid consumption and the incidence of nausea, vomiting and sedation (**N**) (**Level I**).
11. Non-selective NSAIDs and coxibs are effective analgesics of similar efficacy for acute pain (**U**) (**Level I**).
12. Preoperative coxibs reduce postoperative pain and opioid consumption, and increase patient satisfaction (**N**) (**Level I**).

13. Coxibs given in addition to PCA opioids reduce opioid consumption but do not result in a decrease in opioid-related side effects (**N**) (**Level I**).
14. Coxibs and non-selective NSAIDs have similar adverse effects on renal function (**U**) (**Level I**).
15. Non-selective NSAIDs do not significantly increase blood loss after tonsillectomy but do increase the need for reoperation due to bleeding (**N**) (**Level I**).
16. Parecoxib and/or valdecoxib compared with placebo do not increase the risk of cardiovascular adverse events after non-cardiac surgery (**N**) (**Level I**).
17. Coxibs and non-selective NSAIDs are associated with similar rates of adverse cardiovascular effects, in particular myocardial infarction; naproxen may be associated with a lower risk than other non-selective NSAIDs and celecoxib may be associated with a lower risk than other coxibs and non-selective NSAIDs overall (**N**) (**Level I**).
18. Perioperative non-selective NSAIDs increase the risk of severe bleeding after a variety of other operations compared with placebo (**N**) (**Level II**).
19. Coxibs do not impair platelet function; this leads to reduced perioperative blood loss in comparison with non-selective NSAIDs (**S**) (**Level II**).
20. Short-term use of coxibs results in gastric ulceration rates similar to placebo (**U**) (**Level II**).
21. Use of parecoxib followed by valdecoxib after coronary artery bypass surgery increases the incidence of cardiovascular events and is therefore contraindicated (**S**) (**Level II**).

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

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

☑ The risk of adverse renal effects of non-selective NSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents and ACE inhibitors (**U**).

4.3 Adjuvant drugs

4.3.1 Inhalational agents

Nitrous oxide

Nitrous oxide (N_2O) has been used since the inception of anaesthesia for its modest analgesic and sedative properties, with 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 adults, N_2O in oxygen has some analgesic efficacy in labour (Rosen, 2002 **Level I**) and is effective during painful procedures such as bone marrow aspiration (Gudgin et al, 2008 **Level III-3**), venous cannulation (Gerhardt et al, 2001 **Level II**), sigmoidoscopy (Harding & Gibson, 2000 **Level II**) and liver biopsy (Castera et al, 2001 **Level II**), and in relieving acute ischaemic chest pain (O'Leary et al, 1987 **Level II**). In elderly patients (median age 84 years), N_2O provided better analgesia than morphine during bed sore and ulcer care (Paris et al, 2008 **Level II**).

In children, N_2O was effective in reducing pain associated with IV cannulation (Henderson et al, 1990 **Level II**; Hee et al, 2003 **Level III-2**; Ekbom et al, 2005 **Level III-2**), urethral catheterisation (Zier et

al, 2007 **Level III-2**), and laceration repair (Burton et al, 1998 **Level II**; Luhmann et al, 2006 **Level II**). It has been reported to provide analgesia for the pain associated with fracture manipulation in children (Gregory & Sullivan, 1996 **Level III-1**; Evans et al, 1995 **Level III-1**), although its efficacy as an analgesic during very painful procedures may be limited (Babl et al, 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 minutes (Ramsay et al, 2005 **Level II**). The significance of this finding in the clinical setting is unknown.

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 & Morgan, 1998).

Toxicity

N_2O oxidises the cobalt ion of cobalamin (vitamin B12) preventing it from acting as a coenzyme for methionine synthetase (MS); MS also requires 5-methyltetrahydrofolate as a coenzyme (Sanders et al, 2008). MS is required for the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), and therefore the production of rapidly dividing tissues such as bone marrow and GI mucosa, as well as the synthesis of myelin (Sanders et al, 2008).

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 et al, 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 et al, 1982).

Neurotoxicity associated with N_2O use is rare but can be rapid and may be irreversible. Patients deficient in vitamin B12, 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 case reports (Schilling, 1986; Holloway & Alberico, 1990; Flippo & Holder, 1993; Kinsella & Green, 1995; Nestor & Stark, 1996; Rosener & Dichgans, 1996; Sesso et al, 1999; Marie et al, 2000; Waters et al, 2005; Cartner et al, 2007; Wu et al, 2007; Meyers & Judge, 2008; Singer et al, 2008; Somyreddy & Kothari, 2008). Those at risk of vitamin B12 deficiency include some vegetarians (in particular vegans), the newborn of vegetarian mothers, patients with GI pathology, elderly people or patients taking PPIs and H2 blockers, and alcoholics (Schilling, 1986; Rosener & Dichgans, 1996; Nilsson-Ehle, 1998; Schenk et al, 1999; Carmel, 2000; McNeely et al, 2000; Sanders et al, 2008). In individuals who are not vitamin B12 deficient, larger quantities or more prolonged use of N_2O seems to be required before neurotoxicity is seen. Examples have been reported in those abusing the drug (Sanders et al, 2008).

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 B12 deficiency where subacute combined degeneration (SACD) of the spinal cord causes numbness, tingling, paresthesiae, ataxia and spasticity (Weimann, 2003). Involvement of peripheral, autonomic and central nervous systems may also lead to incontinence, diplopia, confusion or impaired cognitive function (Weimann, 2003). In patients with pernicious anaemia, SACD usually responds well to treatment with vitamin B12, although it may take many months and response to treatment may be incomplete (Toh et al, 1997). Patients with SACD related to N_2O exposure may sometimes show improvement after

administration of vitamin B12 +/- methionine (Wu et al, 2007; Meyers & Judge, 2008; Singer et al, 2008) although this is not always the case.

In monkeys exposed continuously to N_2O, SACD is prevented by a diet supplemented with methionine (Scott et al, 1981) and in cultured human fibroblasts, a methionine-rich media diminished the rate of MS activation (Christensen & Ueland, 1993). 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 B12 and folic or folinic acid supplements (Weimann, 2003).

Another consequence of N_2O-induced inactivation of MS 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 et al, 1998 **Level II**; Myles, Chan, Leslie et al, 2008 **Level II**; Nagele et al, 2008 **Level III-3**). Patients who are homozygous for polymorphisms in the gene encoding the enzyme that is an antecedent to MS are at a higher risk of developing abnormal plasma homocysteine concentrations after N_2O anaesthesia (Nagele et al, 2008 **Level III-3**). A subset analysis of data from a large trial of 2050 patients — the ENIGMA trial (Myles et al, 2007) — found a relationship between increased plasma homocysteine levels and all major postoperative complications (Myles, Chan, Leslie et al, 2008 **Level II**) as well as marked impairment of endothelial function (Myles, Chan, Kaye et al, 2008 **Level II**). However, the ENIGMA study looked at patients who were undergoing major surgery that lasted for 2 hours or longer and were given N_2O in a concentration of 70% (compared with a nitrous-free anaesthetic), and not at N_2O used as an analgesic agent in a non-operative setting. The significance of this in respect to N_2O use in this group of patients is unknown.

Methionine given preoperatively to patients undergoing N_2O anaesthesia improved the rate of recovery of MS and prevented the prolonged postoperative rise in plasma homocysteine concentrations (Christensen et al, 1994 **Level IV**). Preoperative administration of oral B vitamins (folate, B6 and B12) also prevent the postoperative increase in homocysteine following N_2O anaesthesia (Badner et al, 2001 **Level II**).

The information about the complications of N_2O comes 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.

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 B12 deficiency;
- screen patients at risk of B12 deficiency by examination of the blood picture and serum B12 concentrations before using N_2O;
- exclude asymptomatic patients with macrocytic anaemia or hypersegmentation of neutrophils until it is established that vitamin B12 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 B12 (both inexpensive and with a good safety profile) and possibly folic or folinic acid to patients repeatedly exposed to N_2O. The 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.

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 drug 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-Penthrane, 2005). Methoxyflurane is also not licensed in the United Kingdom. Although no longer used as an anaesthetic, methoxyflurane has been reintroduced into the health-care market in Australia and New Zealand for use as an analgesic, and is available as a self-administered 'Penthrox®' inhaler, which dispenses 0.2% to 0.4% methoxyflurane (Medical Devices International, 2009).

Methoxyflurane was first described for obstetric analgesia in 1966 (Bodley et al, 1966 **Level IV**) and then used as an analgesic for burns dressings (Packer & Titel, 1969 **Level IV**; Calverley, 1972 **Level IV**; Firn, 1972 **Level IV**; Marshall & Ozorio, 1972 **Level IV**).

There are few studies examining the effectiveness of methoxyflurane as an analgesic for painful procedures. A review of its use as an analgesic in prehospital and emergency care settings found a total of 48 relevant papers although all but one (an abstract only) were observational studies; however, this limited data would suggest that it is effective (Grindlay & Babl, 2009). For example, use of the Penthrox® inhaler in children reduced pain associated with extremity injuries (Babl et al, 2006 **Level IV**) but did not provide adequate analgesia for subsequent fracture manipulation (Babl et al, 2007 **Level IV**). It also provided effective pain relief for adult patients in the prehospital setting (Buntine et al, 2007 **Level IV**). Side effects included hallucinations, vomiting, confusion and dizziness, and sedation/drowsiness was common (26%) in children (Babl et al, 2006 **Level IV**; Buntine et al, 2007 **Level IV**).

Methoxyflurane causes a dose-dependent renal toxicity and, as noted above, renal failure was a key reason behind the withdrawal of the drug from use. Use of an analgesic device delivering higher concentrations of methoxyflurane was reported to have led to two fatalities from renal toxicity (Toomath & Morrison, 1987). 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 & Babl, 2009).

Key messages

1. Nitrous oxide has some analgesic efficacy and is safe during labour (**U**) (**Level I**).
2. Nitrous oxide is an effective analgesic agent in a variety of other acute pain situations (**U**) (**Level II**).
3. Methoxyflurane, in low concentrations, may be an effective analgesia in the hospital and prehospital setting (**N**) (**Level IV**).

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 (**U**).

☑ The information about the complications of nitrous oxide 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 duration of exposure and supplementation with vitamin B12, 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**).

4.3.2 NMDA-receptor antagonists

NMDA receptor/ion channel complexes are sited peripherally and centrally within the nervous system (De Kock & Lavand'homme, 2007). Activation of NMDA receptors via glutamate release from excitatory synapses augments the propagation of nociceptive information and is linked to learning and memory, neural development and neuroplasticity, as well as acute and chronic pain states and opioid-induced tolerance. At the spinal level, NMDA receptor activation results in the development of central sensitisation manifested clinically as hyperalgesia and allodynia (De Kock & Lavand'homme, 2007; Hocking et al, 2007).

The NMDA-receptor antagonists ketamine, dextromethorphan, amantadine, memantine and magnesium have been investigated for the management of acute pain.

Ketamine

In low (sub-anaesthetic) doses, ketamine acts primarily as a non-competitive antagonist of the NMDA receptor, although it also binds to many other sites in the peripheral and central nervous systems (Visser & Schug, 2006; Hocking et al, 2007). The principal effect of ketamine at these doses is as an 'antihyperalgesic', 'antiallodynic' and 'antitolerance' agent and not as a primary analgesic *per se* (Hocking et al, 2007). Consequently, ketamine's main role is as an adjuvant in the treatment of pain associated with central sensitisation such as in severe acute pain, neuropathic pain and 'opioid-resistant' pain. It may also reduce the incidence of chronic postsurgical pain (CPSP) (see Section 9.1) and attenuate opioid-induced tolerance and hyperalgesia (see Section 11.7).

Ketamine may also be useful for the treatment of opioid-resistant or 'breakthrough' cancer pain and, in higher doses or combined with agents such as midazolam, it can provide effective and safe analgesia for painful procedures (see below).

Elia and Tramer (Elia & Tramer, 2005 **Level I**) reviewed a heterogenous group of studies, with varying routes of ketamine administration (parenteral and non-parenteral) and dosing regimens. They found no clinically significant effect on pain scores for up to 48 hours after surgery (although the difference was significant up to 24 hours, pain scores were reduced, on average, by less than 1 cm on a 10 cm VAS). Despite demonstrating a significant (30%) opioid-sparing effect, there was no reduction in opioid-related adverse effects, including PONV.

Bell et al (Bell et al, 2006 **Level I**) also reviewed studies of ketamine given by a variety of routes at a variety of times relative to the surgery, but concentrated their meta-analysis on ketamine infusions used in conjunction with morphine PCA. They also reported opioid-sparing but, in

addition, showed a reduction in the incidence of PONV. Later studies, where continuous ketamine infusions were used for 48 hours after abdominal surgery, have shown similar results. One reported significantly reduced pain scores, PCA morphine consumption, nausea and vomiting, with no ketamine-related adverse effects, compared with placebo (Zakine et al, 2008 **Level II**). The other also reported lower PCA morphine requirements, better pain scores at rest and with movement, as well as less sedation; there were no differences in trail-making test times and errors, dreams or hallucinations (Webb et al, 2007 **Level II**). A 24-hour postoperative infusion of 83 mcg/kg/hr but not 42 mcg/kg/hr in addition to PCA fentanyl after cervical spine surgery was opioid-sparing and improved pain relief (Yamauchi et al, 2008 **Level II**).

While concurrent administration of ketamine reduced PCA opioid requirements and the incidence of nausea and vomiting (Bell et al, 2006 **Level I**), there is conflicting evidence regarding the benefit derived from adding ketamine to the PCA opioid solution. In six studies where ketamine was added to the PCA opioid, results were mixed; pain was reduced in four of these studies and morphine consumption in three (Bell et al, 2006 **Level I**). Three more recent studies showed a lack of benefit after gynaecological (Aubrun et al, 2008 **Level II**) and orthopaedic surgery (Sveticic et al, 2008 **Level II**), or uterine artery embolisation (Jensen et al, 2008 **Level II**). In another, however, the addition of ketamine to morphine PCA reduced pain scores and the incidence of nausea and vomiting, was opioid-sparing, and led to shorter duration of use of PCA compared with PCA morphine alone (Kollender et al, 2008 **Level II**). In a study of post-thoracotomy patients, the addition of ketamine to morphine for PCA was opioid-sparing but failed to improve analgesia; however patients in the ketamine group had better respiratory parameters (Michelet et al, 2007 **Level II**).

Use of a low-dose IV ketamine infusion postoperatively significantly reduced acute pain in patients receiving epidural ropivacaine and morphine analgesia following thoracotomy (Suzuki et al, 2006 **Level II**).

Other outcomes have also been investigated. Parenteral ketamine improved rehabilitation after total knee arthroplasty (Adam et al, 2005 **Level II**). There was no significant difference in postoperative morphine consumption or area of stump allodynia between patients who received either a ketamine or saline infusion for 3 days after leg amputation; interestingly, the incidence of acute stump pain was significantly increased in the ketamine group (Hayes et al, 2004 **Level II**).

Based on these data, the 'routine' use of IV perioperative ketamine is not indicated and the place of ketamine in the treatment of chronic pain and the effects of long-term use remains unclear (Visser & Schug, 2006).

Bolus dose ketamine (0.25 mg/kg) was an effective 'rescue analgesic' in patients with acute postoperative pain that was poorly responsive to morphine (Weinbroum, 2003 **Level II**). In contrast, in a later study, the addition of bolus dose ketamine (0.25 mg/kg) to morphine for rescue analgesia in the recovery room failed to improve analgesia or reduce the incidence of nausea or vomiting (Gillies et al, 2007 **Level II**).

In the emergency department, ketamine used to treat severe trauma pain had a significant morphine-sparing effect without a change in pain scores (Galinski et al, 2007 **Level II**). A low-dose SC ketamine infusion provided better analgesia for acute musculoskeletal trauma pain with less nausea, vomiting and sedation, and improved respiratory function, than intermittent SC morphine injections (Gurnani et al, 1996 **Level II**). Ketamine-midazolam mixtures used for fracture reductions in paediatric patients in the emergency department were associated with less distress and fewer airway interventions than fentanyl-midazolam or propofol-fentanyl combinations (Migita et al, 2006 **Level I**).

Low-dose parenteral ketamine may also improve analgesia in patients with opioid-induced tolerance or hyperalgesia. 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 (Bell, 1999; Eilers et al, 2001; Mitra, 2008). 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 et al, 2008 **Level II**). The evidence for the ability of ketamine to attenuate the acute tolerance and/or OIH seen after intraoperative use of remifentanil infusions is conflicting. Ketamine infusion reduced the area of punctate mechanical hyperalgesia around the wound and postoperative morphine consumption, following high-dose remifentanil infusion during laparotomy (Joly et al, 2005 **Level II**). In paediatric scoliosis surgery, ketamine did not decrease postoperative morphine requirements after remifentanil-based anaesthesia (Engelhardt et al, 2008 **Level II**).

Perioperative ketamine has 'preventive' (Katz & Clarke, 2008 **Level I**), but not 'pre-emptive' (Ong et al, 2005 **Level I**) analgesic effects in the immediate postoperative period. Ketamine reduced the area of wound hyperalgesia and allodynia after nephrectomy (Stubhaug et al, 1997 **Level II**) and laparotomy (De Kock et al, 2001 **Level II**). Perioperative ketamine administration reduced the incidence of CPSP following thoracotomy (Suzuki et al, 2006 **Level II**) and laparotomy (De Kock et al, 2001 **Level II**), possibly reflecting a prolonged 'preventive analgesia' effect. However, there was no significant effect on CPSP following total knee replacement (Adam et al, 2005 **Level II**) or radical prostatectomy (Katz et al, 2004 **Level II**), or on the incidence of phantom or stump pain 6 months after lower limb amputation (Hayes et al, 2004 **Level II**), although this latter study may have been underpowered.

Ketamine showed a significant analgesic effect in patients with neuropathic pain after spinal cord injury (Kvarnstrom et al, 2004 **Level II**).

Adverse effects with short-term systemic administration of ketamine

The addition of low-dose ketamine did not alter the overall incidence of adverse effects compared with opioids alone (Elia & Tramer, 2005 **Level I**). When used in conjunction with PCA morphine, adverse effects were noted to be mild or absent (Bell et al, 2006 **Level I**).

Routes of systemic administration and bioavailability

Ketamine is most commonly administered as a continuous low-dose intravenous infusion, however SC infusion is also used, especially in palliative care, with a bioavailability (similar to IM) of approximately 90% (Clements et al, 1982). Sublingual, intranasal (IN) and transdermal routes have also been used for acute pain management (see Section 6).

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, sublingual 30% and IN 45%: the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara et al, 2003). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both sublingual and oral routes; peak plasma levels were seen at 30 minutes and 120 minutes respectively and terminal half-lives were similar at around 5 hours (Chong et al, 2009). 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.

Dextromethorphan

A review of dextromethorphan for perioperative analgesia concluded that while some studies showed a decrease in opioid consumption and opioid-related side effects, any reduction in pain was not clinically significant and that, 'the consistency of the potential opioid-sparing and pain reducing effect must be questioned' (Duedahl et al, 2006). A meta-analysis was not

performed because of the marked differences in methodology and reporting between trials (Duedahl et al, 2006 2006). However, a systematic review reported that dextromethorphan had 'preventive analgesia' effects (Katz & Clarke, 2008 **Level I**). A later study looking at the effect of four oral doses of dextromethorphan given over 24 hours to patients after abdominal hysterectomy showed better pain relief immediately after surgery but not later at 6 hours and 24 hours (Chau-In et al, 2007 **Level II**).

Magnesium

Systematic reviews of perioperative magnesium, failed to find convincing evidence of improved analgesia (Lysakowski et al, 2007 **Level I**) or any 'preventive analgesic' effects (McCartney et al, 2004 **Level I**). Magnesium added to morphine for PCA was opioid-sparing and led to better pain relief (Unlugenc et al, 2003 **Level II**); added to tramadol it was opioid-sparing but only provided better pain relief for the first 2 hours (Unlugenc et al, 2002 **Level II**).

IV magnesium may be useful in the treatment of migraine, however the studies are contradictory (see Section 9.6.5 for details).

Amantadine and memantine

A bolus dose of IV amantadine had no effect on postoperative analgesia after abdominal hysterectomy (Gottschalk et al, 2001 **Level II**). However perioperative oral amantadine reduced morphine consumption, wound pain on palpation and bladder spasms, after radical prostatectomy (Snijdelaar et al, 2004 **Level II**).

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 months but not 12 months, following traumatic upper limb amputation (Schley et al, 2007 **Level II**). It was not effective in reducing the incidence of postmastectomy pain syndrome (Eisenberg et al, 2007 **Level II**).

Key messages

1. Perioperative low-dose ketamine used in conjunction with patient-controlled analgesia morphine is opioid-sparing and reduces the incidence of nausea and vomiting (**N**) (**Level I** [Cochrane Review]).
2. In general, a perioperative low-dose ketamine infusion is opioid-sparing, but does not produce a clinically significant reduction in pain scores or opioid-related adverse effects (**S**) (**Level I**).
3. Ketamine is a safe and effective analgesic for painful procedures in children (**N**) (**Level I**).
4. Ketamine and dextromethorphan have preventive (**U**) but not pre-emptive analgesic effects (**N**) (**Level I**).
5. Magnesium does not reduce postoperative pain scores or opioid consumption and has no preventive analgesic effect (**N**) (**Level I**).
6. Ketamine may improve analgesia in patients with severe acute pain that is poorly responsive to opioids, although evidence is conflicting (**W**) (**Level II**).
7. Ketamine reduces postoperative pain in opioid-tolerant patients (**N**) (**Level II**).

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

☑ The primary role of low dose ketamine is as an 'antihyperalgesic', 'antiallodynic', 'tolerance-protective' and preventive analgesic, rather than as an analgesic *per se* (**N**).

4.3.3 Antidepressant drugs

There are no published data on the use of antidepressants in the management of acute neuropathic pain, however antidepressants are effective in the treatment of a variety of chronic neuropathic pain states (Collins, Moore, McQuay & Wiffen, 2000 **Level I**; Saarto & Wiffen, 2007 **Level I**; Sultan et al, 2008 **Level I**). When used for the management of pain, the onset of effect is more rapid than when these drugs are used to treat depression.

The updated Cochrane meta-analysis (Saarto & Wiffen, 2007 **Level I**[8]) looking at the use of antidepressant drugs in the treatment of neuropathic pain confirmed the effectiveness of tricyclic antidepressants (TCAs) but that there is very limited evidence for the role of selective serotonin reuptake inhibitor (SSRIs). This analysis also concluded that venlafaxine appears to be as effective as TCAs, but the result is no longer significant as one of the positive venlafaxine studies has subsequently been retracted.

See Table 4.1 for NNTs and NNHs.

Table 4.1 Antidepressants for the treatment of neuropathic pain

Efficacy	NNT (95% CI)
Overall	
TCAs	3.6 (3.0–4.5)
SSRIs	limited evidence of benefit
Duloxetine	5.8 (4.5–8.4)
Diabetic neuropathy	1.3 (1.2–1.5)
Postherpetic neuralgia	2.7 (2.0–4.1)
HIV-related neuropathies	no evidence of benefit
Minor adverse effects	NNH (95% CI)
Pooled diagnoses	
Amitriptyline	6.0 (4.2–10.7)
SSRIs	no dichotomous data available
Major adverse effects (withdrawal from study)	NNH (95% CI)
Pooled diagnoses	
Amitriptyline	28.0 (17.6–68.9)
Duloxetine	15 (11–25)
SSRIs	not different from placebo

Note: CI: confidence interval; TCA: tricyclic antidepressants; SSRI: selective serotonin re-uptake inhibitors.
Source: Adapted from Collins, Moore, McQuay & Wiffen (2000), Saarto & Wiffen (2007), Sultan et al 2008[8]

Currently the use of antidepressants for acute neuropathic pain is mainly based on extrapolation of the above data.

Amitriptyline (Kalso et al, 1996 **Level II**) but not venlafaxine (Tasmuth et al, 2002 **Level II**) was effective in the treatment of neuropathic pain following breast surgery, however the amitriptyline side effects were not well-tolerated. Amitriptyline given to patients with herpes zoster reduced the incidence of postherpetic neuralgia at 6 months (Bowsher, 1997 **Level II**).

[8] This meta-analysis includes a study on venlafaxine that has since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. Independent reanalysis of this meta-analysis using a random effects model (I2 = 51.3%) shows RR 1.87 (95% CI 0.66–5.30). The results for venlafaxine are no longer significant and have been excluded from Table 4.1.

Amitriptyline also provided good control of phantom limb pain and stump pain in amputees (Wilder-Smith et al, 2005 **Level III-1**). There was no significant difference in pain or disability with amitriptyline compared with placebo in spinal cord injury patients with chronic pain (Cardenas et al, 2002 **Level II**), however amitriptyline improved below-level neuropathic pain in patients with depression (Rintala et al, 2007 **Level II**). There are no studies of SSRIs in the treatment of central pain (Sindrup & Jensen, 1999 **Level I**).

Duloxetine is effective for the treatment of both painful diabetic neuropathy and fibromyalgia (Sultan et al, 2008 **Level I**).

There are very limited data on the use of antidepressants in acute nociceptive pain. Desipramine given prior to dental surgery increased and prolonged the analgesic effect of a single dose of morphine but had no analgesic effect in the absence of morphine (Levine et al, 1986 **Level II**). However, when used in experimental pain, desipramine had no effect on pain or hyperalgesia (Wallace et al, 2002 **Level II**). Amitriptyline given prior to dental surgery (Levine et al, 1986 **Level II**) or after orthopaedic surgery (Kerrick et al, 1993 **Level II**) did not improve morphine analgesia.

There is no good evidence that antidepressants given to patients with chronic low back pain improve pain relief (Urquhart et al, 2008 **Level I**).

Note: reversal of conclusions

This reverses the Level 1 conclusion in the previous edition of this document; an earlier meta-analysis had reported improved pain relief.

However, this and the earlier meta-analysis did not differentiate between TCAs and SSRIs, and the former have been shown to be effective compared with the latter (Staiger et al, 2003 **Level I**). There is good evidence for antidepressants in the treatment and prophylaxis of chronic headaches (Tomkins et al, 2001 **Level I**).

Clinical experience in chronic pain suggests that TCAs should be started at low doses (eg amitriptyline 5 to 10 mg at night) and subsequent doses increased slowly if needed, in order to minimise the incidence of adverse effects.

Key messages

1. In neuropathic pain, tricyclic antidepressants are more effective than selective serotonergic re-uptake inhibitors (**S**) (**Level I** [Cochrane Review]).
2. Duloxetine is effective in painful diabetic neuropathy and fibromyalgia (**N**) (**Level I** [Cochrane Review]).
3. There is no good evidence that antidepressants are effective in the treatment of chronic low back pain (**R**) (**Level I** [Cochrane Review]).
4. Tricyclic antidepressants are effective in the treatment of chronic headaches (**U**) and fibromyalgia (**N**) (**Level I**).
5. Antidepressants reduce the incidence of chronic neuropathic pain after herpes zoster (**U**) (**Level II**).

   Note: withdrawal of previous key message:

   Antidepressants reduce the incidence of chronic neuropathic pain after breast surgery

   This has been deleted as the information and evidence supporting it has been withdrawn.

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 selective serotonin re-uptake inhibitors in the management of acute neuropathic pain (**S**).

☑ To minimise adverse effects, particularly in elderly people, it is advisable to initiate treatment with low doses (**U**).

4.3.4 Anticonvulsant drugs

Specific anticonvulsant agents used in the treatment of acute pain

Gabapentinoids (gabapentin/ pregabalin)

A number of meta-analyses have shown that perioperative gabapentinoids improved analgesia (at rest and with movement) and reduced postoperative opioid consumption, but increased the incidence of sedation compared with placebo (Ho et al, 2006 **Level I**; Hurley et al, 2006 **Level I**; Peng et al, 2007 **Level I**; Tiippana et al, 2007 **Level I**). Three of these meta-analyses (Ho et al, 2006 **Level I**; Peng et al, 2007 **Level I**; Tiippana et al, 2007 **Level I**) also reported a decrease in vomiting and pruritus; the NNT was 25 for nausea, 6 for vomiting and 7 for urinary retention (Tiippana et al, 2007 **Level I**). The effects of gabapentin were not dose-dependent in the range of 300 to 1200 mg. (Tiippana et al, 2007 **Level I**). After hysterectomy and spinal surgery specifically, gabapentin improved pain relief and was opioid-sparing, nausea was less in patients after hysterectomy, and there was no difference in sedation (Mathiesen et al, 2007 **Level I**).

Trials analysed in these meta-analyses used a wide variety of gabapentin dosing regimens. It is therefore not possible to recommend a particular regimen and furthermore, conclusions cannot be drawn regarding optimal treatment duration or potential long-term benefits (such as reduced CPSP).

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 et al, 2006 **Level II**).

Gabapentin reduced pain and opioid consumption following acute burns (Cuignet et al, 2007 **Level III-3**) and reduced neuropathic pain descriptors in a small case series of patients with burns injuries (Gray et al, 2008 **Level IV**). Pregabalin reduced the intensity of itch and the Neuropathic Pain Scale descriptor of 'hot pain' (Gray et al, 2008 **Level II**). It was also effective for the treatment of neuropathic pain caused by traumatic or postsurgical nerve injury (Gordh et al, 2008 **Level II**). The incidence and intensity of postamputation pain was not reduced by gabapentin administered in the first 30 days after amputation (Nikolajsen, Finnerup et al, 2006 **Level II**).

Sodium valproate

Sodium valproate did not improve acute nociceptive pain after surgery (Martin et al, 1988 **Level II**) and IV sodium valproate was ineffective in treating acute migraine (Tanen et al, 2003 **Level II**).

Specific anticonvulsant agents used in the treatment of chronic pain

Carbamazepine

A review of carbamazepine for the treatment of chronic neuropathic pain calculated a NNT of 1.8 (CI 1.4 to 2.8) for relief of trigeminal neuralgia; there were insufficient data for a NNT for painful diabetic neuropathy to be calculated. The NNH for a minor adverse effect compared

with placebo was 3.7 (CI 2.4 to 7.8); the NNH for a major adverse event was insignificant (Wiffen, McQuay & Moore, 2005 **Level I**).

Phenytoin

A review of phenytoin for the treatment of chronic neuropathic pain calculated a NNT of 2.1 (CI 1.5 to 3.6) for painful diabetic neuropathy. The NNH for a minor adverse effect compared with placebo was 3.2 (CI 2.1 to 6.3); the NNH for a major adverse event was not significant (Wiffen, Collins et al, 2005 **Level I**).

Gabapentin

A review of gabapentin for the treatment of chronic neuropathic pain calculated a NNT of 4.3 (CI 3.5 to 5.7) overall; the NNTs for painful diabetic neuropathy and postherpetic neuralgia were 2.9 (CI 2.2 to 4.3) and 3.9 (CI 3 to 5.7) respectively (Wiffen, McQuay, Edwards et al, 2005 **Level I**). The NNH for a minor adverse effects compared with a placebo was 3.7 (CI 2.4 to 5.4); the NNH for a major adverse event was not significant. Gabapentin was effective in the treatment of phantom limb pain (Bone et al, 2002 **Level I**) and smaller later trials support the effectiveness of gabapentin in the treatment of central pain after spinal cord injury (Levendoglu et al, 2004 **Level II**; Tai et al, 2002 **Level II**).

Pregabalin

Pregabalin was effective for the management of pain related to diabetic neuropathy (Hurley et al, 2008 **Level I**; Gutierrez-Alvarez et al, 2007 **Level I**) with an NNT of 3.24 (Gutierrez-Alvarez et al, 2007 **Level I**) and an increased risk of sedation and dizziness (Hurley et al, 2008 **Level I**). Pregabalin was effective for persistent neuropathic spinal cord injury pain (Siddall et al, 2006 **Level II**).

Sodium valproate

Sodium valproate was effective for the prevention of migraine (Mulleners & Chronicle, 2008 **Level I**) but ineffective in the treatment of spinal cord injury pain (Drewes et al, 1994 **Level II**).

Lamotrigine

A review of lamotrigine concluded that it was unlikely to be of benefit for the treatment of neuropathic pain (Wiffen & Rees, 2007 **Level I**).

Key messages

1. Gabapentin is effective in the treatment of chronic neuropathic pain (**Q**); lamotrigine is most likely ineffective (**N**) (**Level I** [Cochrane Review]).
2. Carbamazepine is effective in the treatment of trigeminal neuralgia (**N**) (**Level I** [Cochrane Review]).
3. Pregabalin is effective in the treatment of chronic neuropathic pain related to diabetic neuropathy (**N**) (**Level I**).
4. Perioperative gabapentinoids (gabapentin/ pregabalin) reduce postoperative pain and opioid requirements (**U**) and reduce the incidence of vomiting, pruritus and urinary retention, but increase the risk of sedation (**N**) (**Level I**).

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 anticonvulsants in the management of acute neuropathic pain (**U**).

4.3.5 Membrane stabilisers

Perioperative IV lignocaine (lidocaine) infusion was opioid-sparing and significantly reduced pain scores, nausea, vomiting and duration of ileus up to 72 hours after abdominal surgery and also reduced length of hospital stay (Marret et al, 2008 **Level I**). The addition of lignocaine to morphine PCA conferred no benefit in terms of pain relief or side effects (Cepeda et al, 1996 **Level II**).

Intraoperative epidural lignocaine infusion resulted in significantly lower use of patient-controlled epidural analgesia (PCEA) and earlier return of bowel function in the 72 hours following colectomy compared with IV lignocaine; however the latter was still significantly better than placebo (Kuo et al, 2006 **Level II**). Mexiletine improved pain relief and reduced analgesic requirements after breast surgery (Fassoulaki et al, 2002 **Level II**).

IV lignocaine has been used to provide analgesia for burns procedures, however a Cochrane review reported that more trials were required to determine its efficacy (Wasiak & Cleland, 2007 **Level I**).

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 et al, 1990 **Level II**) and in one trial no better than placebo (Reutens et al, 1991 **Level II**). Results for IN lignocaine are conflicting (Maizels et al, 1996 **Level II**; Blanda et al, 2001 **Level II**).

Under experimental conditions, IV lignocaine reduced neuropathic pain in spinal cord injury (Finnerup et al, 2005 **Level II**) and reduced spontaneous pain and brush allodynia in central pain (Attal et al, 2000 **Level II**). Also after spinal cord injury, lignocaine reduced pain in only one of ten patients (Kvarnstrom et al, 2004 **Level II**); mexiletine did not reduce dysesthetic pain (Chiou-Tan et al, 1996 **Level II**).

Both lignocaine and mexiletine were more effective than placebo in treating chronic neuropathic pain, however there was no difference in efficacy or adverse effects when compared with carbamazepine, amantadine, or morphine (Challapalli et al, 2005 **Level I**).There was strong evidence of benefit for use of membrane stabilisers in pain due to peripheral nerve trauma (Kalso et al, 1998 **Level I**). Stump pain but not phantom pain was reduced by IV lignocaine (Wu et al, 2002 **Level II**).

Currently, the use of membrane stabilisers for acute neuropathic pain can only be based on extrapolation of the above data.

Key messages

1. Both lignocaine (lidocaine) and mexiletine are effective in the treatment of chronic neuropathic pain (**S**); there is no difference in efficacy or adverse effects compared with carbamazepine, amantadine, or morphine (**N**) (**Level I** [Cochrane Review]).
2. Perioperative intravenous lignocaine reduces pain and opioid requirements following abdominal surgery (**S**) as well as nausea, vomiting, duration of ileus and length of hospital stay (**N**) (**Level I**).

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 membrane stabilisers in the management of acute neuropathic pain (**U**).

☑ Lignocaine (intravenous or subcutaneous) may be a useful agent to treat acute neuropathic pain (**U**).

4.3.6 Alpha-2 agonists

Systemic administration (oral, IM, IV) of single doses of the alpha-2 agonists clonidine (Bernard et al, 1991 **Level II**; De Kock et al, 1992 **Level II**; Park et al, 1996 **Level II**); and dexmedetomidine (Aho et al, 1991 **Level II**; Jalonen et al, 1997 **Level II**; Arain et al, 2004 **Level II**) decreased perioperative opioid requirements in surgical patients.

The addition of clonidine to morphine for PCA significantly improved postoperative analgesia (for the first 12 hours only) with less nausea and vomiting compared with morphine alone; however there was no reduction in morphine requirements (Jeffs et al, 2002 **Level II**). Higher doses of clonidine resulted in a significant reduction in opioid requirements but a greater degree of sedation and hypotension (Marinangeli et al, 2002 **Level II**).

Intraoperative dexmedetomidine infusion significantly reduced opioid requirements, nausea, vomiting and itch, but not pain or sedation scores compared with placebo, for up to 48 hours after abdominal hysterectomy (Gurbet et al, 2006 **Level II**). A combination of dexmedetomidine and morphine for PCA resulted in significantly better pain relief, a lower incidence of nausea but not vomiting and significant opioid-sparing compared with morphine alone (Lin et al, 2009 **Level II**).

In the intensive care setting, IV dexmedetomidine infusions used for sedation of ventilated patients resulted in a 50% reduction in morphine requirements (Venn et al, 1999 **Level II**).

Key message

1. The use of systemic alpha-2-agonists consistently improves perioperative opioid analgesia but the frequency and severity of side effects may limit their clinical usefulness (**U**) (**Level II**).

4.3.7 Salmon calcitonin and bisphosphonates

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 central nervous system. Salmon calcitonin has a greater potency than mammalian forms of the hormone and is therefore reproduced as a synthetic drug 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 5HT3 antagonist tropisetron reduced its analgesic efficacy, which may be relevant in humans during the treatment of nausea and vomiting (Visser, 2005).

Salmon calcitonin, (IV, SC, IM, IN or rectal) reduces acute pain at rest and on movement and improves mobilisation (in 7 to 28 days) in patients with osteoporotic vertebral fractures and side effects are usually minor and mainly gastrointestinal (Blau & Hoehns, 2003 **Level I**; Knopp et al, 2005 **Level I**).

IV (and likely SC) salmon calcitonin is effective in the treatment of acute phantom limb pain (Jaeger & Maier, 1992 **Level II**). However, it was not effective for chronic phantom limb pain (Eichenberger et al, 2008 **Level II**).

A meta-analysis concluded that salmon calcitonin was beneficial in the treatment of chronic regional pain syndrome (CRPS) (Perez et al, 2001 **Level I**). However, the two placebo-controlled trials of the five in the meta-analysis produced conflicting results. A more recent study found that calcitonin was no more effective than paracetamol in improving pain and function in CRPS over a 2-month period in patients receiving physical therapy following upper limb trauma (Sahin et al, 2006 **Level II**).

The limited evidence available does not support the effectiveness of salmon calcitonin in the treatment of acute and persistent metastatic bone pain (Martinez-Zapata et al, 2006 **Level I**).

Bisphosphonates

IV pamidronate (3 daily doses) reduced pain associated with acute osteoporotic vertebral fractures for up to 30 days post-treatment (Armingeat et al, 2006 **Level II**).

Bisphosphonates reduced sub-acute bone pain associated with metastatic carcinoma of the breast (Pavlakis et al, 2005 **Level I**) or prostate (Yuen et al, 2006 **Level I**) and in multiple myeloma (Djulbegovic et al, 2002 **Level I**).

Key messages

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

4.3.8 Cannabinoids

Cannabinoids are a diverse group of substances derived from natural (plant and animal) and synthetic sources whose effects are mediated via cannabinoid receptors. Although over 60 cannabinoids have been identified in products of the cannabis plants, the most potent psychoactive agent is delta9-tetrahydrocannabinol (delta9-THC) (Hosking & Zajicek, 2008). Potentially useful actions of cannabis include mood elevation, appetite stimulation, an antiemetic effect and antinociception. The clinical use of naturally occurring cannabis is unfortunately limited due to a wide range of side effects, including dysphoria, sedation and impaired psychomotor performance, memory and concentration. Cannabis withdrawal symptoms resemble those of opioid and alcohol withdrawal (Hosking & Zajicek, 2008). There is also concern that chronic exposure can predispose to the development of psychosis in susceptible individuals (Luzi et al, 2008 **Level IV**).

A number of expert committees have examined the scientific evidence assessing the efficacy and safety of cannabinoids in clinical practice (House of Lords, 1998; Joy et al, 1999; NSW Working Party, 2000). Insufficient rigorous scientific evidence was found to support the use of cannabinoids in clinical practice.

In 2001 a qualitative systematic review examined the evidence for cannabinoids as analgesics (Campbell et al, 2001 **Level I**) and found no evidence for clinically relevant effectiveness, but significant side effects.

In acute pain, a number of studies investigated different cannabinoid presentations for postoperative analgesia. No benefit was found with a single dose of oral THC on the second day following hysterectomy in 20 women (Buggy et al, 2003 **Level II**). Unexpectedly, high-dose (2 mg) nabilone in the presence of morphine was associated with increased pain scores in patients who underwent major orthopaedic or gynaecologic surgery (Beaulieu, 2006 **Level II**). A dose escalating study using an oral mixture of THC and cannabidiol (Cannador®) following cessation of PCA after a range of surgical procedures found that the need for rescue analgesia was reduced with increasing dose, but that side effects occurred at the higher dose (Holdcroft

et al, 2006 **Level III-3**). In patients having radical prostatectomy, the addition of daily dronabinol did not alter the analgesic requirement for piritramide (Seeling et al, 2006 **Level II**).

Although the number of clinical trials was small, cannabinoids were mildly effective in the treatment of chronic neuropathic and multiple sclerosis-related pain; the most common adverse effect was dizziness (35% of patients) (Iskedjian et al, 2007 **Level I**).

In patients with a variety of causes for both peripheral and central neuropathic pain, smoking cannabis (low and high dose) was significantly more effective than smoking placebo cigarettes in reducing neuropathic pain; 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 et al, 2008 **Level II**). Smoked cannabis was also more effective than placebo cigarettes in HIV-associated neuropathic pain (Abrams et al, 2007 **Level II**); the rate of responders (30% reduction in pain) in one trial was 46% with cannabis and 18% with placebo (Ellis et al 2009 **Level II**). A cannabidiol/ THC oromucosal spray was more effective than a placebo spray for multiple sclerosis-related neuropathic pain (Rog et al, 2005 **Level II**). Compared with placebo, oromucosal administration of both combined cannabidiol/THC and THC alone were effective for the relief of intractable central neuropathic pain resulting from brachial plexus avulsion (Berman et al, 2004 **Level II**).

It should be noted that all clinical studies to date have design limitations, involve small numbers of patients and only used non-selective highly lipophilic cannabinoid compounds. The possible benefits from more selective agonists have yet to be investigated in the clinical setting.

Key message

1. Current evidence does not support the use of cannabinoids in acute pain management (**S**) but these drugs appear to be mildly effective when used in the treatment of chronic neuropathic pain, including multiple sclerosis-related pain (**N**) (**Level I**).

4.3.9 Glucocorticoids

Surgical tissue trauma leads to the conversion of arachidonic acid to prostaglandins and leukotrienes. NSAIDs inhibit the formation of prostaglandins whereas glucocorticoids also inhibit the production of prostaglandins, leukotrienes and cytokines (Gilron, 2004; Romundstad & Stubhaug, 2007). Several randomised controlled studies have shown that the addition of glucocorticoids reduces postoperative pain and analgesic requirement (see below). Additional benefits include decreased PONV and fatigue (Romundstad et al, 2006; Kehlet, 2007).

However more information is still needed about dose-finding, the effects of repeat dosing, procedure-specific effectiveness and safety (Kehlet, 2007). While good data regarding side effects are still lacking, high doses have been used in elective and emergency surgical patients without an increase in morbidity (Sauerland et al, 2000 **Level I**).

Earlier studies have shown benefit after oral surgery, tonsillectomy, lumbar disc surgery, laparoscopic cholecystectomy, arthroscopic surgery and lung resection (Gilron, 2004; Kehlet, 2007).

Studies looking at the effect of glucocorticoids after surgery include those where comparisons have been made with placebo only and those where comparisons have been made with other analgesics +/- placebo.

Preoperative administration of dexamethasone in patients undergoing total hip arthroplasty led to better dynamic pain relief than placebo, but there were no differences in pain at rest, PCA morphine requirements, wound complications or infection at one month after surgery

(Kardash et al, 2008 **Level II**). Similarly, after ambulatory breast surgery, dexamethasone improved pain relief on movement between 24 and 72 hours postoperatively compared with placebo, but the differences at other time periods were not significant; the power of this study was possibly limited because of the low pain scores in both patient groups — all were also given paracetamol and rofecoxib (Hval et al, 2007 **Level II**). Dexamethasone was no more effective than placebo in reducing back pain after lumbar discectomy, but there was a significant reduction in postoperative radicular leg pain and opioid consumption (Aminmansour et al, 2006 **Level II**). Pain after tonsillectomy was reduced on postoperative day 1 in patients given dexamethasone, although by a score of just 1 out of 10 (Afman et al, 2006 **Level I**); pain relief was also better from day 1 to day 7 (McKean et al, 2006 **Level II**). Compared with lower doses of dexamethasone and placebo, 15 mg IV dexamethasone significantly reduced 24-hour oxycodone requirements after laparoscopic hysterectomy, but there were no differences in pain scores at rest or with movement between any of the study groups (Jokela et al, 2009 **Level II**). While preoperative dexamethasone reduced pain, fatigue, nausea and vomiting in patients undergoing laparoscopic cholecystectomy compared with placebo (Bisgaard et al, 2003 **Level II**), no differences were found in these factors in patients given oral prednisone or placebo (Bisgaard et al, 2008 **Level II**).

After orthopaedic surgery, there was no difference in analgesic effect between methylprednisolone and ketorolac (both were better than placebo); methylprednisolone led to greater opioid-sparing but there was no difference in the incidence of adverse effects (Romundstad et al, 2004 **Level II**). 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 to 72 hour period after surgery (Thagaard et al, 2007 **Level II**). Similarly, after breast augmentation, methylprednisolone and parecoxib provided similar analgesia; however, PONV and fatigue scores were lower in the patients given methylprednisolone (Romundstad et al, 2006).

A combination of gabapentin and dexamethasone provided better pain relief and led to less PONV than either drug given alone after varicocoele surgery; both the combination and the individual drugs were more effective than placebo (Koç et al, 2007 **Level II**). There was no difference in pain scores or PCA morphine requirements during the first 24 hours postoperatively in patients given pregabalin, pregabalin with dexamethasone, or placebo after hysterectomy (Mathiesen et al, 2009 **Level II**).

Glucocorticoids have also been shown to have antihyperalgesic effects in animals and humans (Romundstad & Stubhaug, 2007; Kehlet, 2007). Using 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 et al, 2007 **Level II**). In surgical patients, preoperative administration of methylprednisolone resulted in significantly less hyperesthesia compared with parecoxib and placebo, but there was no reduction in persistent spontaneous or evoked pain (Romundstad et al, 2006 **Level II**).

Key message

1. Dexamethasone, compared with placebo, reduces postoperative pain, nausea and vomiting, and fatigue (**Level II**).

4.3.10 Complementary and alternative medicines

Herbal, traditional Chinese and homeopathic medicines may be described as complementary or alternative medicines (CAMs) because their use lies outside the dominant, 'orthodox' health system of Western industrialised society (Belgrade, 2003). In other cultures these therapies may be mainstream.

CAMs include:

- herbal medicine — substances derived from plant parts such as roots, leaves or flowers;
- traditional Chinese medicine — herbal medicines, animal and mineral substances;
- homeopathy — ultra-diluted substances; and
- others — vitamins, minerals, animal substances, metals and chelation agents.

A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states (WHO, 1996). While the use of CAMs is commonplace, their efficacy in many areas, including in the management of acute pain, has not yet been subject to adequate scientific evaluation and there are limited data.

Preoperative melatonin administration led to reduced PCA morphine requirements and anxiety after surgery (Caumo et al, 2007 **Level II**). Treatment with lavender aromatherapy in the postanaesthesia care unit reduced the opioid requirements of morbidly obese patients after laparoscopic gastric banding (Kim et al, 2007 **Level II**). There is insufficient evidence that aromatherapy is effective for labour pain (Smith et al, 2006 **Level I**).

A review of trials looking at the effectiveness of herbal medicines for acute low back pain (a mix of acute, subacute and chronic pain) found that white willow bark (*Salix alba*), containing salicin, which is metabolised to salicylic acid, provided better analgesia than placebo and was similar to a coxib (rofecoxib) (Gagnier et al, 2006 **Level I**). Devil's claw (*Harpagophytum procumbens*) was also effective and there was moderate evidence that cayenne (*Capsicum frutescens*) may be better than placebo (Gagnier et al, 2006 **Level I**).

In dysmenorrhoea, vitamin B1 (Proctor & Murphy, 2001 **Level I**), vitamin E (Ziaei et al, 2005 **Level II**), Chinese herbal medicine (Zhu et al, 2007 **Level I**), rose tea (Tseng et al, 2005 **Level II**), guava leaf extract (*Psidii guajavae*) (Doubova et al, 2007 **Level II**), aromatherapy (Han et al, 2006 **Level II**) and fennel (*Foeniculum vulgare*) (Namavar Jahromi et al, 2003 **Level III-2**) provided effective analgesia.

Homeopathic arnica provided a statistically significant reduction in acute pain after tonsillectomy (Robertson et al, 2007 **Level II**), however it was ineffective for pain relief after hand surgery (Stevinson et al, 2003 **Level II**) and abdominal hysterectomy (Hart et al, 1997 **Level II**).

Peppermint oil has a NNT of 2.5 for improvement of pain or symptoms in irritable bowel syndrome (Ford et al, 2008 **Level I**).

Adverse effects and interactions with medications have been described with CAMs and must be considered before their use.

Key message

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 (**N**).

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5. REGIONALLY AND LOCALLY ADMINISTERED ANALGESIC DRUGS

5.1 LOCAL ANAESTHETICS

Local anaesthetics exert their effect as analgesics by the blockade of sodium channels and hence impeding neuronal excitation and/or conduction.

5.1.1 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 minutes, the duration of local anaesthetic effect depends very much on the 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 & Wildsmith, 1998).

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). For example, 24-hour continuous perineural infusions of lignocaine resulted in less effective analgesia and more motor block than infusions of the long-acting local anaesthetic agent ropivacaine (Casati, Vinciguerra et al, 2003 **Level II**).

5.1.2 Long-duration local anaesthetics

The three commonly used long-duration local anaesthetic agents, bupivacaine, levobupivacaine and ropivacaine, are structurally related (Markham & Faulds, 1996; McLeod & Burke, 2001; Casati & Putzu, 2005). 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 et al, 1999 **Level II**; Polley et al, 1999 **Level II**). The motor-blocking potency showed a similar ratio of 0.66 (Lacassie et al, 2002 **Level II**).

When comparing bupivacaine with levobupivacaine, the 'percentage' bupivacaine solution is by weight of bupivacaine hydrochloride, whereas % levobupivacaine solution is for the active molecule alone (even though presented as the hydrochloride). This means that the molar dose of equal 'percentage concentration' is 13% higher for levobupivacaine (Schug, 2001). 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 different from unity) (Lyons et al, 1998 **Level II**). Levobupivacaine has been shown to have slightly less motor-blocking capacity than bupivacaine with a levobupivacaine/ bupivacaine potency ratio for epidural motor blockade of 0.87 (95% CI, 0.77-0.98) (Lacassie & Columb, 2003 **Level II**). 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 et al, 2003 **Level II**).

Epidural local anaesthetics

For *postoperative* epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott et al, 1995 **Level II**; Schug et al, 1996 **Level II**). 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 et al, 2000 **Level II**; Macias et al, 2002 **Level II**; Casati, Santorsola et al, 2003 **Level II**). 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 et al, 1996 **Level II**; Muldoon et al, 1998 **Level II**; Merson, 2001 **Level II**). However, this finding has not been supported by other authors.

Ropivacaine 0.2% and levobupivacaine 0.125% provided similar analgesia with similar adverse effects and no motor block when infused via thoracic epidural catheters for lung surgery (De Cosmo et al, 2008 **Level II**). Patient-controlled lumbar epidural analgesia for prostatectomy using ropivacaine 0.2% or levobupivacaine 0.125% resulted in similar pain relief, adverse effects and incidence of motor block (Heid et al, 2007 **Level II**). These two local anaesthetics in these concentrations were also equivalent to 0.125% bupivacaine after hip surgery (Koch et al, 2008 **Level II**). However, epidural ropivacaine 0.165% was inferior to levobupivacaine 0.125% after orthopaedic surgery (Smet et al, 2008 **Level II**). In a comparison between ropivacaine 0.2%, bupivacaine 0.125% and lignocaine 0.5%, the regression of sensory blockade under continuous infusion was least with ropivacaine (Kanai et al, 2007 **Level II**).

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 et al, 2009 **Level II**) as did two concentrations (0.15% and 0.5%) of levobupivacaine in another trial (Dernedde et al, 2008 **Level II**).

Neither infusions of bupivacaine 0.125% nor ropivacaine 0.2% interfered with neurophysiological assessments after scoliosis surgery (Pham Dang et al, 2008 **Level II**).

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory blockade between bupivacaine, levobupivacaine or ropivacaine used for epidural analgesia (Cheng et al, 2002 **Level II**; Casati, Santorsola et al, 2003 **Level II**)

Local anaesthetic/opioid combinations

The quality of pain relief from low-dose epidural infusions of plain local anaesthetic consistently benefits from the addition of adjuvants such as opioids (Crews et al, 1999 **Level II**; Scott et al, 1999 **Level II**; Hubler et al, 2001 **Level II**; Senard et al, 2002 **Level II**) or alpha-2 adrenoceptor agonists (Milligan et al, 2000 **Level II**; Niemi & Breivik, 2002 **Level II**) (see Section 5.3). Potential dose-sparing benefits are more obvious for local anaesthetic side effects (hypotension and motor block) than for opioid-related side effects (Walker et al, 2002 **Level I**).

Comparisons of patient-controlled epidural analgesia (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 et al, 2007 **Level II**). Similarly, there was

no difference in analgesia and no motor blockade 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 et al, 2007 **Level II**). 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 effects (Pitimana-aree et al, 2005 **Level II**).

No studies directly compare fentanyl to morphine when added to local anaesthetic epidural infusions, although a 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 et al, 2005 **Level III-3**).

For information relating to the use of epidural local anaesthetics or opioid/local anaesthetic combinations for *labour* pain see Section 11.1.2.

Peripheral local anaesthetics

A number of studies have compared different local anaesthetics or doses of local anaesthetics used for continuous peripheral nerve blockade (CPNB).

At concentrations of 0.5% or greater, there were no significant differences in onset time and intensity or duration of sensory blockade between bupivacaine, levobupivacaine or ropivacaine in sciatic (Casati et al, 2002 **Level II**), interscalene (Casati, Borghi et al, 2003 **Level II**) or axillary brachial plexus blocks (McGlade et al, 1998 **Level II**). 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 et al, 1998 **Level II**; Casati, Borghi et al, 2003 **Level II**).

A comparison of three concentrations (0.1%, 0.2%, 0.3%) of ropivacaine for continuous femoral nerve blockade following total knee arthroplasty found that infusions of 0.2% and 0.3% ropivacaine had equivalent quality of postoperative analgesia (Brodner et al, 2007 **Level II**). After similar surgery, there was no difference in pain relief or motor block between patient-controlled femoral nerve blockade with 0.125% levobupivacaine and 0.2% ropivacaine (Heid et al, 2008 **Level II**).

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/hr 0.4% (bolus 2 mL) or 8 mL/hr 0.2% (bolus 4 mL). For continuous popliteal nerve blockade, the larger volumes of the dilute local anaesthetic were more likely to cause an insensate limb (Ilfeld et al, 2008 **Level II**); for continuous interscalene nerve block there was no difference between the two solutions (Le et al, 2008 **Level II**), and for continuous infraclavicular nerve block the smaller volumes of the more concentrated local anaesthetic were more likely to cause an insensate limb (Ilfeld et al, 2009 **Level II**).

Another comparison of patient-controlled continuous interscalene blockade using 0.25% levobupivacaine, 0.25% ropivacaine and 0.4% ropivacaine reported less effective pain relief with the lower concentration of ropivacaine (Borghi et al, 2006 **Level II**).

Continuous popliteal sciatic nerve blockade 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 hours with 0.2% levobupivacaine (Casati et al, 2004 **Level II**).

5.1.3 Local anaesthetic toxicity

Direct toxicity

Lignocaine (5%) infused via lumbar subarachnoid microcatheters has been associated with case reports of cauda equina syndrome (Rigler et al, 1991 **Level IV**; Schell et al, 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 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 hours of the procedure and it fully resolves spontaneously within a few days. A meta-analysis was performed of all randomised and pseudo-randomised (Level II and Level III-1) studies comparing the frequency of TNS and neurological complications after spinal anaesthesia with lignocaine to other local anaesthetics; the overall incidence was 14.2% following lignocaine and the relative risk (RR) for developing TNS after spinal anaesthesia with lignocaine compared with other local anaesthetics (bupivacaine, prilocaine, procaine, levobupivacaine, ropivacaine and 2-chloroprocaine) was 7.31 (95% CI 4.16 to 12.86); there was no association with baricity or lignocaine concentration in the individual studies that compared these factors (Zaric et al, 2009 **Level I**).

Systemic toxicity

There are consistent laboratory data showing that the S-enantiomers of the long-acting amide local anaesthetics exhibit less central nervous system (CNS) or cardiac toxicity than the R-enantiomers or the racemic mixtures for doses resulting in equivalent sensory nerve conduction block. It is difficult to define relative toxicities for these agents because it depends on the parameters measured.

There is a lack of scientific data available to determine the safe dose of local anaesthetic. However the upper limit of a safe 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. There are case reports of systemic local anaesthetic toxicity occurring using ultrasound guidance, although a meta-analysis found a significantly decreased risk of vascular puncture using ultrasound (RR 0.16; 95% CI 0.05 to 0.47) (Abrahams et al, 2008 **Level I**).

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 et al, 1989 **Level II**) and 16% higher for levobupivacaine than bupivacaine (Bardsley et al, 1998 **Level II**). 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 & Chang, 2001; Mather et al, 2005). Animal studies confirm that higher systemic doses of ropivacaine and levobupivacaine are required to induce ventricular arrhythmias, circulatory collapse or asystole (Ohmura et al, 2001), with the ranking of toxicity risk being bupivacaine > levobupivacaine > ropivacaine (Groban & Dolinski, 2001).

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 et al, 1989 **Level II**; Knudsen et al, 1997 **Level II**; Bardsley et al, 1998 **Level II**; Mather & Chang, 2001 **Level II**), with bupivacaine being the most toxic and levobupivacaine being less toxic and similar to ropivacaine (Stewart et al, 2003 **Level II**).

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 & Dolinski, 2001).

Case reports of accidental toxic overdose with ropivacaine and bupivacaine suggest that outcomes are more favourable and resuscitation more straightforward (in particular requiring less cardiovascular [CV] support) with ropivacaine (Pham-Dang et al, 2000; Chazalon et al, 2003; Huet et al, 2003; Klein et al, 2003; Soltesz et al, 2003; Khoo & Corbett, 2006; Kimura et al, 2007).

Total plasma levels of local anaesthetic tend to rise during the first 48 hours of postoperative infusion, although free levels remain relatively low (Emanuelsson et al, 1995; Scott et al, 1997). 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.

There is basic scientific evidence and several case reports to support the use of IV lipid emulsion therapy for systemic local anaesthetic toxicity resulting in CV collapse (Felice & Schumann, 2008 **Level IV**). Animal experimental data (Weinberg et al, 2003; Weinberg et al, 1998) have been supported by a few case reports of successful resuscitation following bupivacaine (Rosenblatt et al, 2006), ropivacaine (Litz et al, 2006), levobupivacaine (Foxall et al, 2007), mepivacaine/prilocaine (Litz et al, 2008) and mepivacaine/bupivacaine (Warren et al, 2008) toxicity. The mechanism of action of the lipid emulsion may be due to partitioning of local anaesthetic within the emulsion itself (Weinberg, 2006) or mitochondrial substrate enhancement in the myocardium (Weinberg et al, 2000). Uncertainties relating to dosage, efficacy and side effects still remain and therefore it is recommended that lipid emulsion only be administered after advanced cardiac life support has commenced, including adrenaline administration, and convulsions controlled (Corman & Skledar, 2007 **Level IV**). Guidelines have been established to facilitate management of local anaesthetic toxicity, which now include reference to lipid emulsion therapy (AAGBI, 2007). 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 et al, 2009).

Key messages

1. Lignocaine is more likely to cause transient neurologic symptoms than bupivacaine, prilocaine and procaine (**N**) (**Level I** [Cochrane Review]).
2. The quality of epidural analgesia with local anaesthetics is improved with the addition of opioids (**U**) (**Level 1**).
3. Ultrasound guidance reduces the risk of vascular puncture during the performance of regional blockade (**N**) (**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 when given in low doses for regional analgesia (epidural and peripheral nerve blockade) in terms of quality of analgesia or motor blockade (**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. Lipid emulsion is effective in resuscitation of circulatory collapse due to local anaesthetic toxicity, however uncertainties relating to dosage, efficacy and side effects still remain and therefore it is appropriate to administer lipid emulsion once advanced cardiac life support has begun and convulsions are controlled (**N**) (**Level IV**).

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

☑ Case reports following accidental overdose with ropivacaine and bupivacaine suggest that resuscitation is likely to be more successful with ropivacaine (**U**).

5.2 Opioids

5.2.1 Neuraxial opioids

Opioid receptors were described in the spinal cord of the rat in 1976 (Pert et al, 1976) and the same year a potent analgesic effect of directly applied intrathecal morphine was reported in these animals (Yaksh & Rudy, 1976). Opioid analgesia is spinally mediated via presynaptic and postsynaptic receptors in the substantia gelatinosa in the dorsal horn (Yaksh, 1981). Spinal opioid receptors are 70% mu, 24% delta and 6% kappa (Treman & Bonica, 2001), with 70% of all mu and delta receptors being presynaptic (predominantly small primary afferents) and commonly co-located, and kappa receptors being more commonly postsynaptic. 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), which may contribute to the clinical effect when administered intrathecally (Jaffe & Rowe, 1996). The first clinical use of intrathecal morphine was for analgesia in cancer patients (Wang et al, 1979).

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 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 et al, 1999 **Level I**; Cole et al, 2000 **Level I**). Late onset respiratory depression, which is believed to be a result of the cephalad spread of opioids within the cerebrospinal fluid, is also seen more commonly with hydrophilic opioids such as morphine (Cousins & Mather, 1984).

Intrathecal opioids

The lipid solubility of opioids largely determines the speed of onset and duration of intrathecal analgesia; hydrophilic drugs (eg morphine) have a slower onset of action and longer half-lives in cerebrospinal fluid with greater dorsal horn bioavailability and greater cephalad migration compared with lipophilic opioids (eg fentanyl) (Bernards et al, 2003).

Safety studies and widespread clinical experience with morphine, fentanyl and sufentanil have shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (Hodgson et al, 1999 **Level IV**). Other opioid agonists or partial agonists do not have animal or human safety data.

Early clinical studies used very high intrathecal morphine doses (ie 500 mcg or more), 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 side effects or pain relief (Meylan et al, 2009 **Level I**). A meta-analysis comparing intrathecal morphine doses of less than 300 mcg, equal to or greater than 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 & Tryba, 2009 **Level I**).

Following hip and knee arthroplasty, intrathecal morphine (100 to 300 mcg) provided excellent analgesia for 24 hours after surgery with no difference in side effects; after hip arthroplasty only there was a significant reduction in postoperative patient-controlled (PCA) morphine requirements (Rathmell et al, 2003 **Level II**). Following knee arthroplasty, intrathecal morphine 500 mcg compared with 200 mcg reduced supplemental rescue analgesia (tramadol) over 24 hours with no difference in adverse event rates (Bowrey et al, 2005 **Level II**), and 200 mcg was as effective as 300 mcg with no difference in side effects; both were superior to 100 mcg (Hassett et al, 2008 **Level II**). After hip arthroplasty, 100 mcg and 200 mcg doses of intrathecal morphine produced good and comparable pain relief and reductions in postoperative morphine requirements; 50 mcg was ineffective (Murphy et al, 2003 **Level II**).

When combined with low-dose bupivacaine for Caesarean section, 100 mcg intrathecal morphine produced analgesia comparable with doses as high as 400 mcg, with significantly less pruritus (Girgin et al, 2008 **Level II**). A single dose of morphine (100 mcg) added to a spinal anaesthetic for Caesarean section prolonged the time to first postoperative analgesic administration resulting in at least 11 hours of effective analgesia. Adverse effects included pruritus (43%), nausea (10%) and vomiting (12%). The rate of respiratory depression was low (see below). In these patients, sufentanil and fentanyl showed no analgesic benefits (Dahl et al, 1999 **Level I**).

The addition of 10 mcg sufentanil to 0.4 mg intrathecal morphine did not potentiate postoperative analgesia or reduce intraoperative opioid requirements in patients undergoing major colorectal surgery (Culebras et al, 2007 **Level II**). The addition of intrathecal 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 et al, 2008 **Level II**).

In a more recent study, intrathecal sufentanil provided shorter postoperative analgesia (mean 6.3 hours) than intrathecal morphine (mean 19.5 hours) with no difference in side effects (Karaman et al, 2006 **Level II**). In another comparison of intrathecal morphine (100 mcg) and intrathecal pethidine (10 mg) for analgesia following Caesarean section in a non-blinded study, patients receiving morphine had longer analgesia and fewer intraoperative side effects than the pethidine group, but experienced more pruritus (Kumar et al, 2007 **Level II**).

For more information on effectiveness and side effects related to the use of intrathecal opioids see Section 7.3.

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 re-release back into the epidural space means that elimination from the epidural space is prolonged, resulting in relatively smaller fractions of drug reaching the cerebrospinal fluid (Bernards et al, 2003). Lipophilic opioids (eg fentanyl) have a faster onset but shorter duration of action compared with hydrophilic drugs (eg morphine) (de Leon-Casasola & Lema, 1996; Bernards, 2004).

Morphine is the least lipid soluble of the opioids administered epidurally; it has the slowest onset and offset of action (Cousins & Mather, 1984) and the highest bioavailability in the spinal cord after epidural administration (Bernards, 2004). As it 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 & Lema, 1996).

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 et al, 2001; Bernards, 2004). However, the conflicting results may be due to differing modes of administration. An infusion of epidural 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 et al, 2003 **Level IV**). There is no evidence of benefit of epidural versus systemic administration of alfentanil or sufentanil (Bernards, 2004)

Pethidine is effective when administered epidurally by bolus dose, continuous infusion and by 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 the 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 section epidural pethidine resulted in better pain relief and less sedation than IV pethidine (Paech et al, 1994 **Level II**) but inferior analgesia compared with intrathecal morphine, albeit with less pruritus, nausea and drowsiness (Paech et al, 2000 **Level II**).

Diamorphine (diacetylmorphine, heroin) is rapidly hydrolysed to (monoacetylmorphine) 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 & Lackband, 2001). Epidural administration of diamorphine is common in the United Kingdom and is effective whether administered by intermittent bolus dose or infusion (McLeod et al, 2005).

The quality of epidural analgesia with hydromorphone is similar to morphine (Chaplan et al, 1992 **Level II**). In a comparison of epidural and IV hydromorphone, patients required twice as much IV hydromorphone to obtain the same degree of analgesia (Liu et al, 1995 **Level II**).

The addition of butorphanol to epidural bupivacaine resulted in more rapid and prolonged pain relief compared with butorphanol alone (Bharti & Chari, 2009 **Level II**).

An extended-release suspension of morphine has been developed for epidural use (Depodur™) consisting of morphine molecules suspended in liposome complexes (lipofoam). Extended-release epidural morphine (EREM) has been shown to be effective compared with placebo after hip arthroplasty (Viscusi et al, 2005 **Level II**; Martin et al, 2006 **Level II**) and, using doses of 10 mg or more, 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 hours after hip arthroplasty (Viscusi et al, 2006 **Level III-1**), lower abdominal surgery (Gambling et al, 2005 **Level II**) and Caesarean section (Carvalho et al, 2005 **Level II**; Carvalho et al, 2007 **Level II**).

Respiratory depression has been reported to occur in up to 5.4% of patients depending on the definition used (Carvalho et al, 2005 **Level II**; Gambling et al, 2005 **Level II**; Viscusi et al, 2005 **Level II**; Martin et al, 2006 **Level II**) and it may require prolonged treatment; in one patient naloxone was required for 62 hours (Martin et al, 2006 **Level II**).

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 et al, 2009 **Level II**). When Depodur® was administered within 3 to 15 minutes of a 3 mL test dose of 1.5% lignocaine with adrenaline, higher C_{max} values for morphine were indeed reported compared with C_{max} values when no lignocaine was administered; there was no difference in morphine C_{max} if the interval was greater than 30 minutes (Viscusi et al, 2009 **Level II**). The C_{max} of morphine was unchanged when Depodur® doses were given 15, 30 and 60 minutes after an anaesthetic dose of epidural bupivacaine – 20 ml of 0.25% (Gambling et al, 2009 **Level II**).

5.2.2 Peripheral opioids

Opioid receptors on sensory unmyelinated C nerve fibres mediate peripheral antinociceptive effects in animal studies (Stein et al, 1990). 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 (Schafer, 1999; Smith, 2008; Stein, 1995). An experimental model of inflammatory hyperalgesia caused by ultraviolet light showed that analgesia mediated via peripheral opioid mechanisms could also occur in humans (Koppert et al, 1999 **Level II**). In joint studies, the increase in opioid receptors and their endogenous peptides correlated with the degree of inflammation, being more abundant in rheumatoid arthritis than in osteoarthritis and joint trauma (Mousa et al, 2007), consistent with the clinical observation that peripheral opioids are more effective in the presence of inflammation. 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 et al, 2003 **Level II**) (see also Section 7.5).

In clinical practice, morphine injected as a single dose into the knee intra-articular space produced analgesia that lasted up to 24 hours, but evidence for a peripheral rather than a systemic effect was not conclusive (Gupta et al, 2001 **Level I**; Kalso et al, 2002 **Level I**).

Confounding variables that hinder analysis included the pre-existing degree of inflammation, type of surgery, the baseline pain severity and the overall relatively weak clinical effect (Gupta et al, 2001 **Level I**). When published trials were analysed 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**).

Note: reversal of conclusions

This reverses the Level 1 conclusion in the previous edition of this document; the earlier meta-analyses performed without taking confounding factors into consideration had reported improved pain relief with intra-articular morphine.

The addition of intra-articular sufentanil to a mixture of ropivacaine and clonidine following anterior cruciate ligament repair provided no additional analgesic benefits (Armellin et al, 2008 **Level II**). A mixture of intra-articular bupivacaine and 100 mg tramadol resulted in better pain relief and lower rescue analgesic requirements than use of either drug alone (Zeidan et al, 2008 **Level II**).

There is no evidence for analgesic efficacy of peripheral opioids at non-intra-articular sites, including use with perineural blockade (Picard et al, 1997 **Level I**). 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 et al, 2008 **Level II**), partial thickness burns (morphine) (Welling, 2007 **Level II**), or chronic skin ulceration (morphine) (Vernassiere et al, 2005 **Level II**).

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 et al, 2003 **Level II**). Benefit was also evident in a small comparison of morphine mouthwash 30 mg 3-hourly, with a local anaesthetic-based solution, in mucositis associated with chemoradiotherapy in head and neck cancer patients (Cerchietti et al, 2002 **Level II**).

Key messages

1. Intrathecal morphine produces better postoperative analgesia than intrathecal fentanyl after Caesarean section (**U**) (**Level I**).
2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
3. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo when administered after surgery (**R**) (**Level I**).
4. Evidence for a clinically relevant peripheral opioid effect at non-articular sites, including perineural, is inconclusive (**U**) (**Level I**).
5. Epidural pethidine produces better pain relief and less sedation than IV pethidine after Caesarean section (**U**) (**Level II**).
6. Extended release epidural morphine provides analgesia for up to 48 hours, however central depressant effects, including respiratory depression, may also be increased and prolonged (**N**) (**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**).

5.3 Adjuvant Drugs

5.3.1 Alpha-2 agonists

Neuraxial

Clonidine is an alpha-2 adrenoceptor agonist that acts as an analgesic at the level of the spinal cord. There is no human or animal evidence of neurotoxicity when preservative-free clonidine is administered intrathecally (Hodgson et al, 1999). Epidural clonidine is approved by the United States Food and Drug Administration (FDA) for relief of chronic cancer pain.

Intrathecal clonidine given in doses from 15 to 150 mcg combined with intrathecal local anaesthetic, significantly prolonged the time to two segment block regression but did not affect the rate of onset of a complete block (Elia et al, 2008 **Level I**). Intrathecal clonidine also prolonged the time to first analgesic request (median 101 min, range 35 to 310 min) and duration of motor block but in a non-dose-dependent manner; intraoperative pain was reduced but hypotension was more frequent (RR 1.8; 95% CI 1.4 to 2.3) (Elia et al, 2008 **Level I**). Others have reported that the addition of either clonidine or dexmedetomidine to intrathecal bupivacaine increased the speed of onset and duration of motor and sensory block without additional side effects (Kanazi et al, 2006 **Level II**).

Intrathecal clonidine 100 mcg added to 500 mcg intrathecal morphine resulted in better pain relief and faster time to extubation after cardiac surgery compared with intrathecal morphine alone (Nader et al, 2009 **Level II**). In patients undergoing radical prostatectomy, the addition of clonidine to intrathecal morphine prolonged analgesia compared with intrathecal morphine alone and PCA morphine; intrathecal morphine alone was better than PCA (Andrieu et al, 2009 **Level II**).

A review by Roelants of multiple randomised controlled trials (RCTs) concluded that small doses of intrathecal clonidine (30 mcg) combined with local anaesthetics and opioids prolonged labour analgesia; hypotension may occur and was more common with higher doses of clonidine (Roelants, 2006 **Level II**). Intrathecal clonidine combined with bupivacaine had a postoperative antihyperalgesic effect at 48 hours after elective Caesarean delivery compared with intrathecal bupivacaine-sufentanil and intrathecal clonidine 75 mcg-bupivacaine-sufentanil, however no reduction in pain scores or opioid requirements was observed (Lavand'homme et al, 2008 **Level II**). In another study, the combination of subarachnoid bupivacaine, fentanyl, morphine and clonidine significantly prolonged pain relief following Caesarean section, but with increased sedation (Paech et al, 2004 **Level II**).

The addition of clonidine to PCEA with ropivacaine and morphine after total knee arthroplasty decreased opioid requirements and improved analgesia without increasing side effects (Huang et al, 2007 **Level II**). The addition of clonidine to epidural levobupivacaine, also after hip arthroplasty, significantly reduced postoperative morphine requirements compared with either drug alone (Milligan et al, 2000 **Level II**). 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 & Wilson-MacDonald, 2009 **Level II**).

In children, addition of clonidine to bupivacaine caudal injection increased the duration (Ansermino et al, 2003 **Level I**) and quality of analgesia without an increase in side effects (Yildiz et al, 2006 **Level II**) (see also Section 10.7.2).

Plexus block

There is evidence of analgesic benefit with the addition of clonidine to local anaesthetics for brachial plexus blocks (Murphy et al, 2000 **Level I**) but many of the studies have methodological limitations.

Clonidine improved duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for axillary and peribulbar blocks; side effects appeared to be limited at doses up to 150 mcg (McCartney et al, 2007 **Level I**[9]). The addition of clonidine to local anaesthetic solutions used for single-shot peripheral nerve or plexus blocks also prolonged duration of analgesia and motor block (Popping et al, 2009 **Level I**). The effects of the addition of clonidine to lignocaine were similar to those of adding adrenaline in cervical plexus blockade in terms of block onset and duration, although lignocaine absorption was faster when clonidine was used (Molnar et al, 1997 **Level II**). Addition of clonidine to a popliteal fossa nerve block with bupivacaine did not result in any difference in pain relief but did prolong the analgesic effects (YaDeau et al, 2008 **Level II**). There was no difference in pain relief when clonidine was added to a continuous femoral nerve infusion with ropivacaine (Casati et al, 2005 **Level II**).

The use of clonidine with local anaesthetic or opioid also extended analgesia with thoracic paravertebral blocks (Bhatnagar et al, 2006 **Level II**; Burlacu et al, 2006 **Level II**).

Evidence is lacking for the use of clonidine as an adjunct to local anaesthetics for continuous catheter techniques (McCartney et al, 2007 **Level I**[9]).

Intravenous regional anaesthesia

Addition of dexmedetomidine to lignocaine IV regional anaesthesia (IVRA) increased duration and quality of analgesia (Memis et al, 2004 **Level II**). Clonidine was effective in delaying tourniquet pain with IVRA in volunteers (Lurie et al, 2000 **Level III-2**).

Intra-articular

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 & Plaza, 2004 **Level II**; Alagol et al, 2005 **Level II**).

Intra-articular dexmedetomidine resulted in a longer duration of pain relief compared with IV dexmedetomidine (Al-Metwalli et al, 2008 **Level II**).

5.3.2 Adrenaline

Neuraxial

In postoperative thoracic epidural infusions, the addition of adrenaline (epinephrine) to fentanyl and ropivacaine or bupivacaine improved analgesia (Sakaguchi et al, 2000 **Level II**; Niemi & Breivik, 2002 **Level II**; Niemi & Breivik, 2003 **Level II**). This was not demonstrated with lumbar epidural infusions (Forster et al, 2003 **Level II**). The efficacy of thoracic epidural pethidine infusions after thoracotomy was not improved by addition of adrenaline (Bryson et al, 2007 **Level II**).

The addition of adrenaline (0.2 mg) to intrathecal bupivacaine prolonged motor block and some sensory block modalities (Moore JM et al, 1998 **Level II**).

[9] This systematic review includes a study or studies that have since been withdrawn from publication. Please refer to the Introduction at the beginning of this document for comments regarding the management of retracted articles. Marret et al (Marret et al, *Anesthesiology* 2009; 111:1279–89) re-examined the data included in this review and concluded that exclusion of data obtained from the retracted publications did not significantly alter the results.

5.3.3 Ketamine

Neuraxial

Some commercially available preparations of ketamine contain an untested preservative (benzethonium chloride) and a low pH (pH 3.5 to 5.5) and so cannot be recommended for intrathecal use in humans (Hodgson et al, 1999).

The addition of intrathecal ketamine to bupivacaine did not prolong postoperative analgesia or reduce analgesic requirements, but did lead to significantly more nausea and vomiting, sedation, dizziness, nystagmus and 'strange feelings' (Kathirvel et al, 2000 **Level II**).

Early postoperative analgesia was improved by the use of epidural racemic ketamine with bupivacaine for lower limb amputations, although pain at 1 year was not different; perioperative opioids were not used (Wilson et al, 2008 **Level II**). The combination of ketamine with opioid-based (+/- local anaesthetic) solutions for epidural analgesia improved pain relief (Subramaniam et al, 2004 **Level I**) and may reduce overall opioid requirements (Walker et al, 2002 **Level I**) without increasing the incidence of adverse effects (Walker et al, 2002 **Level I**; Subramaniam et al, 2004 **Level I**).

A combination of bupivacaine, ketamine and midazolam administered intrathecally prolonged the analgesic time following lower limb surgery compared with bupivacaine alone or bupivacaine with ketamine; however the authors cautioned that the safety of such combinations has not yet been established (Murali Krishna et al, 2008 **Level II**).

Use of intrathecal S(+) ketamine with bupivacaine for Caesarean section decreased time to onset and increased spread of the block, but did not prolong the duration compared with fentanyl (Unlugenc et al, 2006 **Level II**).

Caudal epidural ketamine 0.25 to 0.5 mg/kg in children, in combination with local anaesthetic prolonged analgesia with few side effects (Ansermino et al, 2003 **Level I**; Tsui & Berde, 2005) (see also Section 10.7.2).

Peripheral sites

Most studies on the use of ketamine alone or with local anaesthesia, show no analgesic benefit for peripheral neural blockade, such as brachial plexus block for arm surgery, (Lee et al, 2002 **Level II**), intra-articular injection (Rosseland et al, 2003 **Level II**) or wound infiltration such as following Caesarean section (Zohar et al, 2002 **Level II**) or inguinal hernia repair (Clerc et al, 2005 **Level II**), although pain scores were lower with preincisional ketamine versus saline in circumcision (Tan et al, 2007 **Level II**). Adding ketamine to lignocaine IVRA did not result in better pain relief compared with ketamine given intravenously (Viscomi et al, 2009 **Level II**).

Topical

Topical administration of ketamine might result in effective systemic plasma concentrations making it difficult to interpret any local effects (Poyhia & Vainio, 2006). A transdermal ketamine patch (delivering 25 mg over 24 hours) reduced analgesic consumption after gynaecological surgery (Azevedo et al, 2000 **Level II**) but analgesic effects from topical ketamine (3 mL 0.3%) applied to the tonsillar fossa after tonsillectomy, although superior to placebo, added no benefit to topical morphine (Canbay et al, 2008 **Level II**).

Topical ketamine as a mouthwash has been reported to be effective in reducing pain and opioid consumption from oral mucositis at rest and with eating (Slatkin & Rhiner, 2003).

5.3.4 Midazolam

Midazolam, 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 issues remain unclear.

Reports of intrathecal midazolam administration have appeared in the literature for many years, despite concerns regarding potential neurotoxicity (Yaksh & Allen, 2004). Early clinical series (Tucker, Lai et al, 2004 **Level III-2**; Tucker, Mezzatesta et al, 2004 **Level III-2**) and laboratory investigations (Johansen et al, 2004) suggested a low risk of toxicity — neurotoxic damage was not seen in sheep and pigs given continuous intrathecal midazolam (Johansen et al, 2004) and a 1-month questionnaire follow-up of patients who had received intrathecal midazolam failed to show any evidence of neurological or urological complications (Tucker, Lai et al, 2004 **Level III-2**).

A meta-analysis of intrathecal midazolam in perioperative and peripartum patients showed the addition of intrathecal midazolam (typically 2 mg or more) to other spinal medications reduced the incidence of nausea and vomiting and delayed the time to request for rescue analgesia, but had little effect beyond 12 hours (Ho & Ismail, 2008 **Level I**). The incidence of neurological symptoms after intrathecal midazolam was uncommon (1.8%) and did not differ from placebo (Ho & Ismail, 2008 **Level I**).There are insufficient data to exclude the possibility of long-term neurological complications from intrathecal midazolam, although none have yet been reported.

Another study reported that the addition of subarachnoid midazolam for labour pain produced no effect on its own, but potentiated the analgesic effect of intrathecal fentanyl (Tucker, Mezzatesta et al, 2004 **Level II**). Combining intrathecal midazolam (2 mg) with bupivacaine for Caesarean section significantly prolonged the block and reduced nausea without CV or neurological side effects (Prakash et al, 2006 **Level II**).

Midazolam added to bupivacaine for epidural infusion improved analgesia but increased sedation (Nishiyama et al, 2002 **Level II**). In patients having a gastrectomy, single dose preoperative epidural midazolam combined with ketamine improved analgesia and prolonged the time to rescue analgesia compared with epidural ketamine or placebo, with no significant adverse effects (Wang et al, 2006 **Level II**).

Midazolam has been added to caudal epidural analgesia in paediatric surgery; age-related toxicity issues have not been addressed. In combination with bupivacaine it prolonged postoperative analgesia (Kumar et al, 2005 **Level II**; Ansermino et al, 2003 **Level I**).

5.3.5 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 et al, 1999).

Intrathecal neostigmine for perioperative and peripartum analgesia resulted in a slight improvement in pain scores and reduced the need for rescue medication; however, it increased nausea and vomiting (OR 5), bradycardia requiring atropine (OR 2.7) and anxiety, agitation and restlessness (OR 10.3) (Ho et al, 2005 **Level I**). The authors concluded that the significant side effects outweighed any clinical benefit.

Epidural neostigmine combined with an opioid reduced the dose of epidural opioid that is required for analgesia but there may not be any decrease in opioid-related side effects compared with the opioid alone (Walker et al, 2002 **Level I**). Epidural neostigmine in the obstetric population improved postoperative analgesia in most studies without increasing the incidence of adverse events (Habib & Gan, 2006 **Level I**). Epidural neostigmine combined with

sufentanil or clonidine, as initial labour analgesia, was without side effects and allowed a 'mobile epidural'; at the doses studied it produced modest analgesia following Caesarean section (Roelants, 2006 **Level II**). The addition of epidural clonidine to bupivacaine reduced hourly patient-controlled epidural bupivacaine requirements during labour (Ross et al, 2009 **Level I**).

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 & Gan, 2006 **Level I**).

Studies investigating the efficacy of adding neostigmine to the local anaesthetics used for brachial plexus block and intravenous regional anaesthesia reported conflicting results indicating the need for further studies (Habib & Gan, 2006 **Level I**).

5.3.6 Magnesium

The long-term effects of perineural or neuraxial magnesium have not been clarified.

In patients undergoing orthopaedic surgery, supplementation of spinal anaesthesia with combined intrathecal and epidural magnesium sulphate significantly reduced patients' postoperative morphine requirements (Arcioni et al, 2007 **Level II**). Addition of magnesium sulphate to lignocaine IVRA improved intra- and postoperative analgesia and tolerance of the tourniquet (Turan et al, 2005 **Level II**; Kashefi et al, 2008 **Level II**). While the addition of magnesium to intrathecal bupivacaine prolonged the times for block regression and first request for analgesia after knee arthroscopy, time to ambulation was longer in the magnesium group (Dayioglu et al, 2009 **Level II**).

Intra-articular magnesium combined with bupivacaine resulted in better pain relief than either drug given alone or placebo (Elsharnouby et al, 2008 **Level II**).

5.3.7 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.

In treating pain and related muscle spasm in multiple sclerosis, data on the use of botulinum toxin are conflicting and of low quality (Shakespeare et al, 2003). Similarly, the current evidence does not support the use of botulinum toxin injection in trigger points for myofascial pain (Ho & Tan, 2007 **Level I**). In subacute and chronic neck disorders IM botulinum toxin injections have similar effects to saline in improving pain (pooled mean difference: -0.39; CI -1.25 to 0.47) (Peloso et al, 2007 **Level I**); although there is benefit in cervical dystonia (Simpson et al, 2008 **Level I**).

Key messages

1. Intrathecal clonidine improves duration of analgesia and anaesthesia when used as an adjunct to intrathecal local anaesthetics (**N**) (**Level I**).
2. Clonidine improves duration of analgesia and anaesthesia when used as an adjunct to local anaesthetics for peribulbar, peripheral nerve and plexus blocks (**N**) (**Level I**).
3. Intrathecal neostigmine marginally improves perioperative and peripartum analgesia in combination with other spinal medications but is associated with significant side effects (**S**) (**Level I**).

4. Epidural neostigmine combined with an opioid reduces the dose of epidural opioid that is required for analgesia (**U**) (**Level I**).
5. Epidural ketamine (without preservative) added to opioid-based epidural analgesia regimens improves pain relief without reducing side effects (**U**) (**Level I**).
6. Intrathecal midazolam combined with a local anaesthetic prolongs the time to first analgesia and reduces postoperative nausea and vomiting (**N**) (**Level I**).
7. Following Caesarean section, intrathecal morphine provides improved analgesia compared with placebo (**N**) (**Level I**) and more prolonged analgesia compared with more lipophilic opioids (**N**) (**Level II**).
8. Intrathecal clonidine added to intrathecal morphine improves and prolongs analgesia (**N**) (**Level II**).
9. Epidural clonidine reduces postoperative systemic opioid requirements (**N**) (**Level II**).
10. Epidural adrenaline (epinephrine) in combination with a local anaesthetic improves the quality of postoperative thoracic epidural analgesia (**U**) (**Level II**).
11. In obstetrics, epidural neostigmine improves postoperative analgesia without increasing the incidence of adverse events (**N**) (**Level II**).
12. Addition of either clonidine or dexmedetomidine to intrathecal bupivacaine increases the speed of onset and duration of motor and sensory block without additional side effects (**N**) (**Level II**).

5.4 Anti-inflammatory drugs

5.4.1 Corticosteroids

Neuraxial

Use of epidural methylprednisolone resulted in no difference in morphine requirements or pain scores following thoracotomy compared with epidural saline (Blanloeil et al, 2001 **Level II**). Following lumbar disc surgery, the combination of wound infiltration with bupivacaine and epidural/ perineural methylprednisolone improved analgesia and decreased opioid consumption compared with placebo (Mirzai et al, 2002 **Level II**; Jirarattanaphochai et al, 2007 **Level II**). However, epidural administration of either drug on its own was not superior to placebo (Loffinia et al, 2007 **Level II**). Preoperative single dose epidural administration of dexamethasone, with or without bupivacaine, was shown to reduce postoperative pain and morphine consumption following laparoscopic cholecystectomy (Thomas & Beevi, 2006 **Level II**).

Peripheral sites

Intra-articular corticosteroid injections would be expected to have an 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 et al, 1998 **Level II**), in conjunction with opioids (Kizilkaya et al, 2004 **Level II**; Kizilkaya et al, 2005 **Level II**) and/or local anaesthetics (Rasmussen et al, 2002 **Level II**). Dexamethasone on its own was less effective than pethidine or fentanyl (Saryazdi et al, 2006 **Level II**). There may be a higher risk of septic arthritis with intra-articular steroids (Armstrong et al, 1992 **Level IV**). Subacromial injections of corticosteroids have been shown to be effective in treating rotator cuff tendonitis for up to 9 months, and were superior to oral NSAIDs (NNT 2.5; CI 1 to 9]) (Arroll & Goodyear-Smith, 2005 **Level I**).

In patients having hand surgery, IVRA using a combination of lignocaine and dexamethasone resulted in lower pain scores and lower analgesic requirements for 24 hours compared with lignocaine alone or lignocaine IVRA with dexamethasone in the non-operative arm (Bigat et al, 2006 **Level II**).

The addition of dexamethasone to lignocaine for axillary brachial plexus block prolonged the duration of sensory and motor blockade compared with lignocaine alone (Movafegh et al, 2006 **Level II**).

There is insufficient evidence to support the use of injection therapy, including corticosteroids, in subacute and chronic low-back pain. However, it cannot be ruled out that specific subgroups of patients may respond to a specific type of injection therapy (Staal et al, 2009 **Level I**). Lumbar epidural steroid injections may provide short-term relief from acute radicular pain but did not impact on function, need for surgery, or provide long-term pain relief beyond 3 months (Armon et al, 2007 **Level I**).

Topical

Topical corticosteroids have not been shown to have consistent efficacy in acute herpes zoster (Hempenstall et al, 2005 **Level I**).

Key messages

1. Subacromial injections of corticosteroids are superior to oral NSAIDs in treating rotator cuff tendonitis (**N**) (**Level I**).
2. Lumbar epidural steroid administration is effective for short -term relief of acute radicular pain (**N**) (**Level I**).
3. Following knee joint arthroscopy, intra-articular steroids in combination with either local anaesthetic or opioids reduce pain, analgesic consumption and duration of immobilisation (**N**) (**Level II**).
4. Intravenous regional anaesthesia combining dexamethasone with lignocaine improves analgesia for up to 24 hours (**N**) (**Level II**).
5. There is a risk of septic arthritis with intra-articular steroids (**N**) (**Level IV**).

5.4.2 Non-steroidal anti-inflammatory drugs

Peripheral sites

Intra-articular nsNSAIDs such as tenoxicam and ketorolac resulted in improved pain relief after surgery (Elhakim et al, 1996 **Level II**; Cook et al, 1997 **Level II**; Convery et al, 1998 **Level II**; Colbert et al, 1999 **Level II**; Gupta et al, 1999 **Level II**); no long-term follow-up looking at any effect on bone healing has been undertaken.

Topical

With topical application of diclofenac, tissue levels are higher and plasma levels lower than following oral administration (Zacher et al, 2008). Topical diclofenac significantly reduced pain and inflammation in a range of sports, traumatic and inflammatory acute and chronic conditions compared with placebo and was comparable to other topical NSAIDs (although there were no direct comparisons) and oral diclofenac, ibuprofen and naproxen. (Zacher et al, 2008 **Level I**). Topical ketoprofen used for up to one week in acute painful conditions (strains, sprains or sports injuries) had a NNT of 3.8, which was significantly better than other topical NSAIDs, although in non-comparative (head-to-head) trials. (Mason et al, 2004 **Level I**). Topical indomethacin did not have proven efficacy (Moore RA et al, 1998 **Level I**).

There was a small but significant reduction of pain with the use of topical NSAIDs for traumatic corneal abrasions (Calder et al, 2005 **Level I**).

Use of topical ketoprofen patches showed mild clinical benefit over placebo in tendinitis and ankle sprain (NNT 5 to 6) (Mazieres, Rouanet, Guillon et al, 2005 **Level II**; Mazieres, Rouanet, Velicy et al, 2005 **Level II**).

Topical NSAIDs were of limited efficacy in lateral elbow pain providing short-term functional improvement for up to 2 weeks. They resulted in fewer GI side effects compared with oral NSAIDs (Green et al, 2001 **Level I**).

Overall, there are insufficient data to support the use of topical NSAID analgesia in acute and chronic Achilles tendinitis (McLauchlan & Handoll, 2001 **Level I**) or in superficial venous thrombosis of the leg (Di Nisio et al, 2007 **Level I**).

There is insufficient evident to differentiate between routes of administration of NSAIDs in the treatment of low back pain (Roelofs et al, 2008 **Level I**).

Key messages

1. Topical NSAIDs are of limited efficacy in lateral elbow pain and provide short-term functional improvement; they result in fewer gastrointestinal side effects compared with oral NSAIDs (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs added to local anaesthetic solutions for IVRA improve postoperative analgesia (**N**) (**Level I**).
3. Topical NSAIDs are effective in treating acute strains, sprains or sports injuries for up to 1 week with ketoprofen being significantly better than all other topical NSAIDs, and indomethacin similar to placebo (**N**) (**Level I**).
4. Topical diclofenac significantly reduces pain and inflammation in a range of sports, traumatic and inflammatory conditions and in acute musculoskeletal injuries is at least comparable to oral naproxen (**N**) (**Level I**).
5. Topical NSAIDs are effective analgesics for traumatic corneal abrasions (**N**) (**Level I**).

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6. ADMINISTRATION OF SYSTEMIC ANALGESIC DRUGS

Opioid and non-opioid analgesic drugs can be administered systemically by a number of different routes. 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, cost, staff education and supervision available.

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). Frequent assessment of the patient's pain and their response to treatment (including the occurrence of any side effects) rather than strict adherence to a given dosing regimen is required if adequate analgesia is to be obtained.

The text in Sections 6.1 to 6.4 below relates to opioids, non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) and coxibs. For information about oral and parenteral routes of administration of systemically administered adjuvant drugs, refer to Section 4.3.

6.1 ORAL ROUTE

Oral administration of analgesic agents is simple, non-invasive, has good efficacy in most settings and 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 drugs.

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 drug 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 drug and an increased risk of adverse effects.

Rates of absorption will vary according to the formulation of the oral analgesic agent (eg tablet, suspension, controlled-release [CR] preparation). Bioavailability will also vary between drugs because of the effects of first-pass hepatic metabolism following uptake into the portal circulation. Titration of pain relief with oral analgesic drugs is slower compared with some of the other routes of administration discussed below.

Direct comparisons between oral opioid and non-opioid analgesics, or between oral and other routes of administration, are limited. Indirect comparisons, where the individual drugs have been compared with a placebo, have been used to generate a 'league table' of analgesic efficacy (see Table 6.1). This table is based on randomised, double-blind, single-dose studies in patients with moderate to severe pain and shows the number of patients that need to be given the active drug (NNT) to achieve at least 50% pain relief in one patient compared with a placebo over a 4 to 6 hour treatment period (Moore et al, 2003).

The validity of this approach as a true method of comparison of drugs 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 et al, 2005 **Level I**; Oscier & Milner, 2009). However, it may be reasonable, in some circumstances, to extrapolate estimates of analgesic efficacy from one pain model to another (Barden, Edwards, McQuay et al, 2004 **Level I**).

Table 6.1 The 2007 Oxford league table of analgesic efficacy (commonly used analgesic doses)

Analgesic	Number of patients in comparison	At least 50% pain relief (%)	NNT	Lower confidence interval	Higher confidence interval
Etoricoxib 180/240	248	77	1.5	1.3	1.7
Etoricoxib 100/120	500	70	1.6	1.5	1.8
Valdecoxib 40	473	73	1.6	1.4	1.8
Dipyrone 1000	113	79	1.6	1.3	2.2
Ibuprofen 600/800	165	86	1.7	1.4	2.3
Valdecoxib 20	204	68	1.7	1.4	2.0
Ketorolac 20	69	57	1.8	1.4	2.5
Ketorolac 60 (intramuscular)	116	56	1.8	1.5	2.3
Diclofenac 100	545	69	1.8	1.6	2.1
Piroxicam 40	30	80	1.9	1.2	4.3
Celecoxib 400	298	52	2.1	1.8	2.5
Paracetamol 1000 + Codeine 60	197	57	2.2	1.7	2.9
Oxycodone IR 5 + Paracetamol 500	150	60	2.2	1.7	3.2
Bromfenac 25	370	51	2.2	1.9	2.6
Rofecoxib 50	675	54	2.3	2.0	2.6
Oxycodone IR 15	60	73	2.3	1.5	4.9
Aspirin 1200	279	61	2.4	1.9	3.2
Bromfenac 50	247	53	2.4	2.0	3.3
Dipyrone 500	288	73	2.4	1.9	3.2
Ibuprofen 400	5456	55	2.5	2.4	2.7
Bromfenac 100	95	62	2.6	1.8	4.9
Oxycodone IR 10 + Paracetamol 650	315	66	2.6	2.0	3.5
Diclofenac 25	502	53	2.6	2.2	3.3
Ketorolac 10	790	50	2.6	2.3	3.1
Paracetamol 650 + tramadol 75	679	43	2.6	2.3	3.0
Oxycodone IR 10 + Paracetamol 1000	83	67	2.7	1.7	5.6

Analgesic	Number of patients in comparison	At least 50% pain relief (%)	NNT	Lower confidence interval	Higher confidence interval
Naproxen 400/440	197	51	2.7	2.1	4.0
Piroxicam 20	280	63	2.7	2.1	3.8
Lumiracoxib 400	370	48	2.7	2.2	3.5
Naproxen 500/550	784	52	2.7	2.3	3.3
Diclofenac 50	1296	57	2.7	2.4	3.1
Ibuprofen 200	3248	48	2.7	2.5	2.9
Dextropropoxyphene 130	50	40	2.8	1.8	6.5
Paracetamol 650 + tramadol 112	201	60	2.8	2.1	4.4
Bromfenac 10	223	39	2.9	2.3	4.0
Pethidine 100 (intramuscular)	364	54	2.9	2.3	3.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10 (intramuscular)	946	50	2.9	2.6	3.6
Naproxen 200/220	202	45	3.4	2.4	5.8
Ketorolac 30 (intramuscular)	359	53	3.4	2.5	4.9
Paracetamol 500	561	61	3.5	2.2	13.3
Celecoxib 200	805	40	3.5	2.9	4.4
Paracetamol 1500	138	65	3.7	2.3	9.5
Ibuprofen 100	495	36	3.7	2.9	4.9
Oxycodone IR 5 + Paracetamol 1000	78	55	3.8	2.1	20.0
Paracetamol 1000	2759	46	3.8	3.4	4.4
Paracetamol 600/650 + Codeine 60	1123	42	4.2	3.4	5.3
Paracetamol 650 + Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate)	963	38	4.4	3.5	5.6
Aspirin 600/650	5061	38	4.4	4.0	4.9
Paracetamol 600/650	1886	38	4.6	3.9	5.5
Ibuprofen 50	316	32	4.7	3.3	8.0
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2

Analgesic	Number of patients in comparison	At least 50% pain relief (%)	NNT	Lower confidence interval	Higher confidence interval
Aspirin 650 + Codeine 60	598	25	5.3	4.1	7.4
Oxycodone IR 5 + Paracetamol 325	149	24	5.5	3.4	14.0
Ketorolac 10 (intramuscular)	142	48	5.7	3.0	53.0
Paracetamol 300 + Codeine 30	379	26	5.7	4.0	9.8
Bromfenac 5	138	20	7.1	3.9	28.0
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1305	15	16.7	11.0	48.0
Placebo	>10,000	18	N/A	N/A	N/A

Source: Bandolier (www.medicine.ox.ac.uk/bandolier). Reproduced with permission.

6.1.1 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. Both immediate-release (IR) and CR formulations have been used. 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 drugs 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 drugs and, in a small minority of patients, the potential for prescribed opioids to be abused or misused.

Immediate-release formulations

The NNTs of various IR opioids is listed in Table 6.1.

The effectiveness of the different opioids and tramadol increases with the addition of paracetamol.

- Codeine in a single dose of 60 mg is not an effective analgesic agent (Moore & McQuay, 1997 **Level I**). Combined with paracetamol a significant dose response was seen with NNTs of 2.2 for 800 to 1000 mg paracetamol plus 60 mg codeine, 3.9 for 600 to 650 mg paracetamol plus 60 mg codeine, and 6.9 for 300 mg paracetamol plus 30 mg codeine, and the combination extended the duration of analgesia by 1 hour compared with paracetamol alone (Toms et al, 2009 **Level I**).
- Dextropropoxyphene 65 mg is not an effective analgesic agent; it was effective when combined with 650 mg paracetamol (Collins, Edwards et al, 2000 **Level I**).
- Oxycodone (IR), in a single dose of 5 mg showed no benefit over placebo for the treatment of moderate to severe acute pain; doses of 15 mg alone, 10 mg plus paracetamol and 5 mg plus paracetamol are effective (Gaskell et al, 2009 **Level I**).
- Tramadol is an effective analgesic agent (Moore & McQuay, 1997 **Level I**). The combination of tramadol 75 mg or 112.5 mg with paracetamol (acetaminophen) 560 mg or 975 mg was more effective than either of its two components administered alone (McQuay & Edwards, 2003 **Level I**).

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 hours with additional 10 mg doses as needed has been shown to provide better pain relief after hip surgery than IM morphine 5 to 10 mg prn (McCormack et al, 1993 **Level II**).

In comparison with IV morphine patient-controlled analgesia (PCA) alone, regular 4-hourly administration of 20 mg but not 10 mg oral morphine reduced PCA morphine consumption but there were no differences in pain relief or side effects (Manoir et al, 2006 **Level II**).

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 & Schug, 2007) and after epidural analgesia (Lim & Schug, 2001 **Level II**).

Controlled-release formulations

CR formulations also referred to as slow-release (SR) or prolonged-release, may take 3 to 4 hours 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 to 60 minutes. 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. 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 oral oxycodone comprises an IR component as well as the delayed-release compound and therefore has a more rapid onset of action than other CR agents. CR oxycodone may be effective in the immediate management of acute pain (Sunshine et al, 1996 **Level II**; Kampe et al, 2004 **Level II**). However, IR oxycodone 5 mg and paracetamol 325 mg given 6-hourly led to better pain relief than 10 mg CR oxycodone given 12-hourly (Kogan et al, 2007 **Level II**). 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 et al, 2007 **Level II**). CR oral oxycodone was found to be effective as 'step-down' analgesia after 12 to 24 hours of PCA morphine (Ginsberg et al, 2003 **Level IV**).

More recently, a combined formulation of CR oxycodone and naloxone has been studied. Compared with CR oxycodone alone in patients with chronic non-malignant back pain, the combination formulation resulted in similar analgesic efficacy but less bowel dysfunction (Vondrackova et al, 2008 **Level II**). The addition of naloxone may also discourage unauthorised injection of the drug (see Suboxone in Section 11.8).

6.1.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs

A number of nsNSAIDs and coxibs have been shown to be effective as sole therapy in a variety of acute pain settings (see Table 6.1). Those for which there is Level I evidence of efficacy include: aspirin 600 to 1200 mg (Edwards, Oldman et al, 2000 **Level I**), ibuprofen 200 to 400 mg (Derry et al 2009a **Level I**), piroxicam 20 to 40 mg (Edwards, Loke et al, 2000 **Level I**), valdecoxib 20 to 40 mg (Lloyd et al, 2009 **Level I**), naproxen (Derry et al, 2009b **Level I**), ketorolac (Smith et al, 2000 **Level I**), lumiracoxib 400mg (Roy et al, 2007 **Level I**), celecoxib 200 to 400 mg (Derry et al, 2008 **Level I**) and diclofenac 50 to 100 mg (Derry et al, 2009c **Level I**).

The NNTs of each of these drugs is listed in Table 6.1.

In general, there is no good evidence that nsNSAIDs given parenterally or rectally are more effective, or result in fewer side effects, than the same drug given orally for the treatment of postoperative pain (Tramer et al, 1998 **Level I**). Only in the treatment of renal colic do IV nsNSAIDs result in more rapid analgesia (Tramer et al, 1998 **Level I**).

6.1.3 Paracetamol

Paracetamol is an effective analgesic for acute pain (Toms et al 2008 **Level I**; Toms et al, 2009 **Level I**; Weil et al, 2007 **Level I**). However, as noted above, the effects of different analgesics may vary with different pain models (Oscier & Milner, 2009). In a re-analysis of data available for paracetamol, it was found to be significantly less effective for pain relief after orthopaedic than after dental procedures (Gray et al, 2005 **Level I**).

The oral bioavailability of paracetamol is good at between 63% and 89% (Oscier & Milner, 2009). 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 et al, 2004 **Level II**).

In the same doses, orally administered paracetamol was less effective and of slower onset than paracetamol given by IV injection, but more effective and of faster onset than paracetamol administered by the rectal route (see below).

Paracetamol effervescent tablets were absorbed significantly faster than ordinary paracetamol (Rygnestad et al, 2000 **Level II**).

6.2 Intravenous route

Analgesic drugs given by the IV route have a more rapid onset of action compared with most other routes of administration.

6.2.1 Opioids and tramadol

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 drug 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-minute dose intervals as needed and with no limitation on the number of bolus doses administered, was more effective and resulted in no greater incidence of side effects than the same doses given at 10-minute intervals or when a maximum of 5 doses only was allowed (Aubrun et al, 2001 **Level III-3**). In a comparison of IV fentanyl and morphine bolus doses every 5 minutes as needed for prehospital analgesia over a period of just 30 minutes, no difference was found in pain relief or incidence of side effects (Galinski et al, 2005 **Level II**).

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-minute intervals as needed (Macintyre & Schug, 2007).

IV tramadol 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 et al, 2005 **Level II**).

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 drug or, in the surgical setting, by giving it before the patient emerges from general anaesthesia (Pang et al, 2000 **Level II**).

Continuous infusions

A continuous infusion of opioids results in constant blood levels after approximately 4 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 side effects, such as respiratory depression. Very close monitoring is therefore essential with continuous infusions of opioids.

Compared with PCA, continuous IV opioid infusions in a general ward setting resulted in a 5-fold increase in the incidence of respiratory depression (Schug & Torrie, 1993 **Level IV**).

6.2.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs

There are only a limited number of nsNSAIDs or coxibs available for IV injection at present and fewer still where Level I evidence for individual efficacy is available. In single doses as the sole analgesic agent, the coxib parecoxib IV 20 to 40 mg has been shown to be effective (Lloyd et al, 2009 **Level I**).

The formulation of drug used may affect efficacy. Comparison of a polyethylene glycol and benzyl alcohol (PG-BA) diclofenac solution with one that used hydroxypropyl beta-cyclodextrin (HPβCD) to solubilise diclofenac in a small volume showed that IV HPβCD diclofenac resulted in more rapid onset of analgesia (Leeson et al, 2007 **Level II**). The incidence of moderate to severe, but not mild thrombophlebitis may be less with IV diclofenac (Colucci et al, 2009).

In most cases the route of administration does not seem to alter efficacy. IV nsNSAIDs or coxibs are more expensive than oral or rectal nsNSAIDs although their efficacy and likelihood of side effects is similar (Tramer et al, 1998 **Level I**). A more recent comparison of rectal diclofenac and IV parecoxib showed no difference in pain relief, side effects or rescue analgesic requirements (Ng et al, 2008 **Level II**). Efficacy and times to onset of analgesia were similar with IV and IM parecoxib (Daniels et al, 2001 **Level II**).

For renal colic, the onset of action of NSAIDs was faster when given IV compared with IM, oral or rectal administration (Tramer et al, 1998 **Level I**).

6.2.3 Paracetamol

IV paracetamol was an effective analgesic after surgery (Sinatra et al, 2005 **Level II**). It was of faster onset than the same dose given orally (Moller, Sindet-Pedersen et al, 2005 **Level II**) but, as with IV NSAIDs, it is more expensive.

While of equal analgesic efficacy, the incidence of local pain at the infusion site was significantly less after IV paracetamol compared with the prodrug propacetamol (Moller, Juhl et al, 2005 **Level II**).

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.

6.3 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 drug depot when perfusion is restored.

6.3.1 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 to 2.5)% to 37.0 (22.6 to 45.9)% using respiratory rate and oxygen saturation, respectively, as indicators (for comparisons with PCA and epidural analgesia, see Section 7; for comments on respiratory rate as an unreliable indicator of respiratory depression, see Section 4.1.3) (Cashman & Dolin, 2004 **Level IV**).

Single doses of IM morphine 10 mg (McQuay et al, 1999 **Level I**) and IM pethidine (meperidine) 100 mg (Smith et al, 2000 **Level I**) 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 et al, 1992 **Level III-3**).

The quality of pain relief was less with intermittent IM regimens compared with IV PCA (Hudcova et al, 2005 **Level I**).

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 mins (Stuart-Harris et al, 2000). In elderly adults, mean T_{max} after a single SC injection of morphine was 15.9 minutes and the rate of absorption and the variability in the rate of absorption were similar to those reported after IM injection (Semple et al, 1997 **Level IV**). In patients given a second and same dose of SC morphine 5 hours after the first, it was shown that there can also be significant within-patient variations in absorption (Upton et al, 2006).

In children, there was no difference in rate of onset, analgesic effect and side effects when SC injections of morphine were compared with IM morphine injections, and there was a significantly higher patient preference for the SC route (Cooper, 1996 **Level II**; Lamacraft et al, 1997 **Level IV**). A comparison of IM and SC morphine in patients after Caesarean section reported no significant differences in side effects, patient satisfaction or pain relief at rest, but lower pain scores after SC administration at 12, 16 and 20 hours after surgery (Safavi & Honarmand, 2007 **Level II**).

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 minutes IV; 20 minutes SC) and better pain relief between 5 minutes and 25 minutes after injection, but also led to higher sedation scores up to 30 minutes after injection, and higher PCO_2 levels (Tveita et al, 2008 **Level II**). 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 that 3 hours) showed no differences in pain relief or side effects over a 48-hour

period after surgery; pain relief was the same but the incidence of pruritus was lower compared with PCA hydromorphone (Bell et al, 2007 **Level II**).

Treatment algorithms for intermittent SC morphine using age-based dosing are available (Macintyre & Schug, 2007).

Continuous infusions of opioids via the SC route were as effective as continuous IV infusions (Semple et al, 1996 **Level II**).

6.3.2 Non-selective non-steroidal anti-inflammatory drugs and coxibs

There are only a limited number of nsNSAIDs or coxibs 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 (Smith et al, 2000 **Level I**; Lloyd et al, 2009 **Level I**).

6.4 Rectal route

Rectal administration of drugs 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. Drug 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 drug absorbed into the superior rectal vein enters the portal system, subjecting it to hepatic first-pass metabolism.

Potential problems with the rectal route of drug administration relate to the variability of absorption, possible rectal irritation and cultural factors. Some suppositories should not be divided as the drug may not be evenly distributed in the preparation. Contraindications to the use of this route include pre-existing rectal lesions, recent colorectal surgery and immune suppression. Whether the drug is administered to a patient who is awake or under anaesthesia, it is important to obtain prior consent from the patient or guardian.

6.4.1 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.

In cancer patients no differences in either pain relief or adverse effects were found in a comparison of oral and rectally administered tramadol (Mercadante et al, 2005 **Level II**).

6.4.2 Non-selective non-steroidal anti-inflammatory drugs

Rectal administration of nsNSAIDs provides effective analgesia (Tramer et al, 1998 **Level I**). Local effects such as rectal irritation and diarrhoea werereported following use of the rectal route, but other commonly reported adverse effects such as nausea, vomiting, dizziness and indigestion were independent of the route of administration (Tramer et al, 1998 **Level I**).
In a study comparing oral and rectal indomethacin (indometacin) given over a period of 2 weeks, the degree of gastric erosion at endoscopy was the same (Hansen et al, 1984 **Level II**). Consequently, there appears to be no advantage in using nsNSAID suppositories if the oral route is available (Tramer et al, 1998 **Level I**).

6.4.3 Paracetamol

Paracetamol is effective when given by the rectal route (Romsing et al, 2002 **Level I**) although rectal absorption of paracetamol was slower and less predictable than after oral administration, with a bioavailability of between 24% and 98% (Oscier & Milner, 2009). It was also less effective than the same dose administered by the oral route (Anderson et al, 1996 **Level II**; Anderson et al, 1999 **Level IV**). Doses of 1 g rectally after cardiac surgery (Holmer Pettersson et al, 2006 **Level II**) and hysterectomy (Kvalsvik et al, 2003 **Level II**) as well as 2 g given rectally to patients undergoing laparoscopic gynaecological surgery (Hahn, Mogensen et al, 2000 **Level II**) also resulted in subtherapeutic blood levels, although levels may increase to within the therapeutic range after repeat administration (Holmer Pettersson et al, 2006 **Level II**).

In children, similar results have been noted. Initial administration of doses of 25 mg/kg achieved average blood concentrations at the lower end of the therapeutic range and large variations in absorption were reported (Hahn, Henneberg et al, 2000 **Level IV**).

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 et al, 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 & Montgomery, 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 et al, 2001 **Level IV**).

When available, the oral route is therefore preferable.

6.5 Transdermal route

Not all medications applied topically have a local, peripheral action. The term 'transdermal' will be used to describe drugs that while applied to the skin, have predominantly central effects that are the result of systemic absorption of the drug. The term 'topical' will be used in the discussion of drugs — primarily NSAIDs — that are applied topically (including to skin) but have a predominantly peripheral effect.

6.5.1 Opioids

The stratum corneum of the epidermis forms a major barrier to the entry of drugs. However, drugs such fentanyl (Sathyan et al, 2005) and buprenorphine (Skaer, 2006) are available as transdermal preparations. The analgesic effects are a result of systemic effects rather than local peripheral opioid analgesia (Worrich et al, 2007 **Level IV**). The original transdermal fentanyl patches consisted of a reservoir system and rate-controlling membrane. In the newer system, which has the same bioequivalence, the fentanyl is dissolved in the adhesive matrix; the patient's stratum corneum and the characteristics of the drug-in-adhesive matrix control the rate of systemic delivery (Sathyan et al, 2005).

Transdermal 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 peak blood concentration is generally between 24 and 72 hours after initial patch application and after the patch is removed, serum fentanyl concentrations decline gradually, with a mean terminal half-life ranging from 22 to 25 hours (MIMS, 2008).

Transdermal fentanyl patches are currently specifically contraindicated for the management of acute or postoperative pain in many countries (FDA, 2007; eCompendium, 2008; MIMS, 2008) and

their use cannot be recommended. Specific safety alerts have been issued warning against use in opioid-naive patients, and highlighting the risk that increased body temperature, exposure of patches to external heat sources, and concomitant use of CYP3A4 inhibitors may lead to potentially dangerous rises in serum fentanyl levels (FDA, 2005).

However, transdermal fentanyl patches have been trialled in the management of postoperative pain. For example, after hip arthroplasty (Minville et al, 2008 **Level II**) and hysterectomy (Sandler et al, 1994 **Level II**), preoperative use significantly reduced postoperative pain scores and PCA morphine requirements. However, the wide variability of clinical effect (Peng & Sandler, 1999) and the high incidence of respiratory depression that can occur in the postoperative setting (Sandler et al, 1994 **Level II**; Bulow et al, 1995 **Level II**), make transdermal fentanyl preparations unsuitable for acute pain management.

Iontophoretic patient-controlled transdermal delivery systems for fentanyl were introduced for the management of acute pain, but marketing authority was later withdrawn after discovery of a fault that could lead to triggering of the self-activation of the system (see Section 7.1.4).

Transdermal buprenorphine patches are available for the management of chronic and cancer pain (Skaer, 2006). After application of the patch, steady state is achieved by day 3; after removal of the patch, buprenorphine concentrations decrease by about 50% in 12 hours (range 10 to 24 hours) (MIMS, 2008). Given the slow onset and offset of the drug, it is unlikely to be of much use in the management of acute pain.

6.5.2 Other drugs

The results from studies looking at the use of transdermal nicotine patches for the management of postoperative pain have been inconclusive with both a reduction (Hong et al, 2008 **Level II**) and no reduction in pain scores (Habib et al, 2008 **Level II**; Turan et al, 2008 **Level II**), and opioid-sparing (Habib et al, 2008 **Level II**) and no opioid-sparing (Hong et al, 2008 **Level II**; Turan et al, 2008 **Level II**) reported.

Topical administration might result in effective systemic plasma concentrations, as a transdermal ketamine patch delivering 25 mg over 24 hours reduced rescue analgesic consumption after gynaecological surgery (Azevedo et al, 2000 **Level II**) and, in an experimental pain study, use of a ketamine gel reduced capsaicin-induced hyperalgesia (Poyhia & Vainio, 2006).

6.6 Transmucosal routes

Drugs administered by transmucosal routes (IN, sublingual, buccal, and pulmonary) are rapidly absorbed directly into the systemic circulation, thus bypassing hepatic first-pass metabolism. The drugs most commonly administered by transmucosal routes in acute pain management are the more lipid-soluble opioids.

6.6.1 Intranasal route

A variety of drugs can be administered by the IN route, including analgesic drugs. The human nasal mucosa contains drug-metabolising enzymes but the extent and clinical significance of human nasal first-pass metabolism is unknown (Dale et al, 2002). It is suggested that the volume of a dose of any drug given intranasally should not exceed 150 microlitres (0.150 mL) in order to avoid run-off into the pharynx (Dale et al, 2002). Absorption through the nasal mucosa depends on both the lipid solubility and degree of ionisation of the drug (Shelley & Paech, 2008).

Opioids

Single-dose pharmacokinetic data in healthy volunteers for a number of opioids administered by the IN route have been summarised by Dale et al (Dale et al, 2002). The mean bioavailabilities and T_{max} reported were fentanyl 71% and 5 minutes; sufentanil 78% and 10 minutes; alfentanil 65% and 9 minutes; butorphanol 71% and 49 minutes; oxycodone 46% and 25 minutes; and buprenorphine 48% and 30 minutes. A later comparison of IN and IV fentanyl showed mean T_{max} values of 12.8 and 6.0 minutes and times to onset of analgesia of 7 and 2 minutes respectively; the bioavailabilty of IN fentanyl was 89% (Foster et al, 2008 **Level II**).

Hydromorphone, when given to volunteers in doses of 1 mg or 2 mg IN and compared with 2 mg IV, had median times to peak blood concentration after the 1 mg and 2 mg IN doses of 20 minutes and 25 minutes respectively and an overall bioavailability of only 55% (Coda et al, 2003).

Clinical data also exist for the effectiveness of several opioids administered via the IN route, including fentanyl (Toussaint et al, 2000 **Level II**; Manjushree et al, 2002 **Level II**; Paech et al, 2003 **Level II**; Christrup et al, 2008 **Level II**; Foster et al, 2008 **Level II**), butorphanol (Abboud et al, 1991 **Level II**; Wermeling et al, 2005), pethidine (Striebel et al, 1993 **Level II**; Striebel et al, 1995 **Level II**) and morphine (Stoker et al, 2008 **Level II**).

Fentanyl had similar analgesic efficacy when given by the IN or IV routes (Toussaint et al, 2000 **Level II**; Manjushree et al, 2002 **Level II**; Paech et al, 2003 **Level II**) as did butorphanol (Abboud et al, 1991 **Level II**) and morphine (Christensen et al, 2008 **Level II**). IN pethidine was more effective than SC injections of pethidine (Striebel et al, 1995 **Level II**).

In patients undergoing third molar extraction, mean T_{max} values were 12.8 and 6.0 minutes ($P<0.001$), times to onset of analgesia were 7 and 2 minutes ($P<0.001$), and durations of effect were 56 and 59 minutes (P = NS) after IN and IV fentanyl administration respectively (Christrup et al, 2008 **Level II**). Also after third molar extraction, mean times to onset of analgesia were 11 minutes for both 15 mg IN and 7.5 mg IV morphine and efficacy profiles were similar (Christensen et al, 2008 **Level II**).

When fentanyl was used in the prehospital setting, there was no difference in effectiveness between IN fentanyl (180 mcg +/- 2 doses of 60 mcg at > or =5 minute intervals) and IV morphine (2.5 to 5 mg +/- 2 doses of 2.5 to 5 mg at > or =5-minute intervals) (Rickard et al, 2007 **Level II**).

Patient-controlled intranasal analgesia (PCINA) using diamorphine (bolus doses of 0.5mg) was less effective than PCA IV morphine (1 mg bolus doses) after joint replacement surgery (Ward et al, 2002 **Level II**) but provided better pain relief in doses of 0.1 mg/kg compared with 0.2 mg/kg IM morphine in children with fractures (Kendall et al, 2001 **Level II**). In children, IN fentanyl at a dose of 1.7 mcg/kg was shown to be as effective as IV morphine 0.1 mg/kg in children presenting to an emergency department with an acute fracture (Borland et al, 2007 **Level II**) and equivalent to oral morphine for pain relief during burn wound dressing changes (Borland et al, 2005 **Level II**) (see Sections 9.3 and 10.4.2).

A comparison of two different doses of IN sufentanil (0.025 and 0.05 mcg/mL), given as often as every 5 minutes in order to obtain a verbal pain score of less than 4 after inguinal hernia repair or haemorrhoidectomy, confirmed the effectiveness of the nasal route for postoperative analgesia, although the larger doses enabled effective pain relief to be achieved more rapidly (Mathieu et al, 2006 **Level II**).

Adverse effects can be related to the drug 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 with the short-term use of butorphanol and pethidine (Dale et al, 2002).

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 drugs, have not been addressed (Dale et al, 2002).

Other analgesic drugs

IN ketamine has been shown to provide relatively rapid onset of effective pain relief (within 15 minutes); any adverse effects were mild and transient (Christensen et al, 2007 **Level II**).

IN ketorolac has also been shown to be effective; after major surgery 30 mg but not 10 mg IN ketorolac resulted in significant opioid-sparing over 20 hours and better pain relief in the first 6 hours after surgery (Moodie et al, 2008 **Level II**).

6.6.2 Sublingual and buccal routes

When analgesic drugs are administered by the sublingual or buccal routes, their efficacy will in part depend on the proportion of drug swallowed.

Opioids

Sublingual buprenorphine, given as a tablet, has an overall bioavailability of 30% to 50% (Mendelson et al, 1997; Kuhlman et al, 1996) and a long duration of action (mean half-life 28 hours) (Kuhlman et al, 1996). Sublingual buprenorphine 0.4 mg was found to be as effective as 10 mg morphine IM (Cuschieri et al, 1984 **Level II**) and 75 mg pethidine IM after abdominal surgery (Moa & Zetterstrom, 1990 **Level II**).

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 to 1600 mcg. Overall, the bioavailability of OTFC is about 52% compared with IV fentanyl, with peak blood levels achieved in 22 ± 2.5 minutes (Streisand et al, 1991 **Level IV**). The median time to onset of analgesia was about 5 minutes and the relative potency compared with IV morphine was 8–14:1. (Lichtor et al, 1999 **Level II**).

In many countries, regulatory authorities have specifically noted that OTFC must not be used in opioid-naïve patients or in the management of acute and postoperative pain: approval is limited to the management of break-through pain in patients who are opioid-tolerant (FDA, 2007; MIMS, 2008; eCompendium, 2008).

Only a few studies have investigated the postoperative use of OTFC. It was found to be an effective analgesic after orthopaedic (Ashburn et al, 1993 **Level II**) and abdominal surgery (Lichtor et al, 1999 **Level II**) and during burns wound care (Sharar et al, 1998 **Level II**; Sharar et al, 2002 **Level II**). Pain relief at 15 minutes 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 minute study period (Mahar et al, 2007 **Level II**).

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 (FBT) use an effervescent drug delivery technology that enables more rapid absorption and delivery of a larger proportion of the fentanyl dose compared with OTFC (Darwish et al, 2006; Darwish et al, 2007). They were effective in opioid-tolerant patients for the treatment of breakthrough cancer pain (Portenoy et al, 2006 **Level II**; Slatkin et al, 2007 **Level II**), chronic low back pain (Portenoy et al, 2007 **Level II**) and chronic neuropathic pain (Simpson et al, 2007 **Level II**). At present, this formulation is also not approved for use in the acute pain setting.

Other analgesic drugs

A pharmacokinetic study in healthy volunteers calculated the bioavailability of oral ketamine as 20%, sublingual 30% and IN 45%: the pharmacodynamic effects of the active metabolite norketamine were thought to be of potential significance (Yanagihara et al, 2003). The bioavailability of a 25 mg ketamine lozenge was 24% when given by both sublingual and oral routes; peak plasma levels were seen at 30 minutes and 120 minutes respectively and terminal half-lives were similar at around 5 hours. 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 (Chong et al, 2009).

6.6.3 Inhaled

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 (Masood & Thomas, 1996 **Level II**; Ward et al, 1997 **Level II**; Dershwitz et al, 2000 **Level IV**; Thipphawong et al, 2003 **Level II**) and fentanyl (Worsley et al, 1990 **Level II**; Miner et al, 2007 **Level II**). In a small study of 44 patients with post-traumatic thoracic pain, there was no difference in the pain relief obtained from nebulised morphine and PCA morphine (Fulda et al, 2005 **Level II**). In another study of only 28 patients in an emergency department, no patient experienced pain relief 10 minutes after inhalation of morphine (Bounes et al, 2009 **Level III-3**). In children requiring pain relief in an emergency department, nebulised fentanyl was also as effective as IV fentanyl (Miner et al, 2007 **Level II**) (see Sections 9.3 and 10.4.4).

Peak plasma concentrations following administration of morphine via a standard nebuliser occured within 10 minutes but bioavailability was low with a mean of only 5% (Masood & Thomas, 1996 **Level II**). Bioavailability may be improved (up to 59 to 100%) with peak plasma concentrations occurring at 2 minutes using pulmonary drug delivery systems (Ward et al, 1997 **Level II**; Dershwitz et al, 2000 **Level IV**). Similarly, bioavailability of inhaled fentanyl may approach 100% (Mather et al, 1998 **Level IV**).

These systems await further development and thus these data are insufficient to support the routine use of inhaled opioids in acute pain management.

Other analgesic drugs

See Section 4.3.1 for inhaled nitrous oxide and methoxyflurane.

Key messages

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

5. Rectal administration of single doses of paracetamol results in highly variable plasma concentrations that often remain subtherapeutic (**N**) (**Level II**).
6. Intermittent subcutaneous morphine injections are as effective as intramuscular injections and have better patient acceptance (**U**) (**Level II**).
7. Intranasal opioids, in particular the more lipid-soluble drugs such as fentanyl, are effective for the management of acute pain (**N**) (**Level II**).
8. 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**).
9. Transdermal fentanyl should not be used in the management of acute pain because of safety concerns and difficulties in short-term dose adjustments needed for titration; furthermore, in most countries, it lacks regulatory approval for use in other than opioid-tolerant patients (**S**) (**Level IV**).

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 drugs (**U**).
- ☑ 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 drug absorption by other routes (**U**).
- ☑ Controlled-release opioid preparations should only be given at set time intervals (**U**).
- ☑ Immediate-release 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**).
- ☑ Neither oral transmucosal fentanyl citrate nor fentanyl buccal tablets should be used in the management of acute pain because of safety concerns and, in most countries, lack of regulatory approval for use in other than opioid-tolerant patients (**N**).

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7. PCA, REGIONAL AND OTHER LOCAL ANALGESIA TECHNIQUES

7.1 PATIENT-CONTROLLED ANALGESIA

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, however, the term PCA is associated with programmable infusion pumps that deliver opioid medications intravenously, although a variety of other methods and routes of delivery (systemic and regional) using opioids as well as other analgesic agents have been described. For epidural PCA see Section 7.2.3; for regional PCA techniques see Section 7.5.1.

7.1.1 Efficacy of intravenous PCA

Analgesia, patient preference and outcomes

IV opioid PCA provides better analgesia than conventional (IM, SC) opioid regimens, although the magnitude of the difference in analgesia is small (8.012 on a pain scale of 0 to 100); opioid consumption is greater; there are no differences in duration of hospital stay or opioid-related adverse effects other than pruritus, which is increased, and patient satisfaction is higher (Hudcova et al, 2006 **Level I**).

> **Note: reversal of conclusions**
>
> This partly reverses the Level I conclusion in the previous edition of this document; earlier meta-analyses had reported no difference in opioid consumption or opioid-related adverse effects

Other information obtained from published cohort studies, case-controlled studies and audit reports only (ie not RCTs) (Dolin & Cashman, 2002 **Level IV**) suggests that IV PCA may be appreciably more effective than intermittent IM opioid analgesia in a 'real life' clinical setting; patients given IM opioid analgesia were more than twice as likely to experience moderate-to-severe pain and severe pain as those given PCA.

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 versus nurse-administered analgesia following cardiac surgery found no difference in analgesia at 24 hours (a period when nursing attention is likely to be higher) but significantly better pain relief with PCA at 48 hours (Bainbridge et al, 2006 **Level I**). In an emergency department setting, IV PCA was as effective as nurse-administered IV bolus doses of opioid (Evans et al, 2005 **Level II**).

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; Macintyre & Schug, 2007; Macintyre & Coldrey, 2008).

A number of studies have shown that PCA provides less effective pain relief compared with epidural analgesia (see Section 7.2).

Cost of PCA

The use of any analgesic technique, even if it is known to provide more effective pain relief, also requires consideration of the cost involved. There are no good, consistent data on the cost-effectiveness 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 events 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 drugs required; nursing time needed is much less (Jacox et al, 1997; Choiniere et al, 1998 **Level II**; Rittenhouse & Choiniere, 1999; Chang et al, 2004 **Level II**). PCA was more cost-effective than epidural analgesia after major abdominal surgery (Bartha et al, 2006).

7.1.2 Drugs used for parenteral PCA

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 side effects between morphine and other opioids commonly used in PCA, although the results of individual studies are inconsistent.

Pethidine

Compared with morphine, pethidine (meperidine) may lead to less effective pain relief on movement (Bahar et al, 1985 **Level II**; Sinatra et al, 1989 **Level II**; Plummer et al, 1997 **Level II**); no difference in nausea and vomiting (Bahar et al, 1985 **Level II**; Stanley et al, 1996 **Level II**; Woodhouse et al, 1996 **Level II**; Plummer et al, 1997 **Level II**); and less sedation (Sinatra et al, 1989 **Level II**) and pruritus (Sinatra et al, 1989 **Level II**; Woodhouse et al, 1996 **Level II**).

Fentanyl

There was no difference between morphine and fentanyl in terms of pain relief (Howell et al, 1995 **Level II**; Woodhouse et al, 1996 **Level II**) or the incidence of most side effects (Howell et al, 1995 **Level II**; Woodhouse et al, 1996 **Level II**); pruritus was more common with morphine (Woodhouse et al, 1996 **Level II**).

Tramadol

Tramadol by PCA had a similar analgesic effect compared with morphine (Erolcay & Yuceyar, 2003 **Level II**; Unlugenc, Vardar et al, 2008 **Level II**), pethidine (Unlugenc, Vardar et al, 2008 **Level II**) and oxycodone (Silvasti et al, 1999 **Level II**). The majority of studies showed that the incidence of nausea and vomiting was no higher than with pure agonist opioids (Silvasti et al, 1999 **Level II**; Erolcay & Yuceyar, 2003 **Level II**; Unlugenc, Vardar et al, 2008 **Level II**). Tramadol also had a lower risk of respiratory depression and less effect on gastrointestinal motor function compared with other opioids (see Section 4.1.2).

Other comparisons

Other comparisons with morphine include hydromorphone (no difference in pain relief or side effects) (Rapp et al, 1996 **Level II**; Hong et al, 2008 **Level II**), oxycodone (no difference in pain relief or side effects) (Silvasti et al, 1998 **Level II)** and piritramide (equally effective and similar side effects) (Dopfmer et al, 2001 **Level II**).

Remifentanil provided at least equivalent analgesia compared with morphine (Kucukemre et al, 2005 **Level II**; Gurbet et al, 2004 **Level II**) and fentanyl PCA (Gurbet et al, 2004 **Level II**) and may be associated with less nausea and vomiting (Kucukemre et al, 2005 **Level II**; Gurbet et al, 2004 **Level II**).

The combination of two opioids in the PCA syringe has also been investigated. There was no difference in pain scores and side effects between fentanyl-morphine and fentanyl PCA (Friedman et al, 2008 **Level II**). Beneficial effects on pain relief and the incidence of pruritus in a comparison of morphine, nalbuphine and varying combinations of the two drugs were dependent on the ratio of drugs used (Yeh et al, 2008 **Level II**). The addition of alfentanil to morphine resulted in no differences in pain relief or adverse effects compared with morphine alone, although patients who received the alfentanil-morphine mixture rated speed of onset and effectiveness of analgesia as better (Ngan Kee et al, 1999 **Level II**). In contrast, compared with tramadol alone, remifentanil added to tramadol improved pain relief, but increased total opioid dose (Unlugenc, Tetiker et al, 2008 **Level II**).

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 side effects (Woodhouse et al, 1999 **Level II**).

Adverse effects of PCA opioids

As noted above and in Section 7.1.1, meta-analyses and individual studies have shown that the risk of side effects is similar for opioids administered by PCA or more traditional routes, regardless of the opioid used.

A review of published cohort studies, case-controlled studies and audit reports only (ie not RCTs), reported the following incidences associated with the use of PCA: respiratory depression 1.2% to 11.5% (depending whether respiratory rate or oxygen saturation were used as indicators), nausea 32%, vomiting 20.7%, and pruritus 13.8% (Cashman & Dolin, 2004 **Level IV**; Dolin & Cashman, 2005 **Level IV**). 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).

In an audit of 700 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'); of the 13 patients (1.86%) reported with respiratory depression, all had respiratory rates of <10 breaths/min and 11 also had sedation scores of 2 (Shapiro et al, 2005 **Level IV**).

The incidence of PCA-related sedation was reduced significantly in patients given concurrent non-steroidal anti-inflammatory drugs (NSAIDs) (Marret et al, 2005 **Level I**).

Adjuvant drugs

Discussion of adjuvant drugs in this section will be confined to those added to the PCA opioid solution. For additional information see Section 4.3.

Antiemetics

Droperidol added to the PCA morphine solution was an effective antiemetic with an NNT of 2.7 for nausea and 3.1 for vomiting (Tramèr & Walder, 1999 **Level I**). Tramèr's group noted no dose-responsiveness with droperidol (Tramèr & Walder, 1999 **Level I**). However, in a comparison of the effects of the addition of 0.5 mg, 1.5 mg and 5 mg droperidol to 100 mg PCA morphine, the smallest dose had no significant antiemetic effect and the 1.5 mg dose was effective against nausea but not vomiting (Culebras et al, 2003 **Level II**). The 5 mg dose significantly reduced both nausea and vomiting, but at the cost of unacceptable sedation, which was not seen at the other doses. In contrast to the NNTs reported by Tramèr et al (Tramèr & Walder, 1999 **Level I**), these results translate to NNTs of 3.7 for nausea and 8.3 for vomiting; as noted, the higher dose increased the risk of sedation (Culebras et al, 2003 **Level II**).

In another study, coadministration of droperidol and morphine via PCA resulted in morphine-sparing and reduced the frequency of postoperative nausea and vomiting (Lo et al, 2005 **Level II**).

Droperidol given separately was as effective as adding droperidol to PCA morphine (Gan et al, 1995 **Level II**). The cost-benefit and risk-benefit of the routine addition of droperidol to PCA opioids must therefore be considered because all patients receive the drug when not all will need it and some patients might receive inappropriately high doses of droperidol.

Evidence of benefit from the addition of 5HT3 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 antiemetics, but not the patients' perception of this or their satisfaction (Cherian & Smith, 2001 **Level II**). However Tramèr's group (Tramèr & Walder, 1999 **Level I**) concluded that 5HT3 receptor antagonist drugs (eg ondansetron) showed no evidence of worthwhile antinauseant effect, although they may be effective for vomiting with an NNT of approximately 5. A more recent 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 et al, 2007 **Level II**). Another study reported a reduction in vomiting with the addition of ondansetron alone to morphine PCA and a lower incidence of nausea with the addition of a combination of ondansetron plus prochlorperazine (Jellish et al, 2009 **Level II**).

Ketamine

In general, concurrent administration of ketamine reduced PCA opioid requirements and the incidence of nausea and vomiting (Bell et al, 2006 **Level I**). However, the same benefit may not be derived from adding ketamine to the PCA opioid solution, although the evidence is conflicting. In the meta-analyses by Bell et al (Bell et al, 2006 **Level I**), six studies are listed where ketamine was added to the PCA opioid and results were mixed; pain was reduced in four of these studies and morphine consumption in three. A more recent study of 352 patients also showed a lack of benefit (Sveticic et al, 2008 **Level II**), but in another, the addition of ketamine to morphine PCA reduced pain scores and the incidence of nausea and vomiting, was opioid-sparing, and led to shorter duration of use of PCA compared with PCA morphine alone (Kollender et al, 2008 **Level II**). In patients after thoracotomy, although the addition of ketamine to PCA morphine did not improve pain relief it was opioid-sparing, and patients in the ketamine group spent less time with oxygen saturation levels <90% and had better forced expiratory volumes (Michelet et al, 2007 **Level II**).

Naloxone

There was no analgesic benefit of adding naloxone to the PCA morphine solution (Sartain et al, 2003 **Level II**; Cepeda et al, 2002 **Level II**; Cepeda et al, 2004 **Level II**); in 'ultra low doses' but not in the higher dose studies, the incidence of nausea and pruritus was decreased (Cepeda et al, 2004 **Level II**).

Other adjuvants

Ketorolac added to morphine (Chen, Wu et al, 2005 **Level II**; Chen et al, 2009 **Level II**) or tramadol (Lepri et al, 2006 **Level II**) PCA did not improve pain relief or alter the incidence of side effects, however it was opioid-sparing and led to earlier return of bowel function after colorectal surgery (Chen et al, 2009 **Level II**).

The addition of lignocaine (lidocaine) to morphine conferred no benefit in terms of pain relief or side effects (Cepeda et al, 1996 **Level II**).

The addition of clonidine to IV PCA morphine resulted in significantly better pain relief for the first 12 hours only and less nausea and vomiting compared with morphine alone; there was no

reduction in morphine requirements (Jeffs et al, 2002 **Level II**). A combination of dexmedetomidine and morphine resulted in significantly better pain relief, a lower incidence of nausea but not vomiting, and significant opioid-sparing compared with morphine alone (Lin et al, 2009 **Level II**).

Magnesium added to morphine was opioid-sparing and led to better pain relief (Unlugenc et al, 2003 **Level II**); added to tramadol it was opioid-sparing but only provided better pain relief for the first 2 hours (Unlugenc et al, 2002 **Level II**).

7.1.3 Program parameters for intravenous PCA

Bolus dose

While the optimal sized bolus dose should provide good pain relief with minimal side 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, Plummer et al, 1989 **Level II**). 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 et al, 1998 **Level II**). However in this study, each dose was infused over 10 minutes, 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 et al, 2004 **Level II**).

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 per hour, even though they could press the PCA button more frequently (Owen, Plummer et al, 1989 **Level II**).

Initial orders for bolus doses should take into account factors such as a history of prior opioid use (see Section 11.7) and patient age (Macintyre & Schug, 2007; Macintyre & Coldrey, 2008); PCA morphine requirements are known to decrease as patient age increases (Macintyre & Jarvis, 1996 **Level IV**; Gagliese et al, 2008 **Level IV**). Subsequent bolus doses may require adjustment according to patient pain reports or the onset of any side 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, Plummer et al, 1989 **Level II**).

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 et al, 2008 **Level IV**). See also Section 1.2.4 for additional information on the relationship between pain relief and psychological factors in PCA.

Lockout interval

The lockout interval is a safety mechanism that limits the frequency of demands made by 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, side effects or anxiety when lockout intervals of 7 or 11 minutes for morphine and 5 or 8 minutes for fentanyl were used (Ginsberg et al, 1995 **Level II**).

Concurrent background (continuous) infusions

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, Szekely et al, 1989 **Level II**; Parker et al, 1991 **Level II**; Parker et al, 1992 **Level II**; Dal et al, 2003 **Level II**). Large audits of adult patients have also shown that the risk of respiratory depression is increased when a background infusion is added (Notcutt & Morgan, 1990 **Level IV**; Fleming & Coombs, 1992 **Level IV**; Schug & Torrie, 1993 **Level III-2**; Sidebotham et al, 1997 **Level IV**). In adults, the routine use of a background infusion is therefore not recommended, although it may be useful in opioid-tolerant patients (see Section 11.7).

Dose limits

Limits to the maximum amount of opioid that can be delivered over a certain period (commonly 1 or 4 hours) can be programmed into most PCA machines. There is no good evidence of any benefit that can be attributed to these limits.

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 & Schug, 2007; Macintyre & Coldrey, 2008). IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy in the treatment of acute sickle cell pain (Rees et al, 2003 **Level II**).

7.1.4 Efficacy of PCA using other systemic routes of administration

Subcutaneous PCA

Data on the effectiveness of SC PCA compared with IV PCA are variable and inconsistent. Both similar (Urquhart et al, 1988 **Level II**; White, 1990 **Level II**; Munro et al, 1998 **Level II**; Bell et al, 2007 **Level II**) and significantly better (Dawson et al, 1999 **Level II**; Keita et al, 2003 **Level II**) pain relief has been reported, as well as the same (Urquhart et al, 1988 **Level II**; Munro et al, 1998 **Level II**; Dawson et al, 1999 **Level II**; Keita et al, 2003 **Level II**) and a higher incidence of nausea and vomiting (White, 1990 **Level II**) or pruritus (Bell et al, 2007 **Level II**). Compared with IV PCA, SC PCA may (Urquhart et al, 1988 **Level II**; White, 1990 **Level II**; Dawson et al, 1999 **Level II**; Bell et al, 2007 **Level II**) or may not (Munro et al, 1998 **Level II**) result in higher opioid use.

Oral PCA

Oral PCA, using a modified IV PCA system, is as effective as IV PCA (Striebel et al, 1998 **Level II**). 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 et al, 2007 **Level IV**).

Intranasal PCA

Patient-controlled intranasal analgesia (PCINA) fentanyl can be as effective as IV PCA (Striebel et al, 1996 **Level II**; Toussaint et al, 2000 **Level II**; Manjushree et al, 2002 **Level II**; Paech et al, 2003 **Level II**), as is butorphanol (Abboud et al, 1991 **Level II**). As would be expected from the data on IN bioavailability of opioids (see Section 6.6.1), higher doses are needed via the IN route

(Manjushree et al, 2002 **Level II**). PCINA pethidine is as effective as IV pethidine, although larger doses are needed (Striebel, Malewicz et al, 1993 **Level II**), and more effective than SC injections of pethidine (Striebel et al, 1995 **Level II**). Diamorphine PCINA (bolus doses of 0.5mg) was less effective than PCA IV morphine (higher bolus doses of 1 mg were used) after joint replacement surgery (Ward et al, 2002 **Level II**) but provided better pain relief in doses of 0.1 mg/kg compared with 0.2 mg/kg IM morphine in children with fractures (Kendall & Latter, 2003).

Transdermal PCA

A number of studies have reported that the iontophoretic fentanyl patient-controlled transdermal system (PCTS) is comparable with standard IV PCA morphine regimens in terms of pain relief and incidence of side effects (Viscusi et al, 2004 **Level II**; Hartrick et al, 2006 **Level II**; Ahmad et al, 2007 **Level II**; Grond et al, 2007 **Level II**; Minkowitz et al, 2007 **Level II**; Viscusi et al, 2007 **Level II**). However, a meta-analysis showed that while fentanyl PCTS provided good pain relief, it may not be as effective as IV morphine PCA. While there was no difference in Patient Global Assessment, significantly more patients in the PCTS group withdrew because of inadequate analgesia (Poon et al, 2009 **Level I**).

Comparison of ease-of-care and satisfaction measures of the two techniques showed that patients, nurses and physiotherapists found the iontophoretic fentanyl PCTS system easier to use than IV PCA and they were more satisfied with PCTS (Hartrick et al, 2006 **Level II**; Gan et al, 2007 **Level IV**; Grond et al, 2007 **Level II**; Minkowitz et al, 2007 **Level II**).

Maximum blood concentrations of fentanyl were the same if the fentanyl PCTS 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 et al, 2005 **Level II**).

7.1.5 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 or the opioid used.

An early prospective study of 4000 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 et al, 1996 **Level IV**). A similar sized prospective survey of 3785 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 et al, 1994 **Level IV**).

The most common of the 5377 PCA-related errors reported from September 1998 to August 2003 and examined by the United States Pharmacopeia (USP) were improper dose/quantity 38.9%, unauthorised drug 18.4%, omission error 17.6% and prescribing error 9.2%. Other errors included wrong administration technique, wrong drug preparation, wrong patient and wrong route (US Pharmacopeia, 2004 **Level IV**).

A much later retrospective analysis of information (from July 2000 to June 2005) reported to a national voluntary medication error-reporting database, showed that PCA-related medication errors continue. Of 919 241 medication errors reported, 9571 (only 1%) were associated with PCA and of these, just 624 were associated with patient harm; the majority of errors occurred during drug administration (Hicks et al, 2008). Of these, 38% were errors in dose or quantity, 17.4% involved an omission, and 17.3% were related to an unauthorised or wrong drug; human factors were the main cause of errors; distractions (37.8%) and inexperienced staff (26.3%) were the leading contributing factors (Hicks et al, 2008).

For more detail on adverse effects due to the opioid administered, equipment used, or operator and patient-related factors, see Sections 7.1.2, 7.1.6 and 7.1.7 respectively.

7.1.6 Equipment

Both programmable PCA pumps and disposable PCA devices are available.

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 drug delivered. In addition, access to the syringe (or other drug 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 drug from the drug reservoir, and antireflux valves to prevent backflow of drug into the IV infusion line (see later).

Disposable PCA devices

There is a variety of disposable PCA devices.

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 & Dunn, 2006). 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 determining the amount of drug the patient has received accurately, the possibility of inaccurate flow rates, and long-term costs (Skryabina & Dunn, 2006). There may also be security issues as the drug reservoirs for these devices are more readily accessible.

Transmucosal PCA devices

Metered-dose PCINA devices are available. The drugs 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, Pommerening et al, 1993) or smaller volume but with smaller doses than commonly used with IV PCA (eg 9 mcg fentanyl/0.18 mL (O'Neil et al, 1997). 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 et al, 2003).

Transdermal PCA devices

The fentanyl PCTS uses a low-intensity electric current to drive the drug from the reservoir through the skin and into the systemic circulation (Banga, 2005). The IONSYS™ device, which is applied to the chest or upper outer arm, delivers a fixed dose of 40 mcg fentanyl over a 10-minute period following a patient demand and allows delivery of up to 6 doses each hour, up to a maximum of 80 doses in 24 hours (Banga, 2005; Koo, 2005). This device must be replaced every 24 hours, was not available in all countries, and was designed for in-hospital use only.

Despite the potential advantages noted under Section 7.1.4, the marketing authority for the fentanyl PCTS was suspended by the European Medicines Agency in November 2008, after corrosion of a component of the system in one batch was detected (European Medicines Agency, 2008). This fault carries the risk of triggering the self-activation of the system, which could lead

to fentanyl overdose; as this problem could not yet be resolved, the system is currently not available.

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-based; examples from a range of the cases reported are given.

While the number of reports of 'run-away' pumps, where the PCA pump unexpectedly delivers an unprescribed dose of drug (Notcutt & Morgan, 1990), has decreased following changes made to pump design, they continue to occur, including a report of spontaneous triggering (Christie & Cranfield, 1998) and of a frayed wire in the demand apparatus leading to triggering as a result of an electrical short circuit (Doyle & Vicente, 2001).

Uncontrolled syphoning of syringe contents when the PCA machine was above patient level has been reported following cracked glass PCA syringes (Thomas & Owen, 1988; ECRI, 1996), failure of a damaged drive mechanism to retain the syringe plunger (Kwan, 1995), improperly secured PCA cassettes (ECRI, 1995) and broken drug cartridge syringe (Doyle & Keebler, 2008). To minimise the risk of syphoning, the use of antisyphon valves is recommended (ECRI, 1996).

Antireflux (one-way) valves are essential if the PCA infusion is not connected to a dedicated IV line. The non-PCA infusion tubing should have an antireflux 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; Rutherford & Patri, 2004).

7.1.7 Patient and staff factors

Patient factors

Patient factors play a role in the effectiveness of PCA as well as complications that can arise from its use: much of the information regarding complications due to patient factors is case-based — examples from a range of the cases reported are given below. Psychological factors that may affect PCA use and efficacy are discussed in Section 1.2.

Education

Few controlled studies have evaluated the influence of information on PCA use. Of 200 patients surveyed who used PCA, approximately 20% were worried that they may become addicted, and 20% and 30% respectively felt that the machine could give them too much drug or that they could self-administer too much opioid (Chumbley et al, 1998 **Level IV**). In a follow-up study, the same authors 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 side effects and assurance that they would not become addicted (Chumbley et al, 2002 **Level II**).

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 side effects; the structured preoperative interview resulted in no benefits (Chumbley et al, 2004 **Level III-2**). Another comparison of structured education versus routine information showed that overall analgesic efficacy, side effects, and recovery times

were not affected by the education program (Lam et al, 2001 **Level II**). 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 et al, 1999 **Level III-2**; Chen, Yeh et al, 2005 **Level III-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 & Larson, 1990; Fleming & Coombs, 1992; Chisakuta, 1993; Ashburn et al, 1994; Sidebotham et al, 1997; Tsui et al, 1997).

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 et al, 2000; Richards et al, 2004), urinary retention (Hodsman et al, 1988), pulmonary embolism (Meyer & Eagle, 1992) and myocardial infarction (Finger & McLeod, 1995). However, appropriate routine patient monitoring should detect changes in pain scores and analgesic consumption enabling identification of such complications.

Nursing and medical staff

Much of the information regarding complications due to nursing and medical staff factors is case-based — examples from a range of the cases reported are given.

As noted above in Section 7.1.5, operator error is a common safety problem related to PCA use (Ashburn et al, 1994; Looi-Lyons et al, 1996; US Pharmacopeia, 2004). 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 et al, 2003).

A number of reports involve the programming of drug concentrations that were lower than the concentration ordered, with the resultant delivery of an excessive amount of opioid leading to respiratory depression and sometimes death (ECRI, 1997; ECRI, 2002). 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 et al, 2003). It has been suggested that drug concentrations should be standardised within institutions to reduce the chance of administration and programming errors (ECRI, 2002).

Some PCA pumps now incorporate dose-error reduction systems that use internal software to guide manual programming by checking programmed doses against preset limits and alerting the programmer to inappropriate dose or continuous infusion settings; preset dosing protocols can also be used, so that 'standard' settings can be programmed for each of the opioids administered (ECRI, 2006).

Inappropriate prescriptions of supplementary opioids (by other routes) and sedative drugs (including some antihistamines) can lead to oversedation and respiratory depression (Ashburn et al, 1994; Tsui et al, 1997; Lotsch et al, 2002).

7.1.8 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 10.6, 11.2, 11.5 and 11.7 respectively.

Key messages

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**S**) (**Level I** [Cochrane review]).
2. Opioid administration by intravenous PCA leads to higher opioid consumption (**R**), a higher incidence of pruritus (**R**), and no difference in other opioid-related adverse effects (**S**) or hospital stay (**S**) compared with traditional methods of intermittent parenteral opioid administration (**Level I** [Cochrane review]).
3. 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**).
4. Patient preference for intravenous PCA is higher when compared with conventional regimens (**U**) (**Level I**).
5. The addition of ketamine to PCA morphine does not improve analgesia or reduce the incidence of opioid-related side effects (**U**) (**Level I**).
6. Iontophoretic fentanyl PCA may not be as effective as intravenous morphine PCA, with more patients withdrawing from studies because of inadequate pain relief (**Level I**).
7. 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**).
8. There is no analgesic benefit in adding naloxone to the PCA morphine solution; however in ultra-low doses the incidence of nausea and pruritus may be decreased (**U**) (**Level II**).
9. The addition of a background infusion to intravenous PCA does not improve pain relief or sleep, or reduce the number of PCA demands (**U**) (**Level II**).
10. Subcutaneous PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
11. Intranasal PCA opioids can be as effective as intravenous PCA (**U**) (**Level II**).
12. The risk of respiratory depression with PCA is increased when a background infusion is used (**U**) (**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 antisyphon valves and in non-dedicated lines, antireflux valves (**U**).

☑ Drug concentrations should be standardised within institutions to reduce the chance of programming errors (**U**).

☑ Operator error remains a common safety problem (**N**).

7.2 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 and sometimes trauma, and in parturients.

7.2.1 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.

However, the consistent 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, it provided better pain relief than parenteral opioid administration (Werawatganon & Charuluxanun, 2005 **Level I**; Wu et al, 2005 **Level I**; Guay, 2006 **Level I**; Nishimori et al, 2006 **Level I**; Marret et al, 2007 **Level I**).

One meta-analysis of systemic opioids via PCA versus epidural analgesia concluded 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. The epidural group had a lower incidence of nausea/vomiting and sedation, but a higher incidence of pruritus, urinary retention and motor block (Wu et al, 2005 **Level I**). Another meta-analysis reviewed studies looking at the benefits of epidural analgesia in addition to general anaesthesia (Guay, 2006 **Level I**). It included a wide variety of surgical procedures and epidural regimens and reported a reduction in a range of adverse outcomes with epidural analgesia including reduced rate of arrhythmias, earlier extubation, reduced intensive care unit (ICU) stay, reduced stress hormone, cortisol and glucose concentrations as well as reduced incidence of renal failure, when local anaesthetics were used.

Improved pain relief with epidural local anaesthetic drugs led to increased PaO_2 levels and a decreased incidence of pulmonary infections and pulmonary complications overall when compared with systemic opioids (Ballantyne et al, 1998 **Level I**). Similar results were confirmed in a subsequent meta-analysis; however, it is of note that from 1971 to 2006 the baseline risk of pneumonia decreased from 34% to 12% in the opioid group, but remained at 8% in the epidural group, suggesting a decrease in relative benefit of epidural analgesia over time (Popping et al, 2008 **Level I**).

The benefits of epidural analgesia were confirmed when used in patients undergoing abdominal surgery. After a variety of different types of intra-abdominal surgery, pain relief was better but pruritus was also noted to be more likely with epidural analgesia than with PCA opioids (Werawatganon & Charuluxanun, 2005 **Level I**). The majority of trials included in the latter two reviews used thoracic epidural analgesia (TEA) with a local anaesthetic/opioid infusion.

After abdominal aortic surgery and in comparison with systemic opioid administration, epidural analgesia resulted in significantly lower pain scores in the first 3 postoperative days, and reduced duration of intubation and ventilation, rates of cardiovascular (CV) complications, myocardial infarction, acute respiratory failure, gastrointestinal (GI) complications and renal insufficiency (Nishimori et al, 2006 **Level I**). Benefits were found in particular when thoracic epidural catheters were used, but these did not translate into reduced mortality.

After colorectal surgery, epidural analgesia in comparison to systemic opioid analgesia reduced pain scores and duration of ileus, but had no effect on hospital stay; rates of pruritus,

urinary retention and hypotension were increased (Marret et al, 2007 **Level I**). A large retrospective cohort study of 12 817 patients after elective colectomy reported that postoperative epidural analgesia significantly reduced 7-day (OR 0.35) and 30-day (OR 0.54) mortality (Wu, Rowlingson et al, 2006 **Level III-2**).

After lung resection, postoperative epidural analgesia reduced 7-day (OR 0.39) and 30-day (OR 0.53) mortality significantly in a retrospective cohort study of 3500 patients (Wu, Sapirstein et al, 2006 **Level III-2**). TEA in patients after lobectomy resulted in better pain relief and pulmonary function compared with IV morphine (Bauer et al, 2007 **Level II**). When started preoperatively in comparison to postoperatively, TEA reduced the severity of acute post-thoracotomy pain, but not the incidence of chronic pain (Bong et al, 2005 **Level I**).

High TEA used for coronary artery bypass graft (CABG) surgery, resulted 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 were no differences in mortality or the rate of myocardial infarction (Liu et al, 2004 **Level I**). A later study confirmed better pain relief using TEA (continuous infusion) in CABG patients compared with IV morphine PCA, with improved pulmonary function for the first 2 days and decreased atelectasis (Tenenbein et al, 2008 **Level II**); another reported no difference in analgesia, morbidity or pulmonary function when patient-controlled TEA was compared with IV PCA (Hansdottir et al, 2006 **Level II**). High TEA also improved left ventricular function (Schmidt et al, 2005 **Level III-3**; Jakobsen et al, 2009 **Level III-3**) and myocardial oxygen availability (Lagunilla et al, 2006 **Level II**) in patients with ischaemic heart disease prior to CABG surgery, and partly normalised myocardial blood flow in response to sympathetic stimulation (Nygard et al, 2005 **Level III-3**). However, epidural analgesia in patients undergoing CABG surgery has not been shown to improve ischaemic outcome (Barrington, Kluger et al, 2005 **Level II**).

Continuous TEA compared with continuous intrathecal thoracic analgesia after abdominal cancer surgery resulted in similar efficacy and adverse effects (Mercadante et al, 2008 **Level II**).

Thoracic epidural analgesia in combination with NSAIDs and IV nutritional support after major abdominal surgery has been shown to prevent protein loss compared with epidural analgesia alone, or PCA with or without nutritional support (Barratt et al, 2002 **Level II**). Similarly, after colonic surgery, TEA increased the anabolic effect of amino acid infusions in diabetic patients (Lugli et al, 2008 **Level II**) and reduced whole body protein breakdown (Lattermann et al, 2007 **Level II**). However, although epidural anaesthesia/analgesia reduced insulin resistance in comparison to general anaesthesia/systemic analgesia in patients who were insulin resistant preoperatively, it did not affect insulin resistance in those who had no preoperative insulin resistance (Donatelli et al, 2007 **Level II**).

Lumbar epidural analgesia is widely used to provide analgesia after orthopaedic and vascular operations to the lower limbs and urological and other pelvic surgery.

After hip or knee replacement, epidural analgesia provides better pain relief than parenteral opioids, in particular with movement (Choi et al, 2003 **Level I**). Although epidural infusions of local anaesthetics alone or combined with opioids are better than opioids alone, there is insufficient evidence to make conclusions about other outcomes. Used in vascular surgery, lumbar epidural analgesia improves outcome by reducing incidence of graft occlusion (Tuman et al, 1991 **Level II**; Christopherson et al, 1993 **Level II**). However, these findings have not been confirmed by other investigators in retrospective reviews (Pierce et al, 1997 **Level IV**; Schunn et al, 1998 **Level IV**).

Level of administration

Thoracic epidural analgesia 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 were not consistent with lumbar administration (Steinbrook, 1998; Jorgensen et al, 2000 **Level I**). If epidural analgesia was extended for more than 24 hours, a further benefit was a significant reduction in the incidence of postoperative myocardial infarction (Beattie et al, 2001 **Level I**). Benefits of epidural analgesia after abdominal aortic surgery were found in particular with TEA (Nishimori et al, 2006 **Level I**). A comparison of TEA and lumbar epidural administration in patients undergoing gynaecological surgery showed that TEA provided better pain relief only when the incision extended above the umbilicus and led to less motor block but more pruritus (Richman et al, 2007 **Level II**).

In patients with multiple traumatic rib fractures, provision of TEA with local anaesthetics has been shown to reduce the duration of ventilation compared with other forms of analgesia (including lumbar epidural analgesia); although mortality and length of ICU stay was not different in pooled analysis of all routes of epidural administration versus parenteral opioids, and hypotension was more frequent in the epidural groups when TEA with local anaesthetics was used (Carrier et al, 2009 **Level I**). In one study, the risk of nosocomial pneumonia was reduced by TEA compared with parenteral opioids (Bulger et al, 2004 **Level II**).

7.2.2 Drug used for epidural analgesia

Differences in effects and adverse effects can be found with the local anaesthetics, opioids and various adjuvant drugs used in epidural analgesia.

Local anaesthetics

For epidural infusions, dose-ranging studies established that 0.2% ropivacaine was a suitable concentration (Scott et al, 1995 **Level II**; Schug et al, 1996 **Level II**). 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 5.1.2.

Opioids

Opioids alone via the epidural route seem to be of limited benefit. In particular, when administered via a thoracic approach, opioids failed to demonstrate any advantage over parenteral opioids except for a slight reduction in the rate of atelectasis (Ballantyne et al, 1998 **Level I**); there is no benefit on bowel recovery (Steinbrook, 1998; Jorgensen et al, 2000 **Level I**). On the basis of the available studies, the benefits of administering lipophilic opioids alone by the epidural route would 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 et al, 2001 and Section 5.2.1).

For information on the epidural use of morphine, extended-release morphine, pethidine, fentanyl, alfentanil, sufentanil, diamorphine and hydromorphone see Section 5.2.1.

Local anaesthetic-opioid combinations

Combinations of low concentrations of local anaesthetic agents and opioids have been shown to provide consistently superior pain relief compared with either of the drugs alone (Curatolo et al, 1998 **Level I**). Addition of fentanyl to a continuous epidural infusion of ropivacaine reduced the rate of regression of sensory block (Kanai et al, 2007 **Level II**) and decreased the discontinuation of postoperative epidural infusion due to lack of efficacy (Scott et al, 1999 **Level II**).

For more information on the epidural use of different local anaesthetic-opioid drug combinations see Section 5.2.1.

Adjuvant drugs

The efficacy of adding of adjuvant drugs such as adrenaline (epinephrine), clonidine, ketamine, midazolam, neostigmine and magnesium to solutions used for epidural analgesia has also been investigated (see Section 5.3).

7.2.3 Patient-controlled epidural analgesia

The use of patient-controlled epidural analgesia (PCEA) has become increasingly popular; it is based on similar concepts as for other patient-controlled techniques.

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) provided better pain relief with rest and with activity than PCA opioids, but that analgesia with a continuous epidural infusion was superior to PCEA, although the incidence of nausea, vomiting and motor block was higher (Wu et al, 2005 **Level I**).

However, results from other more recent studies are conflicting. In a large study looking specifically at patients 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 et al, 2007 **Level II**). In contrast, comparisons of PCEA and continuous epidural infusions for pain relief after thoracotomy using both high (5 mg/mL) and low (1.5 mg/mL) 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 blockade (Dernedde et al, 2006 **Level II**).

For pain relief during labour, a comparison of demand dose-only PCEA, PCEA with a continuous infusion, and a continuous epidural infusion only during labour, showed that dose-only PCEA resulted in less total epidural dose compared with the other modalities; no differences were noted with respect to pain scores, motor block, duration of labour, number of staff interventions, delivery outcome, and maternal satisfaction score (Vallejo et al, 2007 **Level II**).

Concurrent background (continuous) infusions

The addition of a continuous background infusion to PCEA using bupivacaine and fentanyl following gastrectomy resulted in significantly better dynamic pain scores, higher total doses and a greater incidence of pruritus than PCEA-bolus dose only (Komatsu et al, 1998 **Level II**). The use of a night-time-only infusion with PCEA bupivacaine-fentanyl, also in postgastrectomy patients, resulted in better sleep, but total cumulative doses were similar and pain scores were only better in the morning of the second postoperative day (Komatsu et al, 2001 **Level II**).

However, pain relief is not always improved. After lower abdominal surgery there was no difference in pain scores, but higher total cumulative doses and incidence of side effects when a background infusion was added to PCEA with ropivacaine and fentanyl (Wong et al, 2000 **Level II**). The addition of a background infusion to bupivacaine-fentanyl PCEA did not improve pain relief after pelvic reconstruction (Nolan et al, 1992 **Level II**).

In a systematic review of PCEA in labour analgesia, the use of a continuous background epidural infusion combined with PCEA resulted in improved maternal analgesia and reduced unscheduled clinician interventions (Halpern & Carvalho 2009, **Level I**).

Drugs used in postoperative patient-controlled epidural analgesia

The drugs used for PCEA are the same as those used for continuous epidural infusions (see also Section 5). Generalisations about the efficacy of different drugs and drug combinations administered via PCEA are difficult because of the wide variety of analgesic agents and concentrations used in the various studies.

7.2.4 Adverse effects

Neurological injury

Permanent neurological damage is the most feared complication of epidural analgesia.

A retrospective survey from Sweden put the risk of a severe neurological complication after obstetric epidural analgesia at 1:25 000 and for all other patients at 1:3600; 67% of events resulted in permanent neurological deficit (Moen et al, 2004 **Level IV**). It also identified osteoporosis as a previously neglected risk factor. A review of data from publications reporting adverse events after obstetric epidural analgesia reported a risk estimate of 1: 240 000 for persistent neurological injury and 1:6700 for transient (resolved within one year) neurological symptoms (Ruppen et al, 2006a **Level IV**).

A review of data from published studies of the risk of neurological injury associated with epidural and other regional anaesthesia and analgesia differentiated between the risk of permanent (neurological deficit lasting more than 12 months) neurological injury and transient neuropathy (Brull et al, 2007 **Level IV**). This review focussed on adverse neurological sequelae associated with the technique and did not address the overall risk of epidural haematoma or abscess, nor did it differentiate between obstetric and non-obstetric neuraxial block outcomes. The incidence of transient neuropathy (radiculopathy) after epidural anaesthesia was estimated to be 2.19:10 000. The risk of permanent neurological injury was less and the incidences reported in the studies included in this review ranged from 0 to 7.6:10 000. The rates of paraplegia and cauda equina syndrome associated with epidural anaesthesia were estimated to be 0.09:10 000 and 0.23:10 000 respectively (Brull et al, 2007 **Level IV**).

A project in the United Kingdom assessed the incidence of neurological complications in an estimated 97 925 adult patients with perioperative epidural catheters (Cook et al, 2009 **Level IV**). Depending on the inclusion or exclusion of cases with unlikely causation, pessimistic and optimistic data 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 5800) 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 8100). 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; 1 in 100,000) in the optimistic model.

The worst-case estimate for persistent neurological injury after epidural anaesthesia for vascular and cardiothoracic surgery is 1 in 4600 based on a meta-analysis of case series with an event rate of zero in 14 105 patients; the risk of transient neurological injury was 1 in 1 700 (Ruppen et al, 2006b **Level IV**).

Audit data from a single (non-obstetric) tertiary institution showed that 8210 epidural catheters were inserted over a 16-year period for postoperative pain relief and that two spinal haematomas and six epidural abscesses were diagnosed during this time; only one patient (with an epidural abscess) required surgical decompression and no patient suffered any long-term neurological loss (Cameron et al, 2007 **Level IV**).

The incidence of transient neuropathy after epidural analgesia in large case series was in the range of 0.013 to 0.023% (Xie & Liu, 1991 **Level IV**; Tanaka et al, 1993 **Level IV**; Auroy et al, 1997 **Level IV**).

Epidural haematoma

A major concern is the development of an epidural haematoma with subsequent, potentially permanent, spinal cord injury. A review including case series involving over 1 335 000 patients with epidural analgesia reported seven cases of haematoma (0.0005%) (Wulf, 1996 **Level IV**). On the basis of this case series the possible incidence is in the order of 1 in 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 in 10 300 (Moen et al, 2004 **Level IV**). An even higher incidence of epidural haematoma (1:3100) has been estimated for epidural analgesia in association with inappropriate low molecular weight heparin (LMWH) dose regimens (Horlocker et al, 2003) (see Section 7.4).

A review of data from publications reporting adverse events after obstetric epidural analgesia reported a risk estimate of 1:168 000 for epidural haematoma (Ruppen et al, 2006a **Level IV**).

A meta-analysis of the risks of epidural haematoma associated with epidural anaesthesia/ analgesia in cardiac, vascular and thoracic surgery patients concluded that the maximum risks of epidural haematoma were 1:1700, 1:1700 and 1:1400 respectively (Ruppen et al, 2006b **Level IV**). However, this was a calculated risk only; there were actually no cases of epidural haematoma reported in the studies (14 105 patients) used in this analysis.

In another analysis of a case series after cardiac surgery, the risk of epidural haematoma was calculated at 1:12 000 (95% CI 1:2100 to 1:68 000) — comparable to an obstetric population. 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) (Bracco & Hemmerling, 2007 **Level IV**).

Early diagnosis and, if indicated, immediate decompression (less than 8 hours after the onset of neurological signs) increases the likelihood of partial or good neurological recovery (Horlocker et al, 2010 **Level IV**).

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% to 0.05% (Kindler et al, 1996 **Level IV**; Rygnestad et al, 1997 **Level IV**; Wang et al, 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 days; no infection occurred in any patient whose catheter was in situ for less than 2 days and the majority of patients were immunocompromised (Wang et al, 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 et al, 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 et al, 2004 **Level IV**).

Audit data from the study referred to above (Cameron et al, 2007 **Level IV**) showed that of the 8210 patients with epidural catheters over the period of 16 years, 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 their 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. If the diagnosis of epidural abscess can be made before the onset of any neurological deficit, conservative treatment (antibiotics only) may be effective (Cameron et al, 2007). 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 events after obstetric epidural analgesia reported a risk estimate of 1: 145 000 for epidural space infection (Ruppen et al, 2006a **Level IV**).

Bacterial colonisation of epidural catheter tips is reported to occur in 0% to 28% of patients. (Simpson et al, 2000 **Level IV**; Steffen et al, 2004 **Level IV**; Mishra et al, 2006 **Level IV**; Yuan et al, 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 & Litton, 2006 **Level I**).

An *in vitro* comparison of the antibacterial activity of drugs used in epidural solutions showed that the minimal inhibitory concentration of bupivacaine for *Staphylococcus aureus*, *Enterococcus faecalis* and *Escherichia coli* (growth of *Pseudomonas aeruginosa* was not affected at any of the concentrations investigated) was at concentrations between 0.125% and 0.25%; levobupivacaine and ropivacaine showed no activity against *Staphylococcus aureus*, *Enterococcus faecalis* and *Pseudomonas aeruginosa*, even at the highest concentrations tested, and minimal activity against *Escherichia coli* (minimum inhibitory concentrations 0.5% and 1% respectively); and the addition of fentanyl, clonidine and adrenaline did not improve antibacterial activity (Coghlan et al, 2009 **Level III-2**).

A comprehensive review of infectious complications associated with central neuraxial and peripheral nerve blockade, including epidemiology, factors affecting bacterial colonisation of the epidural catheter as well as use in febrile, infected and immunocompromised patients was published by Horlocker and Wedel (Horlocker & Wedel, 2008).

Respiratory depression

The incidence of respiratory depression with epidural 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% to 1.9%) to 15.1 (5.6% to 34.8%) using respiratory rate and oxygen saturation, respectively, as indicators (see Section 4.1.3 for comments on respiratory rate as an unreliable indicator of respiratory depression); this was very similar to the incidence reported for PCA (Cashman & Dolin, 2004 **Level IV**).

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% to 10.2%) (Cashman & Dolin, 2004 **Level IV**). It is often the result of hypovolaemia (Wheatley et al, 2001).

Postdural puncture headache

Headache following dural puncture may occur with an incidence of 0.4% to 24%. Postdural puncture headache (PDPH) is classically postural in nature and is more common in patients

under 50 years of age and in the parturient. Up to 90% of cases improve spontaneously within 10 days (Candido & Stevens, 2003).

For discussion of possible prevention and treatment see Section 9.6.5.

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. Intolerable side effects may also be an indication for premature discontinuation. In a large prospective audit, 22% of patients had premature termination of postoperative epidural infusions: the most common causes were dislodgement (10%) and inadequate analgesia (3.5%), sensory or motor deficit (2.2%). Most of these failures occurred on or after postoperative day 2 (Ballantyne et al, 2003 **Level IV**). These outcomes supported similar findings by Burstal et al (Burstal et al, 1998 **Level IV**) and reinforce the need for strategies to support epidural analgesia as part of a multimodal approach to acute pain management.

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 (Holte & Kehlet, 2001 **Level I**).

Key messages

1. 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 (**N**) (**Level I** [Cochrane]).
2. For all types of surgery, epidural analgesia provides better postoperative pain relief compared with parenteral (including PCA) opioid administration (**S**) (**Level I** [Cochrane review]); except epidural analgesia using a hydrophilic opioid only (**N**) (**Level I**).
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 IV opioid analgesia (**N**) (**Level I**).
4. Epidural local anaesthetics improve oxygenation and reduce pulmonary infections and other pulmonary complications compared with parenteral opioids (**S**) (**Level I**).
5. Thoracic epidural analgesia improves bowel recovery after abdominal surgery (including colorectal surgery (**S**) (**Level I**).
6. Thoracic epidural analgesia extended for more than 24 hours reduces the incidence of postoperative myocardial infarction (**U**) (**Level I**).
7. Epidural analgesia is not associated with increased risk of anastomotic leakage after bowel surgery (**U**) (**Level I**).
8. Chlorhexidine-impregnated dressings of epidural catheters in comparison to placebo- or povidone-iodine-impregnated dressings reduce the incidence of catheter colonisation (**N**) (**Level I**).
9. The use of continuous background epidural infusion combined with PCEA results in improved maternal analgesia and reduced unscheduled clinician interventions (**N**) (**Level I**).
10. Thoracic epidural analgesia reduces need for ventilation in patients with multiple rib fractures (**S**) (**Level I**) and reduces incidence of pneumonia (**U**) (**Level II**).

11. 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**).
12. The risk of permanent neurological damage in association with epidural analgesia is very low; the incidence is higher where there have been delays in diagnosing an epidural haematoma or abscess (**S**) (**Level IV**).
13. Immediate decompression (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 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 (**N**).

7.3 Intrathecal analgesia

7.3.1 Drugs used for intrathecal analgesia

Local anaesthetics

Local anaesthetics given intrathecally provide only 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). See also Section 5.1.3.

Opioids

Intrathecal opioids have been used for surgical procedures ranging from lower limb orthopaedic surgery to CABG because of their ability to provide prolonged postoperative analgesia following a single dose. Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal intrathecal doses (Hodgson et al, 1999 **Level IV**).

Intrathecal morphine produces analgesia lasting 12 hours or more. Side effects include respiratory depression, nausea, vomiting and pruritus. Early clinical studies used very high intrathecal morphine doses (ie 0.5 mg or more), 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 side effects or analgesia (Meylan et al, 2009 **Level I**). A meta-analysis comparing intrathecal morphine doses of less than 300 mcg, equal to or greater that 300 mcg, and placebo reported a greater risk of respiratory depression with the higher doses of morphine (there was no increased risk with lower morphine doses) and while the incidence of pruritus was increased for all doses, the risk of nausea and vomiting was increased only in those patients given less than 300 mcg morphine (Gehling & Tryba, 2009 **Level I**).

A prospective study of 5969 patients given intrathecal morphine (200 to 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 hours. The incidence of pruritus was 37%, nausea and vomiting 25% and respiratory depression 3% ($PaCO_2$ > 50 mmHg and/or respiratory rate <8) (Gwirtz et al, 1999 **Level IV**).

In patients having abdominal, cardiothoracic or spinal surgery, intrathecal morphine (100 to 500 mcg) reduced pain scores by 1 to 2 cm (using a 10 cm visual analogue scale) for at least 24 hours following the procedure, with morphine-sparing being more pronounced after abdominal than cardiothoracic surgery (Meylan et al, 2009 **Level I**). Intrathecal morphine 50 to 200 mcg ± clonidine after prostatic surgery (Brown et al, 2004 **Level II**), 300 mcg after colorectal surgery (Beaussier et al, 2006 **Level II**), and 500 mcg plus fentanyl 150 mcg after liver resection (Roy et al, 2006 **Level II**) also resulted in better analgesia and lower opioid requirements than morphine PCA during the first 24 hours postoperatively. After CABG surgery, intrathecal morphine reduced systemic morphine use and global pain scores, but increased pruritus; there were no significant effects on mortality, myocardial infarction, dysrhythmias, nausea and vomiting, or time to tracheal extubation (Liu et al, 2004 **Level I**).

Compared with a continuous epidural infusion of ropivacaine after liver resection, patients given intrathecal morphine 200 mcg had higher IV PCA opioid requirements in the postoperative period and more nausea and pruritus; there was no difference in pain relief (De Pietri et al, 2006 **Level II**).

For comparisons of different opioids and doses used for intrathecal analgesia see Section 5.2.1.

Side effects

Typical side effects of intrathecal opioids include nausea and vomiting, pruritus and delayed respiratory depression. The definition of 'respiratory depression' in different investigations often lacks uniformity with a quarter of the studies cited in a review using respiratory rate as the primary marker (Ko et al, 2003). Patients may be hypoxic or hypercapnic with a normal respiratory rate (Bailey et al, 1993 **Level IV**), while others may be able to maintain normocarbia with a lower respiratory rate (Boezaart et al, 1999 **Level II**). 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 et al, 1993 **Level IV**); although desaturation itself is a late indicator when supplemental oxygen is being administered (Shapiro et al, 2005 **Level IV**). See Section 4.1 for the use of sedation as a better clinical early indicator of respiratory depression.

Respiratory depression occurs in up to 1.2% to 7.6% of patients (Meylan et al, 2009 **Level I**) given intrathecal morphine. When measured in opioid-naive volunteers, respiratory depression peaked at 3.5 to 7.5 hours following intrathecal morphine at 200 to 600 mcg doses (Bailey et al, 1993 **Level IV**). Volunteers given 600 mcg had significant depression of the ventilatory response to carbon dioxide up to 19.5 hours later.

When combined with local anaesthetic for analgesia following Caesarean section, the rate of respiratory depression with intrathecal opioids (all opioids and all doses) was low and not significantly different from controls, with a NNH of 476 for respiratory depression (Dahl et al, 1999 **Level I**). In patients following major surgery, the incidence of respiratory depression was increased with intrathecal morphine over control treatment (IV PCA morphine) (OR 7.86; 95% CI 1.54 to 40.3) (Meylan et al, 2009 **Level I**). Clinically detected respiratory depression in the 24 hours following 0.15 mg intrathecal morphine for Caesarean section was noted in 0.26% of a large sample (Kato et al, 2008 **Level IV**).

Pruritus is common after intrathecal morphine, being reported in up to 37% of patients (Gwirtz et al, 1999 **Level IV**), although the number requiring treatment was lower (5.1%). This rate was significantly higher than that for patients receiving IV PCA morphine (OR 3.85; 95% CI 2.40 to 6.15) (Meylan et al, 2009 **Level I**). Pruritus can be difficult to treat and a variety of agents have been used including low dose naloxone, nalbuphine, ondansetron, propofol and antihistamines. The itch is thought to be caused by stimulation of spinal and supraspinal mu-opioid receptors. Nalbuphine (Charuluxananan et al, 2003 **Level II**) and ondansetron (Charuluxananan et al, 2003 **Level II**; Tzeng et al, 2003 **Level II**; Pirat et al, 2005 **Level II**) were effective in reducing spinal opioid-induced pruritus, although this has not been consistently reported (Sarvela et al, 2006 **Level II**; Siddik-Sayyid et al, 2007 **Level II**).

Postoperative nausea and vomiting (PONV) is also common after intrathecal morphine with incidences reported at 30% and 24% respectively, although this rate was similar to IV PCA morphine (Meylan et al, 2009 **Level I**). Ondansetron or scopolamine was equally effective in reducing emesis with intrathecal morphine analgesia for Caesarean section, although scopolamine use was associated with more anticholinergic side effects (Harnett et al, 2007 **Level II**). The combination of ondansetron with either dexamethasone or droperidol had a better antiemetic effect after gynaecological surgery compared with droperidol plus dexamethasone (Sanchez-Ledesma et al, 2002 **Level II**); although dexamethasone plus droperidol was superior to either alone (Wu et al, 2007 **Level II**).

In parturients, reactivation of oral herpes simplex labialis was more frequent (38%) following intrathecal morphine for labour analgesia than IV PCA morphine (16.6%) (Davies et al, 2005 **Level II**).

Adjuvant drugs

A variety of adjuvant drugs has been used with intrathecal analgesia, including clonidine, ketamine, neostigmine and midazolam. Many drugs are not licensed for use as spinal analgesic agents; however adequate evidence from the literature may make their use acceptable. For more detail see Section 5.3.

7.3.2 Combined spinal-epidural versus epidural analgesia in labour

Combined spinal epidural (CSE) analgesia provided faster onset of analgesia compared with epidural analgesia. However, as CSE did not improve satisfaction or mobilisation, and increased the risk of pruritus, clinical advantages over epidural analgesia (either traditional or low dose) are limited (Simmons et al, 2007 **Level I**) (see Section 11.1). Traditional (higher-dose) epidural analgesia, unlike low-dose epidurals, was associated with increased urinary retention compared with CSE (Simmons et al, 2007 **Level I**).

Key messages

1. Intrathecal morphine offers improved analgesia and opioid-sparing for up to 24 hours especially following abdominal surgery (**S**) (**Level I**).
2. Intrathecal morphine doses of 300 mcg or more increase the risk of respiratory depression (**N**) (**Level I**).
3. After major surgery, the incidence of respiratory depression and pruritus is higher with intrathecal morphine compared with IV PCA opioids, but there is no difference in the incidence of nausea and vomiting (**N**) (**Level I**).

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

☑ Clinical experience with morphine, fentanyl and sufentanil has shown no neurotoxicity or behavioural changes at normal clinical intrathecal doses (**U**).

☑ The absence of consistent dose-responsiveness to the efficacy of intrathecal opioids or the adverse event rate, suggests that the lowest effective dose should be used in all circumstances (**N**).

7.4 Regional analgesia and concurrent anticoagulant medications

7.4.1 Neuraxial blockade

The low event rate of epidural haematoma makes RCTs and subsequent evidence-based statements impossible. Information comes only from case reports and case series. An American Society of Regional Anesthesia and Pain Medicine (ASRA&PM) Practice Advisory publication provides a good overview of and guidance on neurological complications in regional anaesthesia (Neal et al, 2008 **Level IV**). The ASRA&PM guidelines on regional anaesthesia in patients receiving antithrombotic or thrombolytic therapy have also been updated (Horlocker et al, 2010).

Such information suggests that the incidence is possibly smaller than that of spontaneous epidural haematoma. Between 1962 and 1992, 326 case reports of spontaneous epidural haematoma were published (Schmidt & Nolte, 1992), while between 1966 and 1996 only 51 cases of epidural haematoma following epidural anaesthesia or analgesia were reported (Wulf, 1996).

Anticoagulation (48% of cases) was the most important risk factor for epidural haematoma following insertion of an epidural needle/catheter, followed by coagulopathy (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 low molecular weight heparin (LMWH) regimens in the USA, where the incidence was reported to be 1 in 3,000 (Horlocker et al, 2003).

In view of the increased risk of epidural haematoma associated with the concurrent use of epidural analgesia and anticoagulants, ASRA&PM published updated evidence-based guidelines on regional anaesthesia in patients receiving antithrombotic or thrombolytic therapy (Horlocker et al, 2010). These statements have to be seen as 'a panel of experts' best faith efforts to offer reasonable pathways for patient management' (Bergqvist et al, 2003) to provide safe and quality patient care while allowing for clinical differences based on individual situations. It is recognised that variances from recommendations outlined in the ASRA&APM guidelines 'may be acceptable based on the judgement of the responsible anesthesiologist' (Horlocker et al, 2010). That is, they will not substitute for an individual risk/benefit assessment of every patient by the individual anaesthetist.

The most relevant statements are summarised as follows (Horlocker et al, 2010):

Antiplatelet medications — NSAIDs 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 COX-2 inhibitors should be considered. Recommended time intervals between discontinuation of other antiplatelet medications and neuraxial blockade

are 4 to 8 hours for eptifibatide and tirofiban, 24 to 48 hours for abciximab, 7 days for clopidogrel and 14 days for ticlopidine.

Unfractionated SC heparin — thromboprophylaxis with SC heparin given *twice-daily* is not a contraindication to neuraxial blockade. 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 days of heparin therapy. Epidural catheters should be removed a minimum of 6 hours after the last heparin dose and not less than 2 hours 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 a day, has not yet been established.

Unfractionated IV heparin — intraoperative anticoagulation with IV heparin should start no sooner that 1 hour after placement of the epidural or spinal needle. Epidural catheters should be removed 2–4 hours after the last heparin dose. A bloody tap may increase the risk, but there are insufficient data to support cancellation of a case. Careful patient monitoring should be continued postoperatively.

Low molecular weight heparin — Epidural catheter placement should occur at least 10–12 hours after standard prophylactic *once-daily* LMWH doses. The first postoperative dose of LMWH dose should be given 6 to 8 hours after surgery and subsequent doses every 24 hours after that. The epidural catheter should be removed at least 10–12 hours after the last dose of LMWH and the next dose should not be given until at least 2 hours after removal. Concurrent administration of other drugs that may affect haemostasis (eg antiplatlet drugs) should be avoided.

Epidural catheters should be removed at least 2 hours before *twice-daily* LMWH dose regimens are started.

Oral anticoagulants (warfarin) — Established warfarin therapy should be discontinued at least 4 to 5 days prior to neuraxial blockade and the INR normalised. Preoperative initiation of warfarin therapy requires an INR check prior to neuraxial blockade if a single dose of warfarin 5 mg was given more than 24 hours preoperatively or a second dose was given. INR should also be checked prior to removal of indwelling epidural catheters if warfarin was administered more than 36 hours preoperatively. An INR < 1.5 is a value estimated to be a safe level for removal, while an INR > 3 requires withholding or reducing warfarin therapy before the catheter is removed.

Fibrinolysis and thrombolysis — Patients receiving fibrinolytic or thrombolytic drugs should not undergo neuraxial blockade except in exceptional circumstances; no data are available on a safe time interval after use of such drugs. 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.

Herbal therapy — Although garlic, ginkgo and ginseng have effects on haemostasis, there are currently no specific concerns about their use with neuraxial blockade.

New anticoagulants — The situation with regard to the newer anticoagulants remains unclear. Recommendations are to avoid neuraxial techniques with thrombin inhibitors present and to use extreme caution in association with fondaparinux, avoiding indwelling catheters.

Recommendations for newer anticoagulants and antiplatelet drugs are also discussed in other reviews (Vitin et al, 2008; Rosencher et al, 2007; Kopp & Horlocker, 2008).

7.4.2 Plexus and other peripheral regional blockade

Significant blood loss rather than neurological deficit seems to be the main risk when plexus or other regional blocks are performed in patients taking anticoagulant medications (Horlocker et al 2003). However, a case series of bleeding complications associated with lumbar plexus blocks and, femoral and sciatic catheters and perioperative anticoagulants suggests that caution is appropriate (Bickler et al, 2006 **Level IV**; Horlocker et al, 2003). The previously quoted evidence-based ASRA&PM guidelines conclude that recommendations for neuraxial block be followed for patients receiving deep plexus or peripheral blocks (Horlocker et al, 2010)

Key messages

1. Anticoagulation is the most important risk factor for the development of epidural haematoma after neuraxial blockade (**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**).

7.5 Other regional and local analgesic techniques

7.5.1 Continuous peripheral nerve blockade

Continuous peripheral nerve blockade (CPNB) extends the duration of postoperative analgesia beyond the finite period that single injection techniques provide. Important technical issues include the technique used for nerve location, the type of continuous catheter equipment, and local anaesthetic infusion choice and management.

Compared with opioid analgesia, CPNB (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as the incidence of nausea, vomiting, pruritus and sedation (Richman et al, 2006 **Level I**).

Compared with general anaesthesia, peripheral nerve block (PNB) was associated with increased induction time, improved analgesia, a decreased requirement for opioids in the postanaesthesia care unit (PACU); but there was no significant reduction in PACU discharge time (Liu et al, 2005 **Level I**). However, it is not clear what proportion of patients received single-shot versus CPNB.

Upper limb

Interscalene

Continuous interscalene analgesia improved pain relief and patient satisfaction and reduced opioid-related side effects compared with IV PCA (Borgeat et al, 1997 **Level II**; Borgeat et al, 1998 **Level II**; Borgeat et al, 2000 **Level II**). Continuous interscalene analgesia also provided better analgesia and reduced opioid requirements following shoulder surgery compared with single injection interscalene blockade (Klein, Grant et al, 2000 **Level II**; Ilfeld et al, 2003 **Level II**; Kean et al, 2006 **Level II**) with higher patient satisfaction (Kean et al, 2006 **Level II**). Compared with a single-injection interscalene block, a 2-day interscalene infusion at home after shoulder surgery was

opioid-sparing and improved pain relief, sleep and patient satisfaction (Mariano et al, 2009 **Level II**). Continuous interscalene nerve blockade compared with placebo following shoulder arthroplasty also reduced time to discharge readiness and was associated with a greater degree of shoulder movement (Ilfeld et al, 2006 **Level II**).

Axillary

There is no consistent evidence that continuous axillary analgesia is better than a single axillary brachial plexus injection of a long-acting local anaesthetic. After elective hand surgery continuous axillary infusions of 0.1%, 0.2% ropivacaine or saline were not sufficient to adequately treat pain without the addition of adjunct agents (Salonen et al, 2000 **Level II**).

Infraclavicular

Use of an infraclavicular brachial plexus catheter in patients at home after upper limb surgery led to better pain relief, patient satisfaction and sleep compared with oral opioid analgesia (Ilfeld, Morey & Enneking, 2002 **Level II**).

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 of local anaesthetic (mg) used; there was no difference in analgesia but satisfaction scores were higher in patients who received the 0.2% infusion (Ilfeld, Le et al, 2009 **Level II**).

Lower limb

Peripheral nerve blocks, including CPNB, after major knee surgery, provided postoperative analgesia that was comparable with that obtained with epidural techniques but with an improved side-effect profile (Fowler et al, 2008 **Level I**).

Femoral nerve and fascia iliaca blocks

Continuous femoral nerve blockade (often called a '3 in 1' block as a catheter placed in the femoral nerve sheath may allow local anaesthetic to reach both the lateral femoral cutaneous and obturator nerves as well as the femoral nerve) provided postoperative analgesia and functional recovery that was better than IV PCA morphine and comparable with epidural analgesia following total knee arthroplasty (Singelyn et al, 1998 **Level II**; Capdevila et al, 1999 **Level II**; Barrington, Olive et al, 2005 **Level II**). It decreased nausea and vomiting compared with morphine and decreased hypotension and urinary retention compared with epidural analgesia (Capdevila et al, 1999 **Level II**; Singelyn et al, 1998 **Level II**). Similar results were reported in a later study. Although continuous femoral nerve blockade provided pain relief that was comparable to both IV morphine and epidural analgesia, the incidence of nausea, vomiting, pruritus and sedation was also reduced compared with morphine and there was again a lower incidence of urinary retention and hypotension compared with epidural analgesia (Singelyn et al, 2005 **Level II**).

Femoral nerve block (either continuous or single shot) combined with spinal or general anaesthesia for total knee arthroplasty led to better analgesia (lower pain intensity scores especially on movement, reduction in supplemental analgesia use) for up to 48 hours compared with parenteral opioid-based techniques (Fischer et al, 2008 **Level I**). In a later study, continuous femoral nerve block also led to better pain relief and opioid-sparing, however there was a reduction in opioid-related side effects and patients were able to achieve better knee flexion in the postoperative period; no functional benefit was seen at 3 months (Kadic et al, 2009 **Level II**).

Femoral nerve block (either single shot or continuous) was more effective than intra-articular local anaesthesia following arthroscopic anterior cruciate ligament reconstruction (Dauri et al, 2003 **Level II**; Iskandar et al, 2003 **Level II**; Dauri et al, 2009 **Level II**). In day case surgical patients,

continuous femoral nerve block (via elastomeric device; mean duration 50 hours) provided more effective analgesia for up to 4 days following anterior cruciate ligament reconstruction than either single-shot femoral nerve block or placebo (saline) block (Williams et al, 2006 **Level II**).

Continuous fascia iliaca block provided similar analgesia to a '3-in-1' block following anterior cruciate ligament repair and the catheter was considered technically easier to insert (Morau et al, 2003 **Level II**). It is likely that many catheters placed as a classic '3-in-1' block were in fact relying on local anaesthetic spread along the plane of the fascia iliaca (Capdevila et al, 1998 **Level II**). Fascia iliaca block is also of benefit in some paediatric procedures (see Section 10.7.1).

For more information on any differences between the local anaesthetics used for femoral nerve blocks see Section 5.1.2.

Sciatic nerve

Following total knee arthroplasty, combined sciatic and femoral nerve blockade did not improve analgesia compared with femoral block alone (Allen et al, 1998 **Level II**). However, after lower extremity surgery (Ilfeld, Morey, Wang et al, 2002 **Level II**) and foot surgery (White et al, 2003 **Level II**), continuous popliteal sciatic nerve analgesia resulted in better pain relief, lower opioid requirements and fewer side effects compared with opioids alone.

A comparison of epidural analgesia and combined sciatic-femoral nerve blockade after total knee arthroplasty showed no differences in pain relief (rest and with movement), side effects (apart from urinary retention, which was greater in the epidural group), rehabilitation or length of hospital stay (Zaric et al, 2006 **Level II**).

For more information on any differences between the local anaesthetics used for sciatic nerve blocks see Section 5.1.2.

Lumbar plexus

Continuous psoas compartment blockade can be used for postoperative analgesia following total hip replacement (Capdevila et al, 2002 **Level IV**) and surgical repair of hip fractures (Chudinov et al, 1999 **Level II**).

Femoral and posterior lumbar plexus blocks compared with placebo for knee and hip arthroplasty respectively reduced the time to discharge readiness (criteria included adequate analgesia, independence from IV analgesia and ambulatory targets) (Ilfeld, Le et al, 2008 **Level II**; Ilfeld, Ball et al, 2008 **Level II**). However, there was no significant reduction in ambulation distance achieved. There was no evidence that either a 4-day continuous lumbar plexus block after hip arthroplasty (Ilfeld, Ball et al 2009 **Level II**) or 4-day continuous femoral nerve block after knee arthroplasty (Ilfeld, Meyer et al 2009 **Level II**) improved health-related quality of life between 7 days and 12 months.

Both continuous posterior lumbar plexus and femoral analgesia significantly reduced 48-hour opioid requirements and pain scores following total knee joint replacement surgery compared with IV PCA morphine (Kaloul et al, 2004 **Level II**). There were no differences in pain scores or morphine consumption between the two regional analgesia groups.

A study comparing continuous femoral nerve, femoral/sciatic nerve and lumbar plexus infusions found that the combination of femoral and sciatic nerve infusion reduced postoperative opioid requirements after total knee replacement, however there were no differences in pain scores or function (Morin, Kratz et al, 2005 **Level II**). Also after knee arthroplasty surgery, epidural analgesia provided better analgesia at 6 hours than a lumbar plexus infusion, but there were no differences in pain at rest or with movement at 24 hours, or in range of movement or mobility (Campbell et al, 2008 **Level II**).

Thoracic

Paravertebral blocks

Following cosmetic breast surgery thoracic paravertebral blockade resulted in modest benefits only; reduced nausea (at 24 hours) and opioid requirements compared with general anaesthesia (Klein, Bergh et al, 2000 **Level II**). After breast cancer surgery, no difference in opioid requirements or pain scores was found (Moller et al, 2007 **Level II**).

Continuous thoracic paravertebral blockade was as effective as thoracic epidural analgesia for pain relief after thoracotomy (Davies et al, 2006 **Level I**), with a better side-effect profile (less urinary retention, hypotension and nausea and vomiting) than epidural analgesia and resulted in a lower incidence of postoperative pulmonary complications (Davies et al, 2006 **Level I**). Similarly, in a comparison of different modes of analgesia for thoracotomy, paravertebral and epidural techniques provided superior analgesia to intrathecal, interpleural, intercostal and systemic opioid techniques; paravertebral blocks resulted in less hypotension than epidural analgesia with local anaesthetic and paravertebral blocks reduced the incidence of pulmonary complications compared with systemic analgesia (Joshi et al, 2008 **Level I**).

Continuous thoracic paravertebral blockade was also effective for pain relief in patients with multiple unilateral rib fractures (Shukula et al, 2008 **Level IV**).

Intercostal and interpleural blocks

There was no evidence that continuous interpleural analgesia provided superior analgesia compared with thoracic epidural analgesia following thoracotomy for minimally invasive direct coronary artery bypass surgery (Mehta et al, 1998 **Level II**). However, after thoracotomy for correction of aortic coarctation or patient ductus arteriosus, thoracic epidural analgesia resulted in better pain relief and pulmonary function than continuous interpleural analgesia (Yildirim et al, 2007 **Level II**).

Continuous epidural analgesia was superior to continuous intercostal analgesia following thoracotomy (Debreceni et al, 2003 **Level II**).

Needle and catheter localising techniques

Stimulating catheters have been compared with non-stimulating catheter techniques in establishing continuous femoral nerve blockade for postoperative analgesia following total knee arthroplasty. There was no difference in quality of postoperative analgesia between these two insertion techniques (Morin, Eberhart et al, 2005 **Level II**; Barrington et al, 2008 **Level II**). Stimulating catheters have also been compared with non-stimulating catheter techniques at other anatomical locations with inconclusive results (Rodriguez et al, 2006 **Level II**; Dauri et al, 2007 **Level II**; Stevens et al, 2007 **Level II**).

Ultrasound guidance has been compared with stimulating and non-stimulating techniques for continuous infraclavicular brachial plexus blockade. The combination of ultrasound and nerve stimulator guidance (with stimulating catheters) resulted in the highest primary success and reduced secondary catheter failure (Dhir & Ganapathy, 2008 **Level II**). In comparison with a peripheral nerve stimulator (PNS), blocks performed using ultrasound guidance were found to be more likely to be successful (RR for block failure 0.41; 95% CI 0.26 to 0.66), faster to perform (mean 1 minute less to perform with ultrasound), and have faster onset (29% shorter onset time; 95% CI 45% to 12%), and longer duration (mean difference 25% longer; 95% CI 12% to 38%) than those performed with PNS guidance (Abrahams et al, 2009 **Level I**). In one RCT comparing blocks performed using PNS or ultrasound guidance, there was no difference in block performance time (but this was only 5 minutes for both techniques), block failure rate, or incidence of postoperative neurological symptoms, however there was enhanced motor block at 5 minutes when ultrasound was used (Liu et al, 2009 **Level II**).

Patient-controlled regional analgesia

Continuous regional analgesia techniques can be provided with continuous infusion alone, a combination of continuous infusion and patient-controlled bolus doses or patient-controlled bolus doses alone. In a comparison with continuous infusions for '3 in 1' nerve blockade, patient-controlled regional analgesia (PCRA) was associated with similar pain scores and patient satisfaction but reduced consumption of local anaesthetic (Singelyn & Gouverneur, 2000 **Level II**). A study in patients having open shoulder surgery concluded that a baseline infusion, with PCRA added to reinforce the block before physiotherapy, was the best choice (Singelyn et al, 1999 **Level II**).

The addition of a background infusion to '3 in 1' PCRA (Singelyn & Gouverneur, 2000 **Level II**) or femoral nerve PCRA (Singelyn et al, 2001 **Level II**) did not improve pain relief or alter the incidence of side effects but could increase total local anaesthetic consumption. The addition of a background infusion to interscalene brachial plexus PCRA did result in better analgesia (Singelyn et al, 1999 **Level II**).

For more information on any differences between the local anaesthetics used for PCRA see Section 5.1.2.

7.5.2 Intra-articular analgesia

Continuous ropivacaine infusion via interscalene or intra-articular catheters were compared following rotator cuff surgery in an outpatient setting. Both study groups had logistical problems and relatively high pain scores following resolution of the surgical block (Klein et al, 2003 **Level II**).

Intra-articular infusions of bupivacaine with adrenaline following shoulder arthroscopy have been associated with gleno-humoral chondrolysis in cases series, and their use has been cautioned against (Hansen et al 2007 **Level IV**; Bailie & Ellenbecker, 2009 **Level IV**). The chondrotoxicity of bupivacaine has been supported by animal experiments (Gomoll et al, 2006).

There is evidence of a small benefit only of intra-articular local anaesthesia for postoperative pain relief after anterior cruciate ligament repair (Moiniche et al, 1999 **Level I**). Femoral nerve block (either single shot or continuous) was more effective than intra-articular local anaesthesia following arthroscopic repair (Dauri et al, 2003 **Level II**; Iskandar et al, 2003 **Level II**).

Following knee arthroplasty, the use of periarticular and intra-articular local anaesthetics in large volumes (eg 170 mL 0.2% ropivacaine) with supplemental doses over 24 hours via an intra-articular catheter resulted in lower opioid requirements for up to 24 hours and less nausea over 5 days compared with systemic morphine (Vendittoli et al, 2006 **Level II**), improved analgesia and earlier ambulation compared with femoral nerve block (Toftdahl et al, 2007 **Level II**), and reduced pain over 32 hours compared with saline (Andersen et al, 2008 **Level II**). The technique has been recently been reviewed (Otte et al, 2008).

Following hip arthroplasty, the use of periarticular and intra-articular local anaesthetics in large volumes with supplemental doses over 24 hours via an intra-articular catheter resulted in improved analgesia for 2 weeks postoperatively and lower opioid requirements for up to 4 days compared with saline (Andersen, Poulsen et al, 2007 **Level II**) and reduced opioid consumption and length of hospital stay compared with epidural analgesia (Andersen, Pfeiffer-Jensen et al, 2007 **Level II**). Plasma levels of ropivacaine after this technique have been reported to be below the toxic range (Vendittoli et al, 2006 **Level IV**; Bianconi et al, 2003 **Level IV**).

In clinical practice, morphine injected as a single dose into the knee intra-articular space produced analgesia that lasted up to 24 hours, but evidence for a peripheral rather than a systemic effect was not conclusive (Gupta et al, 2001 **Level I**; Kalso et al, 2002 **Level I**). Confounding

variables that hinder analysis included the pre-existing degree of inflammation, type of surgery, the baseline pain severity and the overall relatively weak clinical effect (Gupta et al, 2001 **Level I**). When published trials were analysed 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**).

Note: reversal of conclusions

This reverses the Level 1 conclusion in the previous edition of this document; the earlier meta-analyses performed without taking confounding factors into consideration had reported improved pain relief with intra-articular morphine.

7.5.3 Wound infiltration including wound catheters

A meta-analysis reviewed outcomes following postoperative analgesia using continuous local anaesthetic wound infusions (Liu et al, 2006 **Level I**). Analyses were performed for all surgical groups combined and for the four subgroups (cardiothoracic, general, gynaecology-urology and orthopaedics). While there were some minor variations between the subgroups, the results overall (ie for all surgical groups combined) showed that this technique led to reductions in pain scores (at rest and with activity), opioid consumption, PONV and length of hospital stay; patient satisfaction was higher and there was no difference in the incidence of wound infections (Liu et al, 2006 **Level I**).

Continuous infusion of ropivacaine into the wound after appendicectomy was superior to a saline infusion (Ansaloni et al, 2007 **Level II**) as was a continuous wound infusion of bupivacaine after open nephrectomy (Forastiere et al, 2008 **Level II**). Infusion of ropivacaine into the site of iliac crest bone graft harvest resulted in better pain relief in the postoperative period compared with IV PCA alone and significantly less pain in the iliac crest during movement at 3 months (Blumenthal et al, 2005 **Level II**).

Continuous infusion of bupivacaine below the superficial abdominal fascia resulted in more effective analgesia than an infusion sited above the fascia after abdominal hysterectomy (Hafizoglu et al, 2008 **Level II**).

Continuous wound infusion of diclofenac after Caesarean section was as effective as a ropivacaine infusion with systemic diclofenac (Lavand'homme et al, 2007 **Level II**).

Early postoperative abdominal pain was improved after laparoscopic cholecystectomy by the use of intraperitoneal local anaesthetic; the effect was better when given at the start of the operation compared with instillation at the end of surgery (Boddy et al, 2006 **Level I**). There were no differences in pain relief found between systemic pethidine and intraperitoneal administration of pethidine and ropivacaine, alone or in combination (Paech et al, 2008 **Level II**). Preperitoneal infusion of ropivacaine after colorectal surgery resulted in improved pain relief, opioid-sparing and earlier recovery of bowel function (Beaussier et al, 2007 **Level II**).

7.5.4 Topical application of local anaesthetics

Topical EMLA® cream (eutectic mixture of lignocaine and prilocaine) was effective in reducing the pain associated with venous ulcer debridement (Briggs & Nelson, 2003 **Level I**). When compared with EMLA® cream, topical amethocaine provided superior analgesia for superficial procedures in children, especially IV cannulation. (Lander et al, 2006 **Level I**).

Topical tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lignocaine were as effective as EMLA® cream for dermal instrumentation analgesia in the emergency department (Eidelman et al, 2005 **Level I**). See Section 10.4.2 for use in children and Section 9.9.2 for use in the emergency department.

Topical local anaesthetic provided no analgesic benefit when performing flexible diagnostic nasoendoscopy, either alone or in combination with a vasoconstrictor (Conlin & McLean, 2008 **Level I**; Nankivell & Pothier, 2008 **Level I**).

Intraurethral instillation of lidocaine gel provides superior analgesia to lubricating gel during flexible cystoscopy (Aaronson et al, 2009 **Level I**).

Following tonsillectomy, local anaesthetics provided 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 & Saravanappa, 2008 **Level I**).

A meta-analysis concludes that there is insufficient evidence to recommend topical lignocaine as a first-line agent in the treatment of postherpetic neuralgia with allodynia (Khaliq et al, 2007 **Level I**).

7.5.5 Safety

Anticoagulation

Caution should be applied in the use of some peripheral nerve or plexus blocks in patients with impaired coagulation (see Section 7.4.2)

Nerve injury

An ASRA&PM Practice Advisory publication (Neal et al, 2008 **Level IV**) provides a good overview of and guidance on neurological complications in regional anaesthesia, importantly noting that most symptoms resolve within days to weeks and that many factors unrelated to the block itself may contribute perioperative nerve injury (Welch et al, 2009 **Level IV**; Neal et al, 2008 **Level IV**).

Most nerve injury after these techniques presents as residual paraesthesia and rarely as permanent paralysis (persisting for more than 6 to 12 months). A review of data from published studies of the risk of neurological injury associated with epidural and other regional anaesthesia and analgesia differentiated between the risk of permanent neurological injury and transient neuropathy (Brull et al, 2007 **Level IV**). The incidence of transient neuropathy (radiculopathy) after three common forms of peripheral nerve blockade — interscalene brachial plexus block, axillary brachial plexus block and femoral nerve block — was estimated to be 2.84%, 1.48% and 0.34% respectively.

A review of 1416 patients after CPNB for orthopaedic surgery reported three patients with nerve lesions (all after femoral nerve CPNB); full recovery was seen within 10 weeks (Capdevila et al, 2005 **Level IV**). Another prospective audit of 1065 patients after CPBN reported a similar block-related neuropathy rate of 0.22% (Watts & Sharma, 2007 **Level IV**).

The risk of permanent neurological injury (lasting over 12 months) after peripheral neural blockade was much lower. In all the studies included in this review, only one case was reported (out of 22 414 cases with follow-up data recorded), making it a very rare event (Brull et al, 2007 **Level IV**). The Australasian Regional Anaesthesia Collaboration (ARAC) followed up 6069 patients who received 7156 peripheral nerve blocks for neurological and other complications. The incidence of late neurological deficit was 0.4:1000 procedures (Barrington et al, 2009 **Level IV**).

The overall incidence of long-term injury following brachial plexus block ranged between 0.02% and 0.4% depending on the definition of injury and length of follow-up (Borgeat et al, 2001 **Level IV**; Klein et al, 2002 **Level IV**; Neal et al, 2002 **Level IV**; Watts & Sharma, 2007 **Level IV**).

Borgeat et al studied continuous popliteal nerve blockade in 1001 patients with no incidence of neuropathy (Borgeat et al, 2006 **Level IV**) while Compere et al (Compere, Rey et al, 2009 **Level IV**) reported an infection incidence a 0.5% risk of severe neuropathy — 2 patients of the 400 included in the study.

Ultrasound guidance has been shown to reduce the likelihood of intravascular injection (RR 0.16; 95% CI 0.05 to 0.47; P<0.001) but insufficient data are available to determine whether neurological injury is less likely (Abrahams et al, 2009 **Level I**). A review of 1010 consecutive peripheral nerve blocks performed under ultrasound guidance concluded that the incidence of neurological symptoms, most thought to be due to causes others than the block, was similar to that reported for blocks performed using traditional techniques (Fredrickson & Kilfoyle, 2009 **Level IV**).

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).

Toxicity

Local anaesthetic toxicity due to accidental intravascular injection or rapid absorption is a known complication of all peripheral nerve blocks, and was associated with cardiac arrest (1.4 per 10 000) or seizures (7.5 per 10 000) in a prospective survey of over 21 000 cases (Auroy et al, 1997 **Level IV**). The incidence of acute systemic toxicity reported by ARAC was 0.98:1000 procedures (Barrington et al, 2009 **Level IV**). Surveys specifically investigating brachial plexus blocks have reported a higher rate of seizures (0.2%) (Brown et al, 1995 **Level IV**; Borgeat et al, 2001 **Level IV**) (see Section 5.1.3).

Infection

Despite a structured literature search regarding infection in regional analgesia, insufficient prospective trials were found to conduct a meta-analysis (Schulz-Stubner et al, 2008). In a follow-up of 1416 patients with CPNB catheters only one patient had a serious complication (psoas abscess), although a relatively high rate of catheter colonisation (28.7%) occurred (Capdevila et al, 2005 **Level IV**). Unfortunately, the infection control practices were not fully disclosed. In another series, 16% of all CPNB catheters were colonised and the risk factors for colonisation were catheter placement in the groin and repeated changes of the catheter dressing (Morin, Kerwat et al, 2005 **Level IV**). In perineural catheters that were tunnelled, the rate of contamination was just 6% (Compere, Legrand et al, 2009 **Level IV**).

After 48 hours, 57% of femoral nerve catheters were colonised (Cuvillon et al, 2001 **Level IV**).

Wiege et al (Wiegel et al, 2007 **Level IV**) documented an incidence of local inflammation at the catheter site (0.6%) and local infection (0.2%) in femoral and sciatic blocks. The incidence of local inflammation and infection in a study of 2285 patients with CPNB (axillary, interscalene, psoas compartment, femoral, sciatic and popliteal) was 4.2% and 3.2% respectively (Neuburger et al, 2007 **Level IV**). Borgeat et al studied continuous popliteal nerve blockade in 1001 patients with no incidence of infection (Borgeat et al, 2006 **Level IV**) while Compere et al reported an infection incidence of 0.25% — 1 patient of the 400 included in the study — for the same block (Compere, Rey et al, 2009 **Level IV**).

The strongest recommendations for preventive measures are hand hygiene and effective skin preparation, preferably with alcohol-based chlorhexidine solution — as found in the epic2 National Guidelines in the United Kingdom (Pratt et al, 2007). These guidelines recommend full

barrier precautions for central venous catheter placement (cap, mask, sterile gown and gloves; and large drape). Specific trial data for aseptic technique in CPNB is lacking, however in a review of infections associated with CPNB as reported in 12 case series, Capdevila et al (Capdevila et al, 2009 **Level IV**) supported the use of full surgical-type aseptic technique for CPNB procedures.

Identified risk factors for local CPNB catheter inflammation include intensive care unit stay, duration of catheter use greater than 48 hours, lack of antibiotic prophylaxis, axillary or femoral location and frequent dressing changes (Capdevila et al, 2009 **Level IV**). 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 this risk.

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. Compared with opioid analgesia, continuous peripheral nerve blockade (regardless of catheter location) provides better postoperative analgesia and leads to reductions in opioid use as well as nausea, vomiting, pruritus and sedation (**N**) (**Level I**).
3. Femoral nerve block provides better analgesia compared with parenteral opioid-based techniques after total knee arthroplasty (**S**) (**Level I**).
4. Compared with thoracic epidural analgesia, continuous thoracic paravertebral analgesia results in comparable analgesia but has a better side effect profile (less urinary retention, hypotension, nausea, and vomiting) than epidural analgesia and leads to a lower incidence of postoperative pulmonary complications (**N**) (**Level I**).
5. 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 (**N**) (**Level I**).
6. Morphine injected into the intra-articular space following knee arthroscopy does not improve analgesia compared with placebo (**R**) (**Level I**).
7. Intra-articular local anaesthetics reduce postoperative pain to a limited extent only (**U**) (**Level I**).
8. Continuous local anaesthetic wound infusions lead to reductions in pain scores (at rest and with activity), opioid consumption, postoperative nausea and vomiting, and length of hospital stay; patient satisfaction is higher and there is no difference in the incidence of wound infections (**S**) (**Level I**).
9. Intraperitonal local anaesthetic after laparoscopic cholecystectomy improves early postoperative pain relief (**N**) (**Level I**).
10. Intraurethral instillation of lignocaine gel provides analgesia during flexible cystoscopy (**N**) (**Level I**).
11. Continuous interscalene analgesia provides better analgesia, reduced opioid-related side effects and improved patient satisfaction compared with IV PCA after open shoulder surgery (**U**) (**Level II**).
12. Continuous femoral nerve blockade provides postoperative analgesia that is as effective as epidural analgesia but with fewer side effects following total knee joint replacement surgery (**U**) (**Level II**).

13. Continuous posterior lumbar plexus analgesia is as effective as continuous femoral analgesia following total knee joint replacement surgery (**U**) (**Level II**).
14. Intra-articular bupivacaine infusions have been associated with chondrolysis and their use has been cautioned against (**N**) (**Level IV**).

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8. NON-PHARMACOLOGICAL TECHNIQUES

8.1 PSYCHOLOGICAL INTERVENTIONS

The role of psychological interventions in the management of acute pain is generally seen as adjunctive to somatic modalities, but evidence for the value of their contribution is strengthening.

Psychological interventions can be grouped under a number of headings, but, by their very nature, they share some common features. Some of these features may also apply to effective pharmacological and physical interventions. Typically, the treatment provider is encouraged to firstly establish a degree of rapport or acceptance with the patient as well as 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. Interestingly, one of the conclusions that can be drawn from the available studies is that good psychological preparation for surgical interventions can enhance the outcome of such procedures, including length of hospital stay. Thus, skilled combination of 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 or sensory); stress/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.

8.1.1 Provision of information

Procedural information is information given to a patient before any treatment that summarises what will happen during that treatment. Preparatory information has been found to be effective in improving postoperative recovery and reducing pain reports, pain medication use, and length of hospital stay (Johnston & Vogele, 1993) (see also Section 3.1.1).

Sensory information is information that describes the sensory experiences the patient may expect during treatment. Sensory information given alone has some positive, albeit inconsistent, effects compared with no instruction (Suls & Wan, 1989 **Level I**). This review also found that sensory information reduced self-rated pain more than procedural information; however, the effect sizes were variable. Sensory information had no significant effect on postoperative pain perception in patients who underwent two types of elective surgery (Campbell et al, 1999 **Level II**).

Combined sensory-procedural preparatory information yielded the strongest and most consistent benefits in reducing negative affect, pain reports and other related distress (Suls & Wan, 1989 **Level I**). This finding was replicated in a controlled study of ear-piercing in children. In this case, those children whose parents were provided with accurate information about the procedure and sensory (pain) expectations reported significantly less pain and more accurate expectations than controls (Spafford et al, 2002 **Level II**).

However, a recent meta-analysis of 28 trials of different psychological interventions for procedure-related pain in children concluded the evidence for the efficacy of information/ preparation is only tentatively supportive; the evidence is not sufficient to make firm recommendations (Uman et al, 2006 **Level I**).

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**). However, later evidence suggested that this may not be a strong effect (Miro and Raich 1999 **Level II**). Nevertheless, it may be useful to assess a patient's normal approach to managing stress to identify the best option for that patient. A more recent study with over 3000 surgical patients identified four information factors that were each associated with global evaluations — surgical information, recovery information, general information and sensory information (Krupat et al, 2000 **Level III-3**).

8.1.2 Stress and tension reduction

Relaxation

Relaxation training usually involves teaching a patient ways of reducing their feelings of stress/tension by various techniques. The techniques may be taught by recorded audiotape, written or spoken instructions. The use of audiotapes often includes the use of suitable (calming) music. The use of relevant imagery (mental pictures of relaxing scenes) is also often encouraged as an element of relaxation techniques. 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 some (weak) evidence to support the use of relaxation in these settings — three of the seven studies reported significant reductions in pain and distress (Seers & Carroll, 1998 **Level IV**). Methodological shortcomings in the studies 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; 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, and no support for rhythmic breathing or other relaxation techniques (Kwekkeboom & Gretarsdottir, 2006 **Level IV**). Another review of studies using relaxation techniques for burns pain 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 & Gamel, 2006 **Level IV**). 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 et al, 2006 **Level II**).

In contrast, studies of relaxation techniques with cancer patients (with acute pain) provided moderately strong (clinical) support for its effectiveness in improving nausea, pain, pulse rate and blood pressure, as well as emotional adjustment variables (depression, anxiety and hostility) (Luebbert et al, 2001 **Level I**).

Hypnosis

Hypnosis shares many features of relaxation with imagery and has a long history of use in acute pain conditions. While there are many versions of hypnosis, they share the common feature of one person responding to suggestions made by another on experiences involving changes in perception, memory and voluntary actions (Kihlstrom, 1985). The variable or unstandardised nature of hypnotic procedures has made it difficult to compare studies or

draw general conclusions (Ellis & Spanos, 1994), although some more standardised (according to a manual) procedures have been reported (Liossi & Hatira, 2003).

Until recently much of the literature on the use of hypnosis in acute pain has been based on studies with non-RCT designs (Patterson & Jensen, 2003). However, recent papers have displayed more experimental rigour.

Studies using hypnosis for pain control in both the laboratory and clinical settings (eight of the eighteen studies included pain populations) indicated that hypnosis for pain had a moderate to large effect size and provided substantial pain relief for 75% of laboratory and clinical participants (Montgomery et al, 2000 **Level I**).

A review of hypnosis in clinical pain settings (including pain associated with invasive medical procedures, burns wound care, labour and bone marrow aspiration) provided moderate support for the use of hypnosis in the treatment of acute pain (Patterson & Jensen, 2003 **Level I**). Eight of the nineteen studies showed hypnosis to be more effective on pain reports than no treatment, standard care, or an attention control condition; three studies showed hypnosis to be no better than such control conditions, and one study showed mixed results. Eight studies compared hypnosis with other psychological interventions (cognitive-behavioural intervention, relaxation training, distraction, emotional support), and hypnosis was more effective in reducing pain scores in four of the eight studies.

In relation to acute pain in cancer patients, some individual studies have found hypnosis to be superior to other psychological interventions in reducing pain reports (eg Syrjala et al, 1992 **Level II**). In many of the hypnotic studies with cancer patients, the focus has been on acute pain associated with procedures such as bone marrow aspiration, breast biopsy, or lumbar puncture. In each case the findings have supported the use of hypnosis to reduce pain (eg Wall & Womack, 1989 **Level II**; Liossi & Hatira, 1999 **Level II**; Montgomery et al, 2002 **Level II**). A systematic review by Wild and Espie (Wild & Espie, 2004) of hypnosis in paediatric oncology pain concluded the evidence was not consistent enough for general recommendations, but that hypnosis was potentially useful.

8.1.3 Attentional techniques

A range of attention-based strategies have been reported, from those involving distraction from the pain through 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 (eg Logan et al, 1995 **Level II**). Attempting to alter the patient's emotional state, from stress or fear to 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).

There is some evidence to support the benefit of some attentional techniques, often in combination with relaxation, in acute postoperative pain (Raft et al, 1986 **Level II**; Daake & Gueldner, 1989 **Level II**; Good et al, 1999 **Level II**). In childrenand adolescents, a systematic review concluded that distraction is effective in needle-related procedure-related pain (Uman et al, 2006 **Level I**). A more recent comparison of two interventions, guided imagery and relaxation, did not result in any difference in pain relief or analgesic use in elderly patients after colorectal surgery (Haase et al, 2005 **Level II**).

Using thermal pain stimulation in volunteers and measuring pain-related brain activity with fMRI, both opioids and immersive virtual reality (VR) distraction led to reductions in pain unpleasantness and pain-related brain activity; the combination was more effective than opioid alone (Hoffman et al, 2007 **Level III-2**). VR distraction has also been reported to provide

effective analgesia in clinical situations, for example, in burns patients (Hoffman et al, 2000 **Level III-2**; Das et al, 2005 **Level III-2**).

The use of certain music to divert attention from pain and to promote a sense of relaxation and well-being has long been a popular approach. A Cochrane review, which included studies published up to and including 2004, concluded that listening to music reduced pain intensity and opioid requirements after surgery, but that the magnitude of benefit was small (Cepeda et al, 2006 **Level I**). Later systematic reviews of studies investigating the use of music found that pain and anxiety in the perioperative period were reduced in half of the studies examined (Nilsson, 2008 **Level I**) and that anxiety and pain were reduced in children undergoing medical and dental procedures (Klassen et al, 2008 **Level I**).

There is some evidence that rather than shifting attention away from the pain, instructions to focus attention on the pain site can alter pain perception, but possibly mainly among sub-groups of patients (Baron et al, 1993 **Level II**; Logan et al, 1995 **Level II**). The study by Haythornthwaite et al (Haythornthwaite et al, 2001 **Level II**) provides further support for this approach.

The use of mindfulness meditation is a type of attentional technique that includes noting pain sensations. This approach encourages the patient to deliberately experience their pain as calmly as possible, as just another sensation (ie without judging it as good or bad), often while engaging in slowed breathing styles (Kabat-Zinn, 2003). This approach derives from ancient Buddhist methods and was initially described as a stress-reduction technique by Kabat-Zinn. While this technique has been used in people experiencing chronic pain (McCracken et al, 2007 **Level IV**), and has been shown to increase experimental pain tolerance (Kingston et al, 2007 **Level II**), there are no reports on its use in the management of acute pain.

8.1.4 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 often also addressed. This means that interactions between patients and others, especially medical and nursing staff as well as families, may need to be specifically changed 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 or disability. 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 rather than the primary goal.

Critically, in using cognitive-behavioural methods, the patient is necessarily an active participant in the process, rather than a passive recipient, as he or she must apply the methods taught as needed.

Applying pain coping strategies within a cognitive-behavioural intervention

Generally, while some responses by patients to their pain may be helpful, others may not. For example, those who respond with overly alarmist (or catastrophic) thoughts tended to experience more pain and distress, compared with those who did not respond in this way (eg Jensen et al, 1991; Haythornthwaite et al, 2001 **Level II**; Sullivan et al, 2001). 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 catastrophic thoughts about pain has become a key intervention within this approach, whether the pain is acute or persistent (Sullivan et al, 2006). 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 & Monarch, 2002). 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.

In preparation for surgery, painful medical procedures and postsurgical pain and distress, 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. These interventions were effective in achieving improvements in measures of negative affect, length of stay (not cognitive methods in this case) and recovery (Johnston & Vogele, 1993 **Level I**).

A review of studies (randomised and non-randomised) 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. 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 (Powers, 1999 **Level IV**).

Another review included studies (all non-randomised) that used 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. 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 nine of the twenty-three included studies; all nine studies found a clinically significant reduction in pain following behavioural intervention (DuHamel et al, 1999 **Level IV**).

A further review examined the effectiveness of behavioural intervention methods in studies (randomised and non-randomised) looking at the control of aversive side effects of cancer treatment, including pain (Redd et al, 2001 **Level IV**). The most commonly used behavioural interventions included hypnosis, relaxation and distraction via guided imagery. Of the twelve studies investigating the impact of behavioural interventions on cancer treatment-related pain, five were randomised clinical trials with either no treatment or attention control conditions; four of these five supported the efficacy of behavioural intervention and all of the remaining seven studies, incorporating a variety of designs, found a reduction in pain following

behavioural intervention. 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 et al, 2001 **Level IV**).

Reports of benefit after surgery are less common. A study of three cognitive-behavioural interventions for reducing postoperative anxiety and pain following spinal fusion surgery for scoliosis in adolescent patients showed that information plus training in coping strategies achieved the greatest pain reduction (35%) compared with information only, coping strategies only, and a control condition; the effect was most evident in those subjects aged 11 to 13 years, compared to those in the 14 to 18 year age range, where no differences between interventions were found (LaMontagne et al, 2003 **Level II**).

Key messages

1. Listening to music produces a small reduction in postoperative pain and opioid requirement (**N**) (**Level I** [Cochrane Review]).
2. The evidence that information is effective in reducing procedure-related pain is tentatively supportive and not sufficient to make recommendations (**Q**) (**Level I**).
3. Distraction is effective in procedure-related pain in children (**N**) (**Level I**).
4. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative affect and analgesic use (**U**) (**Level I**).
5. Evidence of benefit of hypnosis in the management of acute pain is inconsistent (**W**) (**Level I**).
6. Immersive virtual reality distraction is effective in reducing pain in some clinical situations (**N**) (**Level III-2**).
7. Evidence for any benefit of relaxation techniques in the treatment of acute pain is weak and inconsistent (**N**) (**Level IV**).

8.2 Transcutaneous electrical nerve stimulation

A systematic review published in 1996 concluded that transcutaneous electrical nerve stimulation (TENS) was not effective for the relief of postoperative pain (Carroll et al 1996). The authors noted that non-randomised studies overestimated the beneficial effects of TENS. A later Cochrane review included only RCTs looking at the benefit of TENS in the management of acute pain generally and concluded that there were inadequate data on which to perform a meta-analysis (Walsh et al, 2009). However, these authors excluded studies where TENS was used in combination with other treatments such as analgesic drugs. Hence, only one of the 12 included studies, but 62 of the 116 excluded studies related to postoperative pain.

It had been argued by Bjordal et al (Bjordal et al, 2003 **Level I**) that some of the studies reporting no benefit from TENS may have used ineffective treatment doses — low and possibly ineffective current intensities or sensory threshold intensity. They performed a systematic review of publications using TENS after surgery where 'assumed optimal TENS parameters' were used; that is, if TENS was administered at an intensity described by the patients as 'strong and/or definite subnoxious, and/or maximal non-painful, and/or maximal tolerable', or at a current amplitude of greater than 15 mA. They concluded that strong, subnoxious intensity TENS significantly reduced postoperative analgesic requirements.

The superiority of high-intensity TENS compared with low-frequency TENS, regardless of frequency used, has been demonstrated in further clinical (Olsen et al, 2007 **Level II**) and experimental (Aarskog et al, 2007 **Level II**; Claydon et al, 2008 **Level II**) pain studies.

Use of high-intensity (strong but comfortable) TENS improved pain relief after inguinal herniorrhaphy (DeSantana et al, 2008 **Level II**), laparoscopic tubal ligation (Desantana et al, 2009 **Level II**) and thoracotomy (Erdogan et al, 2005 **Level II**).

TENS was of value in the treatment of primary dysmenorrhoea (Proctor et al, 2002 **Level I**).

Overall, there appeared to be no good evidence for any analgesic effect of TENS during labour although severe pain was less likely to be reported in women receiving TENS to acupuncture points (Dowswell et al, 2009 **Level I**).

Key messages

1. Overall, there is no evidence that TENS is effective for the treatment of pain during labour (**N**) (**Level I** [Cochrane Review]).
2. Certain stimulation patterns of TENS are effective in some acute pain settings (**S**) (**Level I**).

8.3 Acupuncture

Acupuncture compared with sham controls reduced postoperative pain (at 8 hours and 72 hours) and opioid consumption as well as nausea (not vomiting), sedation, pruritus and urinary retention (Sun et al, 2008 **Level I**). 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. Another review looking specifically at auricular acupuncture for postoperative pain control concluded that a meta-analysis was not possible because of the heterogeneity of the primary studies (Usichenko, Lehmann et al, 2008).

Reviews of the effectiveness of acupuncture in other acute pain settings suggest that it may be useful for managing pain during childbirth (analgesic requirements were reduced) (Smith et al, 2006 **Level I**) and dental pain (Ernst & Pittler, 1998 **Level I**).

A meta-analysis of trials comparing acupuncture (traditional- and electro-acupuncture) with placebo acupuncture for the treatment of pain in general concluded that it does result in a small analgesic effect (4 mm on a 100 mm VAS), but that this seemed to lack clinical relevance and could not clearly be distinguished from bias resulting from incomplete blinding (Madsen et al, 2009 **Level I**).The analgesic effect of placebo acupuncture compared with placebo was moderate but very variable, and considerable heterogeneity in the included trials was noted.

Acupressure

Acupressure is a technique derived from acupuncture, where physical pressure is applied to acupuncture points.

Acupressure performed during prehospital transport using ‘true points’ led to better pain relief than acupressure using ‘sham points’ (Kober et al, 2002 **Level II**; Barker et al, 2006 **Level II**; Lang et al, 2007 **Level II**) or no acupressure (Kober et al, 2002 **Level II**).

Key messages

1. Acupuncture reduces postoperative pain as well as opioid-related adverse effects (**N**) (**Level I**).
2. Acupuncture may be effective in some other acute pain settings (**U**) (**Level I**).

8.4 Other physical therapies

8.4.1 Manual and massage therapies

Most publications relating to manual (eg physiotherapy, osteopathy and chiropractic) and massage therapies involve the use of these treatments in low back pain and other musculoskeletal pain. The evidence for these therapies is covered in detail in *Evidence-based Management of Musculoskeletal Pain*, published by the Australian Acute Musculoskeletal Pain Guidelines Group (2003) and endorsed by the NHMRC. For a summary of some of the key messages from this document see Sections 9.4 and 9.5.

There is little consistent evidence of any benefit for the use of massage in the treatment of postoperative pain. Foot massage and guided relaxation did not lower pain scores after cardiac surgery (Hattan et al, 2002 **Level II**). Similarly, massage after abdominal or thoracic (via a sternotomy) surgery did not reduce pain scores or analgesic use, although a significant reduction in the unpleasantness of pain (the affective component of pain) was reported (Piotrowski et al, 2003 **Level II**). However, after a variety of major operations, massage therapy reduced postoperative pain intensity and unpleasantness (Mitchinson et al, 2007 **Level II**). 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 the second and third days after surgery as well as reduced time to first flatus (Le Blanc-Louvry et al, 2002 **Level II**).

8.4.2 Heat and cold

Evidence for any benefits from postoperative local cooling is mixed. Significant reductions in opioid consumption and pain scores after a variety of orthopaedic operations have been reported (Brandner et al, 1996 **Level II**; Barber et al, 1998 **Level II**; Saito et al, 2004 **Level II**); other studies have shown no such reductions (Leutz & Harris, 1995 **Level II**; Edwards et al, 1996 **Level II**; Konrath et al, 1996 **Level II**). Similarly, no benefit in terms of pain relief or opioid requirements was seen after total abdominal hysterectomy (Finan et al, 1993 **Level II**) or Caesarean section (Amin-Hanjani et al, 1992 **Level II**).

There was limited evidence to support the use of local cooling for pain relief from perineal trauma after childbirth (East et al, 2007 **Level I**) and no good quality evidence for its use in the treatment in low back pain (French et al, 2006 **Level I**).

There is moderate evidence from four trials that heat wrap therapy results in a small short-term reduction in pain in patients with acute or sub-acute low-back pain (French et al, 2006 **Level I**).

8.4.3 Other therapies

There is no evidence to support the use of static magnet therapy for the treatment of pain generally (Pittler et al, 2007 **Level I**) and the use of this therapy had no effect on postoperative pain or analgesic requirements (Cepeda et al, 2007 **Level II**).

Postoperative transcranial magnetic stimulation used in patients after gastric bypass surgery led to significant lower PCA opioid requirements (Borckardt et al, 2006 **Level II**).

There was no difference in postoperative analgesic requirements following use of millimetre wave therapy after total knee arthroplasty (Usichenko, Edinger et al, 2008 **Level II**) or healing touch after coronary artery bypass surgery (MacIntyre et al, 2008 **Level II**), although postoperative anxiety was significant reduced in the latter study.

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9. SPECIFIC CLINICAL SITUATIONS

9.1 POSTOPERATIVE PAIN

One of the most common sources of pain is postoperative pain and 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.

In addition to this approach, there is also a need for information on postoperative pain management that relates to the site of surgery and specific surgical procedures (Rowlingson & Rawal, 2003). The development of such procedure-specific guidelines is ongoing: they require considerable effort and resources and have not been addressed in this document. An ambitious project to develop such evidence-based guidelines for the management of postoperative pain was initiated by the PROSPECT group (Neugebauer et al, 2007; Kehlet et al, 2007). Guidelines for the treatment of pain after a number of specific operations can be found at the PROSPECT website (PROSPECT 2009).

9.1.1 Risks of acute postoperative neuropathic pain

Neuropathic pain has been defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' (Merskey & Bogduk, 1994). Acute causes of neuropathic pain can be iatrogenic, traumatic, inflammatory or infective. Nerve injury is a risk in many surgical procedures and may present as acute neuropathic pain in the postoperative period. The incidence of acute neuropathic pain has been reported as 1% to 3%, based on patients referred to an acute pain service, primarily after surgery or trauma (Hayes et al, 2002 **Level IV**). The majority of these patients had persistent pain at 12 months, 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 & Pechon, 2005 **Level IV**). Similarly, a high incidence of acute neuropathic pain in lower limbs due to lumbosacral plexus injury has been reported after pelvic trauma (Chiodo, 2007 **Level IV**).

There is some evidence that specific early analgesic interventions may reduce the incidence of chronic pain (often neuropathic pain) after some operations (eg thoracotomy, amputation). For more details see Sections 1.3 and 9.1.2 and 9.1.3. The prompt diagnosis (Rasmussen et al, 2004) of acute neuropathic pain is therefore important. Management is based on extrapolation of data from the chronic pain setting (see Sections 4.3.2 to 4.3.6).

Key messages

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

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

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

9.1.2 Acute postamputation pain syndromes

Following amputation of a limb, and also breast, tongue, teeth, genitalia and even inner organs such as the rectum, or a deafferentiation injury such as brachial plexus avulsion (Bates & Stewart, 1991; Boas et al, 1993; Dijkstra et al, 2007), 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 et al, 1985; Nikolajsen & Jensen, 2001). 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 et al, 1997).
- *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 et al, 1983). These sensations range from a vague awareness of the presence of the organ via associated paraesthesia, to complete sensation including size, shape, position, temperature and movement.
- *Phantom limb pain* is defined as any noxious sensory phenomenon in the missing limb or organ. The incidence of phantom limb pain is estimated to be 30% to 85% after limb amputation and occurs usually in the distal portion of the missing limb (Jensen et al, 1985; Perkins & Kehlet, 2000; Nikolajsen & Jensen, 2001). Pain can be immediate — 75% of patients will report phantom pain within the first few days after amputation (Nikolajsen et al, 1997) — 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 (see Section 1.3). If preamputation pain was present, phantom pain may resemble that pain in character and localisation (Katz & Melzack, 1990). Intensity of preamputation pain and acute postoperative pain were strong predictors of intensity of chronic pain after amputation (Hanley et al, 2007 **Level III-3**). Preoperative passive coping strategies, in particular catastrophising, were other strong predictors of phantom limb pain 6 months later (Richardson et al, 2007 **Level III-3**).

There is a strong correlation between phantom limb and stump or site pain and they may be inter-related (Jensen et al, 1983; Kooijman et al, 2000). All three of the above phenomena can coexist (Nikolajsen et al, 1997).

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 et al, 2009 **Level IV**).

Prevention

Evidence for the benefit of epidural analgesia in the prevention of all phantom limb pain is inconclusive (Halbert et al, 2002 **Level I**). However, an analysis of studies on phantom limb pain prophylaxis showed that perioperative (pre, intra and postoperative) epidural analgesia reduced the incidence of severe phantom limb pain (NNT 5.8) (Gehling & Tryba, 2003 **Level III-2**).

A small observational study found that while the overall incidence of long-term phantom limb pain was similar in patients given ketamine (bolus dose followed by an infusion, started prior to skin incision and continued for 72 hours postoperatively) compared with no ketamine, the incidence of severe phantom limb pain was reduced in the ketamine group (Dertwinkel et al, 2002 **Level III-3**). Another study looking at the effects of ketamine reported a numerical but not statistically significant difference in the incidence of phantom limb pain at 6 months after amputation (47% in the ketamine group and 71% in the control group) (Hayes et al, 2004

Level II). No preventive effect of perioperative ketamine given by the epidural route was reported in another study (Wilson et al, 2008 **Level II**).

Perioperative gabapentin was ineffective in reducing incidence and severity of phantom limb pain (Nikolajsen et al, 2006 **Level II**).

Infusions of local anaesthetics via peripheral nerve sheath catheters, usually inserted by the surgeon at the time of amputation, are a safe method of providing excellent analgesia in the immediate postoperative period (Pinzur et al, 1996 **Level II**; Lambert et al, 2001 **Level II**). However, they are of no proven benefit in preventing phantom pain or stump pain (Halbert et al, 2002 **Level I**).

Therapy

A survey in 1980 identified over 50 different therapies used for the treatment of phantom limb pain (Sherman et al, 1980), suggesting limited evidence for effective treatments. This was confirmed by a systematic review (Halbert et al, 2002).

Calcitonin by IV infusion is effective in the treatment of acute phantom limb pain (Jaeger & Maier, 1992 **Level II**). Calcitonin may also be given subcutaneously or intranasally (Wall & Heyneman, 1999). It was not effective for chronic phantom limb pain (Eichenberger et al, 2008 **Level II**).

- Ketamine, an NMDA-receptor antagonist (see Section 4.3.2), provided short-term relief of stump and phantom limb pain (Nikolajsen et al, 1996 **Level II**; Eichenberger et al, 2008 **Level II**).
- Oral controlled-release (CR) morphine (Huse et al, 2001 **Level II**) and IV infusions of morphine reduced phantom limb pain (Wu et al, 2002 **Level II**). Morphine was superior to mexiletine (53% vs 30% pain relief) in treating postamputation pain; the NNT for 50% pain relief was 5.6 (Wu et al, 2008 **Level II**).
- Gabapentin was effective in reducing phantom limb pain (Bone et al, 2002 **Level II**).
- IV lignocaine (lidocaine) significantly reduced stump pain but had no effect on phantom pain (Wu et al, 2002 **Level II**).
- Amitriptyline and tramadol provided good control of phantom limb and stump pain in amputees (Wilder-Smith et al, 2005 **Level II**).
- Injections of local anaesthetic into painful myofascial areas of the contralateral limb reduced phantom limb pain and sensations (Casale et al, 2009 **Level II**).

Non-pharmacological treatment options for phantom limb pain are also effective. These include sensory discrimination training (Flor et al, 2001 **Level II**), mental imagery of limb movement (MacIver et al, 2008 **Level IV**; Ulger et al, 2009 **Level IV**) and motor imagery, consisting of 2 weeks each of limb laterality recognition, imagined movements and mirror movements (Moseley, 2006 **Level II**).

Key messages

1. Continuous regional blockade via nerve sheath catheters provides effective postoperative analgesia after amputation, but has no preventive effect on phantom limb pain (**U**) (**Level II**).
2. Calcitonin, morphine, ketamine, gabapentin, amitriptyline and tramadol reduce phantom limb pain (**S**) (**Level II**).
3. Sensory discrimination training and motor imagery reduce chronic phantom limb pain (**S**) (**Level II**).
4. Ketamine, lignocaine (lidocaine), tramadol and amitriptyline reduce stump 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**).

9.1.3 Other postoperative pain syndromes

Increasing evidence for the development of postoperative chronic pain syndromes has led to more detailed study of a number of them. The information below does not discuss aspects of surgical techniques that may influence the incidence of chronic pain.

Risk factors that predispose to the development of chronic postsurgical pain include the severity of pre and postoperative pain, intraoperative nerve injury (see Section 1.3). Again, specific early analgesic interventions may reduce the incidence of chronic pain after some operations.

Post-thoracotomy pain syndrome

Post-thoracotomy pain syndrome is one of the most common chronic pain states. It is thought to be caused primarily by trauma to intercostal nerves and most patients relate their pain directly to the site of surgery (Karmakar & Ho, 2004; Wildgaard et al, 2009). However, myofascial pain syndromes as a consequence of thoracotomy have also been described (Hamada et al, 2000 **Level IV**).

Epidural analgesia initiated prior to thoracotomy and continued into the postoperative period resulted in significantly fewer patients reporting pain 6 months later compared with patients who had received IV PCA opioids for postoperative analgesia (45% vs 78% respectively) (Senturk et al, 2002 **Level II**). There was no statistically significant difference in the incidence of chronic pain between patients given pre-emptive epidural analgesia (initiated prior to surgery) and patients in whom epidural analgesia was commenced after surgery — 39.6% vs 48.6% (Bong et al, 2005 **Level I**).

The addition of low-dose IV ketamine to thoracic epidural analgesia reduced the severity and need for treatment of post-thoracotomy pain at 1 and 3 months postoperatively (Suzuki et al, 2006 **Level II**). However, another study showed that perioperative IV ketamine in addition to interpleural local anaesthetic did not prevent chronic neuropathic pain up to 4 months after thoracotomy (Duale et al, 2009 **Level II**).

Cryoanalgesia, which provides effective pain relief in the immediate postoperative period (De Cosmo et al, 2008), caused an increased incidence of chronic pain (Ju et al, 2008 **Level II**).

Postmastectomy pain syndrome

Chronic pain after mastectomy is common. In one epidemiological study the incidence was 24% at 18 months (Vilholm et al, 2008a **Level IV**); another study looking at patients more than 5 years after surgery (with no recurrence of cancer) reported an incidence of 29% (Peuckmann et al, 2009 **Level IV**). Phantom breast pain has also been described, however, the incidence was low in the range of 7% at 6 weeks and 1% at 2 years (Dijkstra et al, 2007 **Level III-3**); phantom sensations are more common — reported in 19% of patients more than 5 years after surgery (Peuckmann et al, 2009 **Level IV**). Significant predictors for the development of postmastectomy chronic pain were radiotherapy and younger age (Peuckmann et al, 2009 **Level IV**). Other risk factors were higher postoperative pain scores and inclusion of major reconstructive surgery (Chang, Mehta et al, 2009 **Level IV**).

Sensory testing (thermal thresholds, cold allodynia, and temporal summation on repetitive stimulation) showed that postmastectomy pain is a neuropathic pain condition (Vilholm et al, 2009 **Level III-2**).

Preincisional paravertebral block reduced prevalence and intensity of pain 12 months after breast surgery (Kairaluoma et al, 2006 **Level II**). Perioperative use of gabapentin or mexiletine after mastectomy reduced the incidence of neuropathic pain at 6 months postoperatively, from 25% in the placebo to 5% in both treatment groups (Fassoulaki et al, 2002 **Level II**). Similar protective results were achieved by the same group by the use of a eutectic mixture of local anaesthetics alone (Fassoulaki et al, 2000 **Level II**) or in combination with gabapentin (Fassoulaki et al, 2005 **Level II**).

Levetiracetam was ineffective in the treatment of postmastectomy syndrome (Vilholm et al, 2008b **Level II**).

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 et al, 2008 **Level IV**). Ejaculatory pain is a feature of this syndrome and occurs in around 2.5% of patients (Aasvang et al, 2007 **Level IV**).

Very young age may be a protective factor as hernia repair in children under 3 months age did not lead to chronic pain in adulthood (Aasvang & Kehlet, 2007 **Level IV**).

Mesh removal and selective neurectomy of macroscopically injured nerves reduced impairment in patients with postherniorrhaphy pain syndrome (Aasvang & Kehlet, 2009 **Level III-3**).

Posthysterectomy pain syndrome

Chronic pain is reported by 5% to 32% of women after hysterectomy (Brandsborg et al, 2008). In most women the pain was present preoperatively; at a 1 to 2 year follow-up, pain was reported as a new symptom in 1% to 15% of patients (Brandsborg et al, 2008). 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 non-pelvic pain were associated with the presence of pain 4 months after surgery (Brandsborg et al, 2009 **Level III-3**). For pain reported 1 year after surgery, risk factors were preoperative pelvic and non-pelvic pain and previous Caesarean section; there was no difference found between vaginal or abdominal hysterectomy (Brandsborg et al, 2007 **Level IV**).

Patients given perioperative gabapentin and a postoperative ropivacaine wound infusion had lower opioid requirements after surgery and less pain one month later compared with patients given placebo, although there was no difference in pain scores for the first 7 postoperative

days (Fassoulaki et al, 2007 **Level II**). Spinal anaesthesia in comparison with general anaesthesia reduced the risk of chronic postsurgical pain after hysterectomy (OR: 0.42; CI 0.21 to 0.85) (Brandsborg et al, 2007 **Level IV**).

Key messages

1. Perioperative epidural analgesia reduces the incidence of post-thoracotomy pain syndrome (**N**) (**Level II**).
2. Cryoanalgesia for thoracotomy relieves postoperative pain but increases the risk of post-thoracotomy pain syndrome (**N**) (**Level II**).
3. Preincisional paravertebral block and perioperative use of gabapentin, mexiletine and/or eutectic mixture of local anaesthetic reduce the incidence of postmastectomy pain (**N**) (**Level II**).
4. Post-thoracotomy, postmastectomy, postherniotomy and posthysterectomy pain syndromes occur frequently (**N**) (**Level IV**).

9.1.4 Day-stay or short-stay surgery

Over 60% of surgery is now performed on a day-stay basis. Adequate postoperative pain management is often the limiting factor when determining whether a patient can have surgery performed as a day procedure. Provision of 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 general (Segerdahl et al, 2008a **Level IV**) and a paediatric population (Segerdahl et al, 2008b **Level IV**). Another survey from a single institution found that even at 3 and 4 days after day-stay surgery, 10% and 9% of patients respectively reported moderate to severe pain (Greengrass & Nielsen, 2005 **Level IV**). The best predictive factor was the presence of preoperative pain; other factors included preoperative high expectations of postoperative pain, anticipation of pain by clinicians and younger age (Gramke et al, 2009 **Level IV**).

Adverse effects of pain

Inadequate analgesia may delay patient discharge; pain was the most common cause of Phase 1 recovery delays affecting 24% of patients overall (Pavlin et al, 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 et al, 1996; Michaloliakou et al, 1996). The most common reason for unplanned hospital admission across 14 day-surgery units in Finland was unrelieved pain (Mattila & Hynynen, 2009 **Level III-2**).

Inadequate pain management may cause sleep disturbance (Strassels et al, 2002 **Level IV**) and limit early mobilisation, which may be crucial for early return to normal function and work (Strassels et al, 2002 **Level IV**).

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 — see relevant sections of this document:

- systemically administered analgesic drugs (Section 4);
- regionally and locally administered analgesics drugs (Section 5); and
- regional and other local analgesia techniques (Section 7).

However, certain local and regional techniques offer specific benefits to patients after day-stay or short-stay surgery; these issues are discussed here. In particular, there has been increasing interest in the use of 'single-dose' as well as continuous peripheral nerve blockade (CPNB) in patients discharged home.

Local infiltration

Infiltration of local anaesthetic reduced requirements for opioid analgesics after day surgery and leads to a lower incidence of nausea and vomiting (Eriksson et al, 1996 **Level II**; Michaloliakou et al, 1996 **Level II**).

After day-stay hernia repair, wound infiltration with levobupivacaine provided analgesia for 24 hours (Ausems et al, 2007 **Level II**). Local infiltration was superior to opioid and tenoxicam after minor laparoscopic surgery (Salman et al, 2000 **Level II**). Infiltration of the trocar site for day-case laparosopic cholecystectomy was more effective if done prior to incision than postoperatively (Cantore et al, 2008 **Level II**). However, after day-case laparoscopic gynaecological surgery, wound infiltration did not significantly reduce pain or opioid requirements (Fong et al, 2001 **Level II**).

Continuous wound infusions with local anaesthetics

There were only limited analgesic benefits for the first postoperative day with the continuous infusion of local anaesthetic after outpatient inguinal hernia repair (Schurr et al, 2004 **Level II**; Lau et al, 2003 **Level II**).

Single-dose peripheral nerve blockade

Peripheral nerve blocks (PNBs) are useful in ambulatory surgery as they provide site-specific anaesthesia with prolonged analgesia and minimal haemodynamic changes. The decision to discharge ambulatory patients following PNB with long-acting local anaesthesia is controversial as there is always the potential risk of harm to an anaesthetised limb.

A prospective study including 1119 upper and 1263 lower extremity blocks demonstrated that long-acting PNBs were safe and that patients could be discharged with an insensate limb (Klein et al, 2002 **Level IV**). 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.

Ilioinguinal and iliohypogastric nerve block

Herniorrhaphy performed under ilioinguinal and iliohypogastric nerve block led to superior pain relief, less morbidity, less urinary retention and cost advantages (Ding & White, 1995 **Level II**). The analgesic benefit with bupivacaine lasted around 6 hours (Toivonen et al, 2001 **Level II**).

Paravertebral block

Paravertebral blocks provided better analgesia than more distal nerve blocks after inguinal herniorrhaphy with earlier discharge, high patient satisfaction and few side effects (Klein et al, 2002 **Level II**). Their successful use has also been reported after outpatient lithotripsy (Jamieson & Mariano, 2007 **Level IV**). While paravertebral blocks after major ambulatory breast surgery provided good analgesia (Weltz et al, 1995 **Level II**), after minor breast surgery in a day-care setting, the benefits were small and may not justify the risk (Terheggen et al, 2002 **Level II**).

Upper and lower limb blocks

A single-dose femoral nerve block with bupivacaine for anterior cruciate ligament reconstruction provided 20 to 24 hours of postoperative analgesia (Mulroy et al, 2001 **Level II**). There was an associated decreased requirement for recovery room stay and unplanned hospital admission, thereby having the potential to create significant hospital cost savings

(Williams et al, 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 to a similar extent (Williams et al, 2003 **Level IV**).

Interscalene plexus block provided safe and effective analgesia after ambulatory shoulder surgery (Bishop et al, 2006 **Level IV**; Faryniarz et al, 2006 **Level IV**). 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 et al, 2004 **Level II**).

Continuous peripheral nerve blockade

Patients may suffer intense pain following resolution of a peripheral nerve block although it maximises pain relief in the first 12 to 24 hours (Chung et al, 1997 **Level IV**). CPNB using perineural catheters and continuous infusions of local anaesthetic led to sustained postoperative analgesia (Ilfeld, Morey, Wang et al, 2002 **Level II**; Ilfeld, Morey & Enneking, 2002 **Level II;** Zaric et al, 2004 **Level II**), was opioid-sparing (Ilfeld, Morey, Wang et al, 2002 **Level II**; Ilfeld, Morey & Enneking, 2002 **Level II**; Ilfeld et al, 2003 **Level II**) and resulted in less sleep disturbance (Ilfeld, Morey, Wang et al, 2002 **Level II**; Ilfeld, Morey & Enneking, 2002 **Level II**) and improved rehabilitation (Capdevila et al, 1999 **Level II**). Patients achieved discharge criteria significantly earlier in a number of ambulatory settings: after total shoulder arthroplasty with use of continuous interscalene blocks (21 vs 51 hours) (Ilfeld et al, 2006 **Level II**); after hip arthroplasty with use of continuous lumbar plexus block (29 vs 52 hours) (Ilfeld, Ball et al, 2008 **Level II**); and after total knee arthroplasty with the use of continuous femoral nerve blocks (25 vs 71 hours) (Ilfeld, Le et al, 2008 **Level II**). These benefits have the potential to reduce hospital costs (Ilfeld et al, 2007 **Level III-3**).

Compared with a single-injection interscalene block, a 2-day interscalene infusion at home after shoulder surgery was opioid-sparing and improved pain relief, sleep and patient satisfaction (Mariano et al, 2009 **Level II**).

Patient-controlled delivery of the infusion improved analgesia and function more than a continuous infusion and even more so compared with IV morphine PCA (Capdevila et al, 2006 **Level II**).

The safety and efficacy of CPNBs in an ambulatory setting has been confirmed in adult (Swenson et al, 2006 **Level IV**; Fredrickson et al, 2008 **Level IV**) and paediatric patients (Ganesh et al, 2007 **Level IV**; Ludot et al, 2008 **Level IV**).

Inadvertent intravascular catheter placement should be excluded prior to patient discharge using a test dose of local anaesthetic and adrenaline (epinephrine) (Rawal et al, 2002). Patients and their carers should be given extensive oral and written instructions about management, side effects and care of the local anaesthetic catheter, and have 24-hour a day telephone access to an anaesthesiologist during the postoperative period while CNPB is in use (Swenson et al, 2006), as 30% of patients make unscheduled phone calls regarding catheter infusions despite been given adequate written and verbal instructions (Ilfeld, Morey & Enneking, 2002 **Level II**). 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 et al, 2006 **Level IV**), although patients may have significant anxiety about catheter removal at home (Ilfeld et al, 2004 **Level IV**).

Detailed reviews of the use of CPNBs for ambulatory surgery have been published (Cheng et al, 2008; Ilfeld & Enneking, 2005).

Non-pharmacological techniques

Non-pharmacological techniques such as transcutaneous electrical nerve stimulation (TENS), acupuncture, hypnosis, ultrasound, 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 & Lisander, 1996 **Level II**). Continuous-flow cold therapy has been shown to be effective following outpatient anterior cruciate ligament reconstruction, also reducing analgesic requirements (Barber et al, 1998 **Level II**).

Key messages

1. Infiltration of the wound with local anaesthetic agents provides good and long-lasting analgesia after ambulatory surgery (**U**) (**Level II**).
2. Peripheral nerve blocks with long-acting local anaesthetic agents provide long-lasting postoperative analgesia after ambulatory surgery (**U**) (**Level II**).
3. Single shot infraclavicular blocks provide effective analgesia and less nausea following hand and wrist surgery and earlier ambulation and hospital discharge compared with general anaesthesia (N) (**Level II**).
4. Continuous peripheral nerve blocks provide extended analgesia after ambulatory surgery (**U**) (**Level II**), leading to reduced opioid requirements, less sleep disturbance, earlier achievement of discharge criteria and improved rehabilitation (**N**) (**Level II**).
5. Continuous peripheral nerve blocks have been shown to be safe at home, if adequate resources and patient education are provided (**U**) (**Level IV**).
6. Pain relief after ambulatory surgery remains poor (**N**) (**Level IV**) and is a common cause of unplanned readmissions (**N**) (**Level III-3**).

9.1.5 Cranial neurosurgery

There is a widespread belief that intracranial surgery does not result in much patient discomfort and pain. However, recent surveys have shown that patients may have significant pain in the early phase after intracranial surgery. In one survey, 69% of patients reported moderate to severe pain on the first postoperative day (Gottschalk et al, 2007 **Level IV**). These findings are in line with another study that found incidences of 56% moderate and 25% severe pain (Thibault et al, 2007 **Level IV**). Similar numbers of up to 80% are confirmed in a review of the literature on this topic (Nemergut et al, 2007).

However, the pain is not as severe as, for example, after spinal surgery (Klimek et al, 2006 **Level III-2**) or other surgical procedures such as extracranial maxillary/mandibular surgery or lumbar surgery (Dunbar et al, 1999 **Level III-2**). The pain is said to be more severe after an infratentorial rather than a supratentorial approach (Gottschalk et al, 2007 **Level IV**; Thibault et al, 2007 **Level IV**). These differences are disputed only by one small study (Irefin et al, 2003 **Level III-2**). Non-craniotomy neurosurgery, for example trans-sphenoidal surgery, seems to be associated with very limited pain and minimal morphine requirements (Flynn & Nemergut, 2006 **Level IV**).

It is noteworthy that craniotomy can lead to significant chronic headache. Six months after supratentorial craniotomy for aneurysm repair, 40% of patients reported headache according to the International Headache Society classification, of whom 10.7% had acute and 29.3% chronic headache (Rocha-Filho et al, 2008 **Level IV**). There were no differences between patients with or without subarachnoid haemorrhage.

The management of postoperative pain after intracranial surgery is often poor. The problems of postcraniotomy analgesia were analysed in a survey of United Kingdom neurosurgical centres (Roberts, 2005 **Level IV**); the principal analgesic was IM codeine, only three of twenty-three centres used morphine and only one used PCA. Pain was only assessed in 57% of cases (Roberts, 2005 **Level IV**). This practice had not changed since 1995 when IM codeine was the primary analgesic used by 97% of centres (Stoneham & Walters, 1995 **Level IV**).

A number of reasons are likely to contribute to this, such as concerns about the adverse effects of opioids and their ability to interfere with recovery and neurological assessment, as well as the concern that opioid-induced respiratory depression will lead to hypercarbia and increased intracranial pressure (Nemergut et al, 2007). Similarly, there is a concern that non-steroidal anti-inflammatory drugs (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 et al, 2007); the limited number of available heterogeneous trials have many weaknesses in study design and methodology. The question remains as to whether all craniotomies are the same with regard to analgesic requirements (Nemergut et al, 2007).

Treatment of acute postoperative pain after cranial neurosurgery

Paracetamol

A trial comparing paracetamol (acetaminophen) alone with paracetamol plus tramadol or paracetamol plus nalbufin was stopped early as paracetamol alone gave ineffective pain relief in most patients (Verchere et al, 2002 **Level II**).

Non-selective non-steroidal anti-inflammatory drugs

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 et al, 1999 **Level II**). However, a single-centre, retrospective cohort study of 6668 cases over 5 years identified an association between the development of postoperative haematoma and the use of aspirin or non-selective NSAIDs (nsNSAIDs) (Palmer et al, 1994 **Level IV**).

Coxibs

There was some limited benefit with the use of parecoxib over placebo at 6 hours, but not at other time points in the first 24 hours postoperatively, with regard to pain scores and morphine use in one study (Jones et al, 2009 **Level II**). Another study identified better pain control and an opioid-sparing effect of rofecoxib compared with placebo (Rahimi et al, 2006 **Level II**).

Opioids

Not surprisingly, PCA morphine or PCA morphine with ondansetron was superior to placebo after infratentorial craniotomy (Jellish et al, 2006 **Level II**). Morphine was also more effective than codeine following craniotomy; this was found for IM prn administration of both compounds (Goldsack et al, 1996 **Level II**) but also in a comparison of PCA morphine with IM codeine (Sudheer et al, 2007 **Level II**). PCA fentanyl was more effective than prn IV fentanyl and did not increase the risk of adverse effects after craniotomy (Morad et al, 2009 **Level II**).

Codeine 60 mg IM was more effective than tramadol 50 mg or 75 mg IM (Jeffrey et al, 1999 **Level II**) and morphine PCA was better than tramadol PCA (Sudheer et al, 2007 **Level II**).

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 et al, 2003 **Level II**) and sufentanil (Gerlach et al, 2003 **Level II**).

Local anaesthetic scalp block

A comparison between scalp nerve block and morphine showed no relevant differences in any analgesic parameters (Ayoub et al, 2006 **Level II**). Scalp infiltration was also no more effective that IV fentanyl (Biswas & Bithal, 2003 **Level II**).

However, comparisons of scalp blocks with bupivacaine or ropivacaine and placebo showed better analgesia with the local anaesthetic blocks in a number of trials (Bloomfield et al, 1998 **Level II**; Nguyen et al, 2001 **Level II**; Law-Koune et al, 2005 **Level II**; Bala et al, 2006 **Level II**; Gazoni et al, 2008 **Level II**; Batoz et al, 2009 **Level II**). Scalp infiltration with ropivacaine also reduced the incidence of persistent pain 2 months after craniotomy, from 56% to 8 % (Batoz et al, 2009 **Level II**).

A comparison between SC local anaesthetic infiltration and occipital/supraorbital nerve block showed no difference between groups in the postoperative period, but nerve blocks were less painful than infiltration analgesia (Watson & Leslie, 2001 **Level II**).

Adjuvant drugs

Clonidine did not improve analgesia after supratentorial craniotomy (Stapelfeldt et al, 2005 **Level II**).

Key messages

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

9.2 Acute pain following spinal cord injury

Acute pain following spinal cord injury (SCI) is common, with over 90% of patients experiencing pain in the first 2 weeks following injury (Siddall et al, 1999 **Level IV**); however the range of described prevalence varies between 26% and 96% (Dijkers et al, 2009 **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 (Siddall et al, 2002). Neuropathic pain associated with a lesion of the central (somatosensory) nervous system is termed central pain (Loeser & Treede, 2008). Phantom pain and complex regional pain syndromes may also develop in patients with SCI.

Table 9.1 Taxonomy of acute pain associated with spinal cord injury

Pain type	Location relative to level of injury	Description, structures and pathology
Neuropathic pain	Above level	pain located in an area of sensory preservation peripheral nerve or plexus injury
	At level	'segmental pain' at level of the injury spinal cord lesion (central pain) nerve root lesion (cauda equina) combined cord and root lesions syringomyelia
	Below level	pain below the level of injury spinal cord lesion (eg central dysaesthesia syndrome) phantom pain
	Other	complex regional pain syndrome
Nociceptive pain	Somatic	musculoskeletal pain (eg vertebral fracture, muscle spasms, overuse syndromes) procedure-related pain (eg pressure sore dressings)
	Visceral	urinary tract (eg calculi) gastrointestinal tract
Other		dysreflexic headache

The taxonomy of acute pain associated with spinal cord injury in Table 9.1 is based on Siddall (Siddall et al, 2002).

Treatment of acute neuropathic pain after spinal cord injury

There are no studies specifically examining the treatment of acute neuropathic pain following SCI. Treatment must therefore be based on evidence from studies of chronic central pain and other neuropathic pain syndromes. An algorithm for the treatment of pain in patients with SCI has been promulgated (Siddall & Middleton, 2006).

Opioids and tramadol

Under experimental conditions, IV alfentanil decreased central pain following SCI compared with placebo and ketamine (Eide et al, 1995 **Level II**). IV morphine decreased tactile allodynia but had no effect on other neuropathic pain components in SCI and poststroke patients (Attal et al, 2002 **Level II**). Tramadol was effective for the treatment of neuropathic pain after spinal cord injury but the incidence of side effects was high (Norrbrink & Lundeberg, 2009 **Level II**).

Ketamine

Ketamine infusion decreased neuropathic pain in SCI patients (Eide et al, 1995 **Level II**; Kvarnstrom et al, 2004 **Level II**).

Membrane stabilisers

Under experimental conditions, IV lignocaine reduced neuropathic pain in SCI (Finnerup, Biering-Sorensen et al, 2005 **Level II**) and reduced spontaneous pain and brush allodynia in central pain (Attal et al, 2000 **Level II**). Other trials have found that lignocaine reduced pain in only one of ten SCI patients (Kvarnstrom et al, 2004 **Level II**) and that mexiletine was ineffective (Chiou-Tan et al, 1996 **Level II**). Lignocaine was most effective in the treatment of neuropathic pain due to peripheral nerve lesions (Kalso et al, 1998 **Level I**).

Antidepressants

There was no significant difference in pain or disability in SCI patients with chronic pain treated with amitriptyline or placebo (Cardenas et al, 2002 **Level II**); however amitriptyline improved below-level neuropathic pain in patients with depression (Rintala et al, 2007 **Level II**). There are no studies of selective serotonin reuptake inhibitors (SSRIs) in the treatment of central pain (Finnerup, Otto et al, 2005 **Level I**).

Anticonvulsants

Pregabalin significantly reduced central pain and improved sleep, anxiety and global impression of change in patients with SCI, compared with placebo (Siddall et al, 2006 **Level II**). Smaller trials supported the effectiveness of gabapentin in decreasing central pain and improving quality of life (Levendoglu et al, 2004 **Level II**; Tai et al, 2002 **Level II**). Lamotrigine reduced spontaneous and evoked pain in patients with incomplete SCI (Finnerup et al, 2002 **Level II**). Valproate was ineffective in the treatment of SCI pain (Drewes et al, 1994 **Level II**).

Intravenous anaesthetics

An IV bolus of low-dose propofol reduced the intensity of central pain and allodynia for up to 1 hour in approximately 50% of patients (Canavero & Bonicalzi, 2004 **Level II**).

Non-pharmacological techniques

Self-hypnosis as well as electromyelograph (EMG) biofeedback training led to reduced pain intensity in patients with SCI; in some aspects self-hypnosis was superior to EMG biofeedback (Jensen et al, 2009 **Level II**).

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 must therefore be based on evidence from other studies of nociceptive and visceral pain.

Key messages

1. Gabapentinoids (gabapentin/pregabalin) (**S**), intravenous opioids, ketamine or lignocaine (lidocaine) (**U**) tramadol, self-hypnosis and electromyelograph biofeedback (**N**) are effective in the treatment of neuropathic pain following spinal cord injury (**Level II**).

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

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

9.3 ACUTE BURN INJURY PAIN

Acute pain following burn injury can be nociceptive and/or neuropathic in nature and may be constant (background pain), intermittent or procedure-related. There is limited evidence for the management of pain in burn injury and treatment is largely based on evidence from case reports and case series, or data extrapolated from other relevant areas of pain medicine.

Burn pain is often undertreated, particularly in the elderly (Choiniere, 2001). However, effective pain management after acute burn 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 35% to 58% of burn patients (Choiniere et al, 1989; Dauber et al, 2002).

Immediately after the injury, simple measures such as cooling (Davies, 1982), covering, elevating and immobilising the burn may provide analgesia (Kinsella & Booth, 1991; Gallagher, Rae & Kinsella, 2000). With severe burn pain, analgesia is best achieved by titration of IV opioids.

Opioid doses do not require adjustment, as the pharmacokinetics of morphine are unchanged in burns patients (Perreault et al, 2001). Absorption of IM and SC opioids may be unreliable in the presence of hypovolaemia and vasoconstriction associated with burns (Kinsella & Rae, 2008).

PCA with morphine is effective for burn pain in adults (Choiniere et al, 1992 **Level II**) and children (Gaukroger et al, 1991 **Level IV**). Conversion to oral opioids is possible once normal gastrointestinal (GI) function has returned; even severe burn injury does not affect gastric emptying or the absorption of oral paracetamol (Hu et al, 1993 **Level III-2**).

Opioids may be supplemented with non-opioid drugs. There is experimental evidence for beneficial effects of ketamine (Ilkjaer et al, 1996) and dextromethorphan (Ilkjaer et al, 1997) on hyperalgesia, and clinical evidence of an opioid-sparing effect with clonidine (Viggiano et al, 1998 **Level II**).

Gabapentin reduced pain and opioid consumption following acute burns injury (Cuignet et al, 2007 **Level III-3**) and reduced neuropathic pain descriptors in a small case series (Gray et al, 2008 **Level IV**).

Parenteral methylprednisolone or ketorolac reduced secondary hyperalgesia surrounding an experimental burn injury in human volunteers, however further clinical research is required (Stubhaug et al, 2007 **Level II**).

9.3.1 Management of procedural pain

Procedural pain may be difficult to manage in burn patients. Dressing changes may be associated with frequent and prolonged periods of pain with up to 84% of burn patients reporting extreme, intense pain during therapeutic procedures (Ashburn, 1995). The choice of dressing has an effect on time to healing and pain during dressing change; biosynthetic dressings have been found to be superior (Wasiak et al, 2008 **Level I).**

Opioid therapy is the mainstay of analgesia for burn procedures. However, very high doses may be required (Linneman et al, 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 et al, 2004 **Level II**) or alfentanil (Sim et al, 1996 **Level IV**) administered via PCA or target-controlled infusions (Gallagher, Rae, Kenny et al, 2000 **Level IV**) have been used successfully to provide analgesia during burn dressing changes. IN fentanyl was a viable alternative to oral morphine in children for burn dressings (Borland et al, 2005 **Level II**). In adults, there was no difference in pain scores or rescue analgesic requirements between IN fentanyl and oral morphine for burn dressings (total surface less than 26%) (Finn et al, 2004 **Level II**). Oral transmucosal fentanyl provided similar analgesia to oral oxycodone (Sharar et al, 2002 **Level II**) and hydromorphone (Sharar et al, 1998 **Level II**) with a similar side-effect profile, for daily burn care in children and adolescents (see Section 10.4.1).

Nitrous oxide (N_2O), ketamine and IV lignocaine infusions (Jonsson et al, 1991 **Level IV**) have also been used to provide analgesia for burn procedures (see Sections 4.3.1, 4.3.2 and 4.3.5), however a Cochrane review reported that more trials were required to determine the efficacy of lignocaine (Wasiak & Cleland, 2007 **Level I**).

PCA with a ketamine and midazolam mixture was effective and well-tolerated when used for analgesia and sedation during burn dressings (MacPherson et al, 2008 **Level IV**).

Sedation, as an adjunct to analgesia, can improve pain relief. This has been shown for lorazepam combined with morphine (Patterson et al, 1997 **Level II**); patient-controlled sedation with propofol may also be effective (Coimbra et al, 2003 **Level IV**). A propofol/ketamine combination resulted in less 'restlessness' during burn dressing changes compared with a propofol/fentanyl combination, with no difference in emergence phenomena (Tosun et al, 2008 **Level II**). Dexmedetomidine may be effective for sedation in the intensive care unit for paediatric burn patients but further trials are required (Walker et al, 2006 **Level IV**).

Topical analgesic techniques, such as lignocaine (Brofeldt et al, 1989 **Level IV**) or morphine-infused silver sulfadiazine cream (Long et al, 2001 **Level IV**) may be effective, however a topical gel dressing containing morphine was no more effective than other gel dressing in reducing burn injury pain in the emergency department (Welling, 2007 **Level II**).

9.3.2 Non-pharmacological pain management

Hypnosis, distraction, auricular electrical stimulation, therapeutic touch techniques and massage therapy have been used for the treatment of burn pain, including procedural pain. A lack of prospective randomised trials makes comparisons with conventional therapies difficult (Kinsella & Rae, 2008) (see Section 8.1.3). A study comparing two psychological support interventions, hypnosis and stress-reducing strategies, found that visual analogue scale (VAS) anxiety scores were significantly better after hypnosis although there was no significant difference in pain reports (Frenay et al, 2001 **Level II**).

Distraction by virtual reality (VR) techniques reduced pain scores in children during burn dressings (Das et al, 2005 **Level III-3**) including in a hydrobath (Hoffman et al, 2008 **Level III-3**) and following burn physical rehabilitation (Sharar et al, 2007 **Level III-3**). Simply watching television during burn care may be as effective as VR in reducing pain scores (van Twillert et al, 2007 **Level III-3**).

Augmented reality techniques (interactive computer programme) produced a statistically significant reduction in pain compared with usual care during paediatric burn dressings lasting longer than 30 minutes, however further research is required to determine the clinical utility of these methods (Mott et al, 2008 **Level II**).

Key messages

1. The use of biosynthetic dressings is associated with a decrease in time to healing and a reduction in pain during burn dressings changes (**N**) (**Level I** [Cochrane Review]).
2. Opioids, particularly via PCA, are effective in burn pain, including procedural pain (**S**) (**Level II**).
3. Augmented reality techniques (**N**) (**Level II**), virtual reality or distraction techniques (**N**) (**Level III-3**) reduce pain during burn dressings.
4. Gabapentin reduces pain and opioid consumption following acute burn injury (**N**) (**Level III-3**).
5. PCA with ketamine and midazolam mixture provides effective analgesia and sedation for burn dressings (**N**) (**Level IV**).

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

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

☑ Acute pain following burn injury requires aggressive multimodal and multidisciplinary treatment.

9.4 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 non-specific 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 process, immunosuppression, penetrating wound, drug abuse by injection), history of trauma or minor trauma, history of osteoporosis and taking corticosteroids, past history of malignancy, age greater than 50 years, failure to improve with treatment, unexplained weight loss, pain at multiple sites or at rest and absence of aggravating features (Australian Acute Musculoskeletal Pain Guidelines Group, 2003). A full neurological examination is warranted in the presence of lower limb pain and other neurological symptoms (eg weakness, foot drop, cauda equina syndrome, loss of bladder and/or bowel control).

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).

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). In view of the high quality and extensiveness of these guidelines, no further assessment of these topics has been undertaken for this document. 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 9.5 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).

Since their publication, a number of further guidelines have been published that are worth considering. These include:

- *The Health Care Guideline: Adult Low Back Pain of the Institute for Clinical Systems Improvement* (ICSI, 2008).
- *The Guideline on Management of Acute Low Back pain by the Michigan Quality Improvement Consortium* (Michigan Quality Improvement Consortium, 2008).
- *Clinical Guidelines for Best Practice Management of Acute and Chronic Whiplash-Associated Disorders* (South Australian Centre for Trauma and Injury Recovery and endorsed by NHMRC) (TRACsa, 2008).
- *American Pain Society and American College of Physicians clinical practice guidelines*. These cover both acute and chronic low back pain (Chou & Huffman, 2007a; Chou & Huffman 2007b; Chou et al 2007).

The relevant key messages of these guidelines are very similar to the ones presented here.

Key messages

1. Acute low back pain is non-specific 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, 'activity-focused' printed and verbal information, and behavioural therapy interventions are beneficial in acute low back pain (**U**) (**Level I**).
3. Advice to stay active, exercises, multimodal therapy and pulsed electromagnetic therapy (in the short term) are 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**).

9.5 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). In view of the high quality and extensiveness of these guidelines, no further assessment of these topics has been undertaken for this document.

The following is an abbreviated summary of key messages from these guidelines 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).

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, 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 plan (**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**).

9.6 Acute medical pain

9.6.1 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 chronic pancreatitis or irritable bowel syndrome and may require a multidisciplinary pain management approach.

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 et al, 2007 **Level I**) or in children (Kim et al, 2002 **Level II**; Green et al, 2005 **Level II**), or lead to increased errors in clinical management (Ranji et al, 2006 **Level I**).

Renal colic

NsNSAIDs, opioids (Holdgate & Pollock, 2005 **Level I**) and metamizole (dipyrone) (Edwards, Meseguer et al, 2002 **Level I**) provided effective analgesia for renal colic. NsNSAIDs reduced requirements for rescue analgesia, produced less vomiting than opioids (particularly pethidine [meperidine] (Holdgate & Pollock, 2005 **Level I**) and reduced the number of episodes of renal colic experienced before passage of the renal calculi (Kapoor et al, 1989 **Level II**; Laerum et al, 1995 **Level II**).

Onset of analgesia was fastest when nsNSAIDs were administered intravenously (Tramer et al, 1998 **Level I**) although suppositories were also effective (Lee et al, 2005 **Level II**). A combination of IV ketorolac and 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 et al, 2006 **Level II**).

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 et al, 2000 **Level II**).

The smooth muscle relaxant buscopan failed to improve analgesia when combined with nsNSAIDs (Jones et al, 2001 **Level II**), opioids (Holdgate & Oh, 2005 **Level II**) or metamizole (Edwards, Meseguer et al, 2002 **Level I**). Papaverine was as effective as IV diclofenac in the initial treatment of renal colic, but required increased use of rescue analgesia (Snir et al, 2008 **Level II**). 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 et al, 2008 **Level II**).

IV ondansetron produced analgesia in 42% of patients with renal colic but was less effective than IM diclofenac (Ergene et al, 2001 **Level II**). IN desmopressin was also an effective analgesic, either alone, or in combination with IM diclofenac (Lopes et al, 2001 **Level II**).

Renal calculus expulsive therapy using the specific alpha-blocker tamsulosin was superior to comparative smooth muscle relaxants such as phloroglucinol or nifedipine in terms of increased stone expulsion and a reduction in analgesia requirements, surgical interventions, duration of hospital stay and days off work (Dellabella et al, 2005 **Level II**).

TENS applied over the painful flank during prehospital transport, reduced pain scores, anxiety and nausea in patients with renal colic (Mora et al, 2006 **Level II**).

IV fluid therapy had no effect on pain outcomes or stone transition in renal colic (Worster & Richards, 2005 **Level I**).

Biliary colic and acute pancreatitis

All opioids increase sphincter of Oddi tone and bile duct pressures in animal and human experimental models (Thompson, 2001). Morphine increased sphincter of Oddi contractions more than pethidine during cholecystectomy (Thune et al, 1990 **Level IV**).

There are no clinical studies comparing opioids in the treatment of pain associated with biliary spasm or acute pancreatitis (Thompson, 2001). 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 minutes in patients in the emergency department (Olsen et al, 2008 **Level II**).

Parenteral nsNSAIDs such as ketorolac, tenoxicam or diclofenac were at least as effective as parenteral opioids and more effective than buscopan in providing analgesia for biliary colic (Goldman et al, 1989 **Level II**; Al-Waili & Saloom, 1998 **Level II**; Dula et al, 2001 **Level II**; Henderson et al, 2002 **Level II**; Kumar, Deed et al, 2004 **Level II**) and may also prevent progression to cholecystitis (Goldman et al, 1989 **Level II**; Akriviadis et al, 1997 **Level II**; Al-Waili & Saloom, 1998 **Level II**; Kumar, Deed et al, 2004 **Level II**).

IM atropine was no more effective than saline in the treatment of acute biliary colic (Rothrock et al, 1993 **Level II**).

Irritable bowel syndrome and colic

There was weak evidence that antispasmodics (smooth muscle relaxants) reduced pain in irritable bowel syndrome, but no evidence of an analgesic effect with antidepressants or bulking agents (Quartero et al, 2005 **Level I**). Peppermint oil may also reduce pain (Pittler & Ernst, 1998 **Level I**) and was as effective as buscopan in reducing upper (Hiki et al, 2003 **Level II**) and lower GI spasm (Asao et al, 2003 **Level II**).

Primary dysmenorrhoea

NsNSAIDs are highly effective analgesics in dysmenorrhoea. While no difference was found between the different nsNSAIDs included in an analysis in terms of efficacy, ibuprofen had the least adverse effects (Marjoribanks et al, 2003 **Level I**). Paracetamol was less effective than naproxen, ibuprofen, mefenamic acid and aspirin; again, ibuprofen had the most favourable risk-benefit ratio (Zhang & Li Wan Po, 1998 **Level I**). NsNSAIDs also reduced bleeding and pain associated with the use of an intrauterine-device (Grimes et al, 2006 **Level I**).

Vitamin B1 (Proctor & Murphy, 2001 **Level I**), vitamin E (Ziaei et al, 2005 **Level II**) chinese herbal medicine (Zhu et al, 2007 **Level I**), rose tea (Tseng et al, 2005 **Level II**), guava leaf extract (*Psidii guajavae*) (Doubova et al, 2007 **Level II**), aromatherapy (Han et al, 2006 **Level II**) and fennel (*Foeniculum vulgare*) (Namavar Jahromi et al, 2003 **Level III-2**) are also effective.

High frequency TENS was effective in primary dysmenorrhoea (Proctor et al, 2002 **Level I**). The effectiveness of acupuncture in primary dysmenorrhoea is undetermined due to methodological problems in available studies (Yang et al, 2008 **Level I**).

Abdominal migraine

Abdominal migraine is a neurogastrointestinal disorder, usually of male children, characterised by recurrent attacks of acute abdominal pain, nausea, vomiting and often headaches. Pizotifen was found to be effective for prophylaxis and treatment (Symon & Russell, 1995 **Level II**) (see Section 9.6.5).

Key messages

1. Provision of analgesia does not interfere with the diagnostic process in acute abdominal pain (**S**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs, opioids and intravenous metamizole (dipyrone) provide effective analgesia for renal colic (**N**) (**Level I** [Cochrane Review]).
3. Non-selective 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. High frequency TENS is effective in primary dysmenorrhoea (**N**) (**Level I** [Cochrane Review]).
5. The onset of analgesia is faster when non-selective NSAIDs are given intravenously for the treatment of renal colic (**U**) (**Level I**).
6. Antispasmodics and peppermint oil are effective for the treatment of acute pain in irritable bowel syndrome (**U**) and gastrointestinal spasm (**N**) (**Level I**).
7. Non-selective NSAIDs and vitamin B1 are effective in the treatment of primary dysmenorrhoea (**U**) (**Level I**).
8. There is no difference between pethidine and morphine in the treatment of renal colic (**U**) (**Level II**).
9. Parenteral non-selective NSAIDs are as effective as parenteral opioids in the treatment of biliary colic (**U**) (**Level II**).

9.6.2 Herpes zoster-associated pain

Herpes zoster (HZ) (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 (Schmader & Dworkin, 2008). There is a marked increase in the risk of shingles with increasing age and with diseases and drugs that impair immunity: the lifetime risk is estimated at 20% to 30%, and up to 50% in those who reach 85 years of age (Schmader & Dworkin, 2008).

HZ-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 (postherpetic neuralgia). The pain varies in intensity and is described as 'burning', 'throbbing' or 'shooting'; itching, dysaesthesias, and allodynia may also be present (Dworkin et al, 2008). In the majority of cases, HZ is an acute self-limiting disease, although not infrequently, it may progress to postherpetic neuralgia (PHN) (pain that persists for more than 3 months after the onset of HZ). The incidence of PHN increases with age (over 50 years), occurring in up to 75% of patients aged 70 years or over who had shingles (Johnson & Whitton, 2004). Early, aggressive treatment of HZ infection and pain may reduce the incidence of PHN, although data on preventive strategies are limited.

Prevention of herpes zoster

A live attenuated VZV vaccine (Zostavax®) is available for the prevention of HZ (and PHN) in individuals over 60 years of age. A large, multicentre, randomised placebo-controlled trial (The Shingles Prevention Study) demonstrated its efficacy, with a reduction in the incidence of HZ by 51.3%, PHN by 66.5 % and HZ-associated 'burden of illness' by 61.1% (Oxman et al, 2005). The estimated number-needed-to-vaccinate to prevent a case of HZ was 11 (CI: 10-13) and for PHN 43 (CI: 33-53) (Brisson, 2008 **Level III-3**). The Advisory Committee for Immunization Practices of the US Centres for Disease Control and Prevention recommends vaccination with live, attenuated VZV for all persons aged 60 years or over, even if they have had a previous episode of HZ (Harpaz et al, 2008) as has the Pharmaceutical Benefits Advisory Committee of the Australian Government Department of Health and Ageing (PBAC, 2008).

Treatment of herpes zoster-associated pain

Antiviral agents

Acyclovir, valaciclovir or famciclovir, given within 72 hours of onset of the rash accelerated the resolution of HZ pain (Beutner et al, 1995 **Level II**; Wood et al, 1996 **Level I**; Jackson et al, 1997 **Level I**; Tyring et al, 2000 **Level II**). Famciclovir, in various doses and frequencies, was as effective as acyclovir for HZ-related outcomes, including pain (Shafran et al, 2004 **Level II**; Shen et al, 2004 **Level II**). Famciclovir or valaciclovir have replaced acyclovir as the drugs of choice in the treatment of HZ, because of more favourable pharmacokinetics and simpler dosing profiles (Cunningham et al, 2008).

Opioids, tramadol and paracetamol

HZ-associated pain may be severe and early and effective treatment is essential. Multimodal analgesia, with regular paracetamol in addition to an opioid such as oxycodone (Dworkin et al, 2007; Cunningham et al, 2008; Dwyer & Cunningham, 2002) 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 days of HZ compared with placebo, although the group of patients taking oxycodone had a much higher rate of withdrawal from the trial, primarily because of constipation (Dworkin et al, 2009 **Level II**).

Corticosteroids

Prednisolone added to acyclovir during HZ resulted in a modest reduction in pain intensity and improved the rate of skin lesion healing for up to 14 days, with no effect on the overall recovery rate at 3 weeks (Wood et al, 1994 **Level II**). Prednisolone, either as monotherapy or in combination with acyclovir, increased the likelihood of being 'pain-free' at 1 month by a factor of 2.3 (95% CI: 1.4 to 3.5), however there was no difference in the rate of skin healing, compared with placebo (Whitley et al, 1996 **Level II**).

Anticonvulsants

Administration of a single dose of gabapentin (900 mg) during HZ reduced acute pain intensity by 66% (33% for placebo) and also reduced the area and severity of allodynia, for up to 6 hours (Berry & Petersen, 2005 **Level II**), however no analgesic benefit was found when gabapentin was administered for 28 days (Dworkin et al, 2009 **Level II**).

Topical lignocaine

Topical lignocaine patches (5%) applied for 12 hours twice daily (on intact skin) during HZ, significantly reduced pain intensity and improved patient's global impression of pain relief, compared with a control vehicle patch: the incidence and severity of adverse events was low with both treatments (Lin et al, 2008 **Level II**).

Aspirin

Topical aspirin, in either moisturiser or diethyl ether, was an effective analgesic in HZ, compared with similar preparations containing indomethacin, diclofenac or placebo (De Benedittis et al, 1992 **Level II**) or oral aspirin (Balakrishnan et al, 2001 **Level II**).

Neuraxial or sympathetic blockade

A review of neuraxial (including sympathetic) blockade for the treatment of HZ-associated pain found that 71% (12/15) of studies (Kumar, Krone et al, 2004), only one of which was an RCT (Pasqualucci et al, 2000 **Level II**), reported a reduction in either the incidence or severity of HZ-associated pain to 1 month. In a subsequent RCT, there was a significant difference in the incidence (and to a lesser extent the intensity) of HZ pain in patients who received a single epidural methylprednisolone and bupivacaine injection, compared with those who received antiviral therapy and analgesia as 'standard care'; the NNT for complete resolution of HZ pain at 1 month with the epidural injection was 10 (van Wijck et al, 2006 **Level II**). However, given the modest clinical effects on acute pain and no effect on the incidence of PHN, the routine use of epidural local anaesthetic and steroid injection during HZ was not supported. Evidence of benefit for sympathetic blockade in the treatment of HZ-associated pain was conflicting (Kumar, Krone et al, 2004).

Prevention of postherpetic neuralgia

Immunisation of persons aged 60 years or older with live attenuated VZV vaccine, reduces the incidence of PHN (Oxman et al, 2005) and is now recommended as the standard of care, including for those who have experienced a previous episode of HZ (Harpaz et al, 2008).

During HZ, the early administration amitriptyline (for 90 days) (Bowsher, 1997 **Level II**) significantly reduced the incidence of PHN. However, contrary to the previous literature (Wood et al, 1996 **Level I**; Jackson et al, 1997 **Level I**; Beutner et al, 1995 **Level II**; Tyring et al, 2000 **Level II**), the use of the antiviral agent acyclovir or famcyclovir did not significantly reduce the incidence of PHN (Li et al, 2009 **Level I**).

Note: reversal of conclusion

This reverses the Level 1 conclusion in the previous edition of this document; earlier meta-analyses reported a reduced incidence of PHN.

Similarly, systemic corticosteroids (He et al, 2008 **Level I**) or an epidural injection with methylprednisolone and bupivacaine (van Wijck et al, 2006 **Level II**) were ineffective preventive strategies.

In the review by Kumar et al (Kumar, Krone et al, 2004) five of eight studies (63%) looked at prevention of PNH (one RCT only) and suggested that neuraxial blockade during HZ reduced the incidence of PHN at 6 months. The RCT found that local anaesthetic and steroid injections via an epidural catheter, for up to 21 days during HZ, significantly reduced the incidence (but not the intensity) of pain for 1 to 6 months, compared with systemic antiviral therapy plus prednisolone; however such an approach has limited practical application (Pasqualucci et al, 2000 **Level II**).

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 of postherpetic neuralgia (**R**) (**Level I**) [Cochrane Review]).
2. Immunisation of persons aged 60 years or older with varicella-zoster virus vaccine reduces the incidence of herpes zoster and postherpetic neuralgia (**N**) (**Level II**).
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 oxycodone controlled release, provide analgesia in herpes zoster (**N**) (**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.

9.6.3 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; non-typical presentations can occur, particularly in the elderly patient (see Section 11.2). Reducing ischaemia by optimising myocardial oxygen 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, including the use of supplemental oxygen (Pollack & Braunwald, 2008; Cannon, 2008).

Nitroglycerine was effective in relieving acute ischaemic chest pain; however, the analgesic response did not predict the diagnosis of coronary artery disease (Henrikson et al, 2003 **Level IV**).

In patients with suspected acute coronary syndrome, IV morphine significantly reduced pain within 20 minutes of administration; morphine doses were low (average of 7 mg over 3 days)

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 ECG, male sex and a history of angina or cardiac failure (Everts et al, 1998 **Level IV**).

Morphine provided better analgesia than IV metoprolol (Everts et al, 1999 **Level II**) 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 et al, 2000 **Level II**). However a large retrospective audit reported increased mortality in patients treated with morphine, either alone or in combination with nitroglycerine (independent of other confounders), in non-ST segment elevation acute coronary syndrome (Meine et al, 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 & Saarnivaara, 2001 **Level II**). Morphine was similar to buprenorphine (Weiss & Ritz, 1988 **Level II**) and pethidine (Nielsen et al, 1984 **Level II**) 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 et al, 2007 **Level II**).

In patients with chest pain due to cocaine-induced acute coronary syndrome, the addition of IV diazepam or lorazepam to treatment with sublingual nitroglycerine provided superior analgesia (Baumann et al, 2000 **Level II**; Honderick et al, 2003 **Level II**).

In acute coronary syndrome, hyperbaric oxygen therapy reduced time to relief of ischaemic pain, although insufficient evidence exists to recommend its routine use (Bennett et al, 2005 **Level I**).

N_2O in oxygen was effective in relieving acute ischaemic chest pain, with a significant reduction in beta-endorphin levels (O'Leary et al, 1987 **Level II**).

TENS reduced the number and duration of ischaemic events during unstable angina, however without a significant effect on pain (Borjesson et al, 1997 **Level II**).

NSAIDs may be useful in the treatment of acute pain in pericarditis (Schifferdecker & Spodick, 2003).

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 box ☑ represents conclusions based on clinical experience and expert opinion.

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

9.6.4 Acute pain associated with haematological disorders

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 et al, 2009).

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 and most frequently reported in the back, legs, knees, arms, chest and abdomen and may last from hours to weeks. 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 et al, 2009).

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 et al, 2003). Detailed clinical guidelines for managing acute painful crises in sickle cell disease are listed in Rees et al (Rees et al, 2003). The implementation of clinical practice guidelines for acute pain treatment in sickle cell crisis leads to more timely and more effective analgesia (Morrissey et al, 2009 **Level III-3**).

Overall, there is only very limited evidence for analgesic interventions in acute pain crises of sickle cell disease and meaningful meta-analyses cannot be performed (Dunlop & Bennett, 2006 **Level I**).

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 et al, 1992 **Level II**; Zipursky et al, 1992 **Level II**). However, nocturnal oxygen desaturation was associated with a significantly higher rate of painful sickle cell crises in children (Hargrave et al, 2003 **Level IV**).

Rehydration

There was insufficient evidence to suggest any benefit from fluid replacement therapy in reducing pain associated with sickle cell crises (Okomo & Meremikwu, 2007 **Level I**).

NsNSAIDs

Single-dose parenteral ketorolac did not reduce opioid requirements in painful vaso-occlusive crisis (Wright et al, 1992 **Level II**; Hardwick et al, 1999 **Level II**).

Opioids

In treating acute pain during a sickle cell crisis, IV opioid loading improved the analgesic efficacy of subsequent oral and PCA opioid therapy (Rees et al, 2003 **Level II**). A continuous IV morphine infusion shortened the duration of severe pain compared with intermittent parenteral opioids (Robieux et al, 1992 **Level II**) and PCA with morphine reduced opioid dose and related side effects (with a tendency to reduced length of hospital stay) compared with continuous infusion (van Beers et al, 2007 **Level II**). The use of inpatient morphine PCA, rapidly converted to oral CR morphine for use at home reduced the length of hospital stay by 23% and subsequent emergency department visits and readmissions by approximately 50%, compared with IM pethidine (Brookoff & Polomano, 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 et al, 1997 **Level II**). The use of oral opioids at home reduced the number of emergency department visits and hospital admissions for sickle cell pain (Conti et al, 1996

Level III-3; Friedman et al, 1986 **Level III-3**). However in children, the incidence of acute sickle chest syndrome, and plasma levels of morphine and M6G, was significantly higher with oral morphine compared with IV infusion (Kopecky et al, 2004 **Level II**).

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 of the 35 patients received excessive opioids and 'overdose' directly contributed to death in 5 out of the 35 (NCEPOD, 2008). In two-thirds of patients, there were inadequate observations of sedation and respiratory rates after opioid administration and IM pethidine administration was prevalent.

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 et al, 2003).

Inhaled nitric oxide

Nitric oxide (NO) deficiency or defective NO-dependent mechanisms may underlie many of the processes leading to vaso-occlusion. Inhaled NO may be of benefit in painful acute vaso-occlusive crises in children; however, further studies are required (Weiner et al, 2003 **Level II**).

Corticosteroids

Parenteral corticosteroids appear to reduce the duration of analgesia requirements and length of hospital stay, without major side effects, during sickle cell crises (Dunlop & Bennett, 2006 **Level I**). 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 et al, 1994 **Level II**).

Epidural analgesia

In severe crises, where pain is unresponsive to other measures, epidural analgesia has been used effectively (Yaster et al, 1994 **Level IV**).

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 & Olujohungbe, 2001 **Level I**).

Niprisan (an antisickling agent), zinc and piracetam (which prevent red blood cell dehydration) may reduce the incidence of painful sickle cell crises (Wambebe et al, 2001, **Level II**; Riddington & De Franceschi, 2002 **Level II**). The evidence for pircetam, however, is insufficient to support its use (Al Hajeri et al, 2007 **Level I**).

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 et al, 2001 **Level IV**). Haemophilia patients may also have pain syndromes associated with human immunodeficiency virus /acquired immunodeficiency syndrome (HIV/AIDS) (see Section 9.6.8). Recurrent acute pain may have a significant adverse impact on mood, mobility and quality of

life in haemophilia patients; biopsychosocial assessment and treatment should be considered (Wallny et al, 2001 **Level IV**).

Many haemophilia patients use Factor VIII to decrease pain associated with a bleeding episode (Wallny et al, 2001 **Level IV**). Higher-dose Factor VIII replacement reduced the number of patients with restricted joint movement after an acute haemarthrosis (Aronstam et al, 1983, **Level II**). Joint aspiration may reduce pain and improve joint function (Baker, 1992).

Although there is no good evidence available, opioids, simple analgesics, cold therapy and bandaging have been used in treating acute pain associated with haemophilia. NsNSAIDS have been used to provide analgesia in haemophilic arthropathy, but there are no data on their use in acute haemarthrosis. Coxibs may be of benefit due to a lack of platelet inhibitory effects (see Section 4.2). IM analgesics should be avoided due to the risk of bleeding.

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 (ALA) 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 central nervous system (CNS) toxicity (neuropsychiatric symptoms, seizures, brainstem and pituitary dysfunction); some patients may have a cutaneous photosensitivity (Visser & Goucke, 2008).

Pain management in acute porphyria is based on treatment of the disease, including resuscitation and supportive care, ceasing 'triggers', the early administration of hem arginate (Herrick et al, 1989 **Level II**), and possibly high-dose IV dextrose or cimetidine administration ('disease modifying agents') (Rogers, 1997).

Specific evidence for pain management in acute porphyria is limited. Analgesia is based largely on the use of IV and (later) oral opioids (Anderson et al, 2005; Herrick & McColl, 2005). Opioids such as pethidine (Deeg & Rajamani, 1990) or tramadol, and other 'analgesics' (such as tricyclic antidepressants [TCAs]) that lower seizure threshold should be avoided in acute porphyria, because of increased seizure risk.

The safety of nsNSAIDs or coxibs in acute porphyria has not been established; paracetamol, buscopan (for colic) or N_2O in oxygen, are considered safe (Anderson et al, 2005; Stoelting & Dierdorf, 1993).

There may be a place for IV low-dose ketamine or regional analgesia, although the safety of these approaches has not been established in acute porphyria. Ketamine does not induce ALA synthetase in rats (Harrison et al, 1985) and has been used for anaesthesia in porphyria patients without apparent problems (Capouet et al, 1987). However one case report noted increased porphyrin levels in a patient after induction with ketamine (Kanbak, 1997).

As metoclopramide is contraindicated and the safety of 5HT3 antagonists is as yet unclear, droperidol has been suggested as the antiemetic of choice in acute porphyria (Anderson et al, 2005).

Key messages

1. Parenteral corticosteroids appear to reduce the duration of analgesia requirements and length of hospital stay, without major side effects, during sickle cell crises (**S**) (**Level I** [Cochrane Review]).
2. There is insufficient evidence to suggest that fluid replacement therapy reduces pain associated with sickle cell crises (**N**) (**Level I** [Cochrane Review]).
3. Hydroxyurea is effective in decreasing the frequency of acute crises, life-threatening complications and transfusion requirements in sickle cell disease (**U**) (**Level I**).
4. 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 (**U**) (**Level II**).
5. Oxygen supplementation does not decrease pain during a sickle cell crisis (**U**) (**Level II**).

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**).

9.6.5 Acute headache

Headaches are a common cause of acute pain. 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 rule out serious cranial pathologies such as tumour, infection, cerebrovascular abnormalities, acute glaucoma and temporal arteritis (Silberstein, 2000; Steiner & Fontebasso, 2002).

The most frequent causes of acute headache are episodic tension-type headache (TTH) and migraine (Headache Classification Subcommittee of the IHS, 2004). Less frequent causes include 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 post-traumatic headache, postdural puncture headache (PDPH), headache attributed to substance use or its withdrawal and cervicogenic headache (Headache Classification Subcommittee of the IHS, 2004).

Comprehensive guidelines for the evaluation and treatment of acute headaches including migraine have been promulgated (Edlow et al, 2008; Steiner et al, 2007; Evers et al, 2006), including for children and adolescents (Lewis et al, 2004).

Episodic 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 a mild to moderate 'pressing' or 'tight pain' (sometimes with pericranial tenderness), not worsened by movement and not associated with nausea. Photophobia or phonophobia may occasionally be present (Headache Classification Subcommittee of the IHS, 2004).

The symptoms and pathogenesis of TTH may overlap with migraine, chronic daily headache, medication overuse headache and cervicogenic headache (Goadsby, 2003). Psychological, physical and environmental factors are important in TTH and should be addressed during assessment and treatment (Holroyd, 2002).

Treatment

Simple analgesics such as nsNSAIDs, paracetamol (Prior et al, 2002 **Level II**; Steiner et al, 2003 **Level II**) or aspirin (Steiner et al, 2003 **Level II**), either alone or in combination, provided effective analgesia in TTH. Ketoprofen, ibuprofen and naproxen were equally effective and superior to paracetamol (Lange & Lentz, 1995 **Level I**; Dahlof & Jacobs, 1996 **Level II**).

The addition of caffeine to paracetamol, aspirin (Migliardi et al, 1994 **Level I**) or ibuprofen (Diamond et al, 2000 **Level II**) significantly improved analgesia and a paracetamol-aspirin-caffeine combination was more effective than placebo and all three component drugs alone, in terms of analgesia outcomes and time to effect (Diener et al, 2005 **Level II**). IV magnesium was ineffective in treating acute TTH in the emergency department (Frank et al, 2004 **Level II**).

Acupuncture is an effective non-pharmacological intervention in TTH (Linde et al, 2009 **Level I**).

Migraine

Migraine is common, with a prevalence of 6% to 8% in males and 12% to 14% in females (Evers et al, 2006). Migraine headache is usually unilateral and is often severe, disabling and worsened by movement. Nausea, vomiting, photophobia and phonophobia are common and 20% of migraineurs experience an aura.

Most migraines are successfully managed by the patient and his or her family doctor, with up to 57% of patients not seeking medical attention for significant attacks (Mitchell et al, 1998). However a small number of patients fail to respond and present for treatment at emergency departments; approximately 80% of patients have tried their usual medications including simple analgesics or triptans before presentation (Larkin & Prescott, 1992; Shrestha et al, 1996) (see Section 9.9.2).

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 the successful treatment of migraine (Steiner et al, 2007).

Analgesia outcomes in migraine trials are usually listed as the proportion of patients who are either:

- pain free at 2 hours;
- report significant pain relief at 2 hours (no headache or mild headache); or
- report a sustained response over 24 hours (migraine stays away for at least a day).

Many trials fail to document associated outcomes such as improvement in nausea, vomiting or disability (Moore et al, 2003).

Strategies for the use of migraine medications

There are three major strategies for the use of analgesics in the treatment of acute migraine (Lipton, Stewart et al, 2000):

- *Stratified care* — where for each attack, the severity and disability caused by the migraine is assessed. 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 hours; 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) and European Federation of Neurological Societies (Evers et al, 2006) have recommended a 'stratified care' approach; later British guidelines promote the use of 'step-up' regimens during each attack (Steiner et al, 2007).

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 (or domperidone in children) (Evers et al, 2006).

Combined soluble aspirin 900 mg and metoclopramide 10 mg was of similar analgesic efficacy to sumatriptan in mild acute migraine (Oldman et al, 2002 **Level I**) and may be considered first-line treatment. Effervescent aspirin 1000 mg was as effective as sumatriptan 50 mg orally, with fewer side effects (Lampl et al, 2007 **Level I**). Ibuprofen (200 to 400 mg) was effective in achieving pain-free status within 2 hours, but was no different to placebo for pain outcomes at 24 hours (Suthisisang et al, 2007 **Level I**). Paracetamol 1000 mg was effective, usually for mild-to-moderate migraine (Lipton, Baggish et al, 2000 **Level II**).

A paracetamol-aspirin-caffeine combination was superior to placebo and each component drug alone in terms of analgesia and time to effect (Diener et al, 2005 **Level II**). It was also more effective than oral sumatriptan 50 mg in the early treatment of migraine headache (without associated nausea, vomiting or disability) (Goldstein et al, 2005 **Level II**) and was better than ibuprofen in terms of analgesic endpoints and speed of onset (Goldstein et al, 2006 **Level II**). Combined tramadol and paracetamol was superior to placebo for improved migraine headache outcomes to 24 hours and reduced photo/phonophobia (but not nausea) at 2 hours (Silberstein et al, 2005 **Level II**).

Dipyrone was also effective for the treatment of migraine and episodic TTHs (Ramacciotti et al, 2007 **Level I**).

Table 9.2 Simple analgesics for the treatment of migraine

Analgesic regimen	NNT*	Source
Aspirin 600 to 900 mg +metoclopramide 10 mg	3.2	Oldman et al, 2002 **Level I**
Paracetamol 1000 mg	5.2	Lipton, Baggish et al, 2000 **Level II**
Ibuprofen 200 to 400 mg	8.0	Suthisisang et al, 2007 **Level I**

* Simple analgesics for the treatment of migraine: 2-hour pain response (nil or mild residual headache at 2 hours).

Over-the-counter analgesics

Sixty percent of patients treat their migraines exclusively with over-the-counter (OTC) analgesics; however most trials of OTC medications excluded patients with severe headaches and related symptoms (nausea and vomiting) or disability.

When data from 11 trials of adequate study design were combined, OTC analgesics such as paracetamol (alone or in combination with caffeine), aspirin (alone or in combination with either caffeine and/or paracetamol) and ibuprofen, were more effective than placebo at reducing moderate-to-severe headache (mild or no pain) within 2 hours, with a significant minority of patients achieving pain-free status within 2 hours (Wenzel et al, 2003 **Level I**).
Up to 76% of patients returned to normal functioning after 2 hours, especially if their migraine

symptoms and disability were mild-to-moderate. No OTC agent was found to be superior. However, OTC medications are only indicated in migraineurs with mild-to-moderate symptoms (Wenzel et al, 2003 **Level I**).

Triptans

Triptans are effective in the treatment of acute migraine, particularly in the presence of severe pain and disability, where simple analgesia has failed to provide adequate relief in the past. As there is considerable interindividual response to the different triptans, patients should trial a variety of drugs and doses until the most suitable regimen is found (Silberstein, 2000; Oldman et al, 2002 **Level I**).

The route of administration of a triptan may affect its efficacy, speed of onset and tolerability. SC injections and nasal sprays provide fast onset of symptom relief and higher efficacy, however injections are less well tolerated by patients. In contrast, oral triptans are well tolerated but have a slower onset of action and lower reliability due to gastric stasis associated with migraine. Therefore, if the oral route is used, the triptan should preferably be given early in an attack (Dahlof, 2002). Suppositories are well tolerated and avoid problems with oral absorption.

Table 9.3 lists commonly prescribed triptans with NNT for pain-free response at 2 hours.

Table 9.3 Table of triptans

Drug	Route	NNT (95% Confidence intervals) *
Sumatriptan 6 mg	SC	2.1 (1.9–2.4)
Rizatriptan 10 mg	oral	3.1 (2.9–3.5)
Eletriptan 80 mg	oral	3.7 (3.2–4.2)
Zolmitriptan 5 mg	oral	3.9 (3.4–4.6)
Eletriptan 40 mg	oral	4.5 (3.9–5.1)
Sumatriptan 20 mg	IN	4.6 (3.6–6.1)
Sumatriptan 100 mg	oral	4.7 (4.1–5.7)
Rizatriptan 2.5 mg	oral	4.7 (4.0–5.7)
Zolmitriptan 2.5 mg	oral	5.9 (4.5–8.7)
Sumatriptan 50 mg	oral	7.8 (6.1–11)
Naratriptan 2.5 mg	oral	8.2 (5.1–21)
Eletriptan 20 mg	oral	10 (7–17)
Aspirin 900 mg plus metoclopramide 10 mg	oral	8.6 (6.2–14)

* NNTs to provide 2-hour pain-free response in migraine patient.

Source: Bandolier (at http://www.medicine.ox.ac.uk/bandolier); reproduced with permission.

Comparative randomised trials of triptans and other antimigrainals do not give a clear picture of relative efficacy. Oral triptans were found to be superior to oral ergotamine — most likely because the bioavailability oral of ergotamine is extremely low (<1%). Of the nine trials that met the inclusion criteria for review, six compared sumatriptan (two zolmitriptan and one eletriptan) with other migraine treatments. In seven of the nine studies reviewed, differences between triptan and other drugs for migraine endpoints were not dramatic. Triptans were no more effective than nsNSAIDs (and in most cases aspirin) and in several RCTs they produced

more side-effects than an aspirin-metoclopramide combination (Tfelt-Hansen, 2008; Lipton et al, 2004).

A combination of sumatriptan-naproxen as a single tablet for acute migraine, was superior to monotherapy with each component drug alone or placebo, in terms of pain-free outcome from 2 to 24 hours, with an adverse effects profile no worse than sumatriptan alone (Brandes et al, 2007 **Level II**).

The most frequent adverse events associated with triptans are dizziness, fatigue, sleepiness, nausea, chest tightness and paraesthesiae. The average incidence of any adverse events reported using various triptans ranged from approximately 18% to 50%. Sumatriptan has the greatest incidence and range of reported adverse events in placebo-controlled trials (Dahlof, 2002). Triptans may have significant sensory side effects, particularly an increase in light touch-evoked allodynia and thermal sensitivity (Linde, 2004).

Concern about adverse cardiac events is the main reason why only 10% of patients with migraine receive a triptan for acute therapy (Dahlof, 2002). A sensation of chest tightness occurred in 0.1 to 0.2% of patients who received almotriptan compared with 3 to 5% of patients on sumatriptan (Dahlof, 2002). There is no association between a lifetime history of migraine, with or without aura, and coronary artery disease related angina (Rose et al, 2004). However, chest tightness may not always be due to a cardiac cause (Dahlof, 2002). In a positron emission tomography study, sumatriptan did not affect myocardial perfusion or the ECG in migraine patients who had no history of ischaemic heart disease (Lewis et al, 1997).

Frequent use of triptans may lead to triptan-induced rebound headaches (Silberstein & Welch, 2002; Limmroth et al, 2002).

Ergot derivatives

Ergotamine and dihydroergotamine preparations have been used for many years to treat migraine, although they are rapidly being superseded by the triptans.

Intranasal (IN) dihydroergotamine (2 mg) has a NNT of 2.5 for 2-hour headache response in migraine (Oldman et al, 2002 **Level I**). As a single agent, parenteral dihydroergotamine may not be as effective as other migraine treatments (Colman et al, 2005 **Level I**). It was less effective than chlorpromazine (Bell et al, 1990 **Level II**) or sumatriptan (Winner et al, 1996 **Level II**), with increased side effects (Bell et al, 1990 **Level II**). However, when dihydroergotamine was combined with an antiemetic such as metoclopramide, the efficacy of this combination was similar to valproate, ketorolac and opioids (Colman et al, 2005 **Level I**).

Opioids and tramadol

Opioids are of limited benefit in the treatment of migraine. Morphine without an antiemetic was no more effective than placebo (Nicolodi, 1996 **Level II**). Butorphanol was effective when given by the IN or IM route (Elenbaas et al, 1991 **Level II**; Diamond et al, 1992 **Level II**; Hoffert et al, 1995 **Level II**).

Pethidine in particular, is not recommended for the treatment of migraine, due to lack of evidence of efficacy and the risk of developing dependency. Pethidine was less effective than dihydroergotamine or antiemetics for the treatment of migraine; however, it was of similar efficacy to ketorolac (Friedman et al, 2008 **Level I**). Pethidine was no more effective than dihydroergotamine, chlorpromazine, dimenhydrinate, metoclopramide, promethazine or NSAIDs (Lane et al, 1989 **Level II**; Stiell et al, 1991 **Level II**; Davis et al, 1995 **Level II**; Scherl & Wilson, 1995 **Level II**).

IM tramadol was similar to diclofenac for pain response at 2 hours in migraine (approximately 80% of patients) (Engindeniz et al, 2005 **Level II**).

Antiemetics and major tranquillisers

Metoclopramide, as monotherapy or in combination, was effective for the treatment of headache and nausea, in mild-to-moderate migraine, and is considered first-line therapy in the emergency department (Colman et al, 2004 **Level I**). IV prochlorperazine was also more effective than metoclopramide for initial emergency department treatment of migraine (Coppola et al, 1995 **Level II**); buccal prochlorperazine was superior to an oral ergotamine-caffeine combination or placebo (Sharma et al, 2002 **Level II**). A combination of indomethacin, prochlorperazine and caffeine was more effective than sumatriptan (Di Monda et al, 2003 **Level II**). Parenteral chlorpromazine (Bigal, Bordini & Speciali, 2002 **Level II**) or low-dose IM droperidol were also effective (Richman et al, 2002 **Level II**); the latter was associated with a 13% incidence of akathisia.

Other drug treatments

Dexamethasone was similar to placebo in the treatment of migraine, however a single dose was associated with a 26% reduction in recurrence rate (NNT 9) within 25 hours and offered a degree of migraine prophylaxis (Colman et al, 2008 **Level I**; Singh et al, 2008 **Level I**).

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 et al, 1990 **Level II**) and in one trial no better than placebo (Reutens et al, 1991 **Level II**). IN lignocaine may be effective (Maizels et al, 1996 **Level II**).

IV magnesium may be useful in the treatment of migraine, however the studies are contradictory. Magnesium sulphate was effective in a small placebo-controlled trial (Demirkaya et al, 2001 **Level II**), with another trial demonstrating a reduction in all of the symptoms of migraine with aura (including headache), but only in photo/phonophobia in migraine without aura (Bigal, Bordini, Tepper et al, 2002 **Level II**). However, other studies showed that a combination of magnesium and metoclopramide was less effective than metoclopramide plus placebo (Corbo et al, 2001 **Level II**) and there was no significant difference between magnesium, metoclopramide or placebo (Cete et al, 2005 **Level II**).

IV sodium valproate was ineffective in treating a migraine attack (Tanen et al, 2003 **Level II**).

Placebo

A significant placebo effect was observed in migraine trials, particularly if the treatment was administered by injection (Macedo et al, 2006 **Level I**) and it may be more common in children and adolescents (Evers et al, 2009 **Level I**).

Hyperbaric oxygen therapy

Limited evidence demonstrated that hyperbaric oxygen therapy was effective in terminating migraine attacks within 40 minutes in at least 70% of patients, compared with sham therapy (NNT 2; 95% CI 1 to 2), but there was no effect on nausea and vomiting, rescue analgesic requirements or migraine prevention; further research was recommended (Bennett et al, 2008 **Level I**).

Status migrainosis

Status migrainosis is described as a severe, unremitting, debilitating, migraine, lasting more than 72 hours, which is not attributable to another disorder and is otherwise typical in quality to the patient's usual migraine; it is considered a neurological emergency and usually requires hospital admission (Headache Classification Subcommittee of the IHS, 2004). 'Status' is often associated with a super-imposed TTH and multiple unsuccessful trials of migraine treatments, usually triptans, therefore medication overuse headache must also be considered.

Treatment of status migrainosis with parenteral nsNSAIDs or steroids (usually dexamethasone) is recommended (Evers et al, 2006; Steiner et al, 2007; Colman et al, 2008 **Level I**; Singh et al, 2008 **Level I**). IV droperidol was effective within 2 hours in 88% to 100% of patients with refractory migraine or 'status' respectively; the recurrence rate within 24 hours was 10% to 23%. Sedation or extrapyramidal symptoms (usually restlessness) developed in two-thirds of patients (Wang et al, 1997 **Level IV**).

Paediatric migraine

Migraine headaches are common in children and increase in frequency through to adolescence from 3% (ages 3 to 6) to 8% to 23% (ages 11 to 16). General principles of treatment are in accordance with adult migraine management but require due consideration of paediatric pharmacological issues. Not all children require pharmacological intervention. Medications shown to be effective in adults may not be appropriate for children, where paediatric safety and efficacy studies have not been conducted.

Guidelines and evidence-based reviews for the treatment of migraine in children and adolescents have been promulgated (Lewis et al, 2004; Bailey & McManus, 2008 **Level I**; Silver et al, 2008 **Level I**).

In children, ibuprofen or paracetamol are recommended as first-line treatments for acute migraine. For adolescents (over 12 years of age), sumatriptan nasal spray is effective and should be considered (Lewis et al 2004). Ibuprofen or sumatriptan were effective for relief of headache (NNT 2.4 and 7.4 respectively) and complete pain relief (NNT 4.9 and 6.9 respectively) at 2 hours. Paracetamol, zolmitriptan, rizatriptan or dihydroergotamine were not significantly better than placebo, but the number of RCTs in children is small (Silver et al, 2008 **Level I**). For adolescents (over 12 years of age), IN sumatriptan was effective, however the data are limited and further studies are required (Damen et al, 2005 **Level I**).

A systematic review of migraine treatments for children in the emergency department found only one RCT performed in this setting after other treatments had failed. This showed that prochlorperazine was more effective than ketorolac; other RCTs reported that ibuprofen or paracetamol were more effective than placebo; the data for triptans were unclear, with oral sumatriptan or ergotamine being ineffective (Bailey & McManus, 2008 **Level I**).

Psychological interventions, such as relaxation training, biofeedback and cognitive-behavioural therapy, reduced the intensity of headache in children and treatment success could be maintained for at least 1 year, although comparative efficacy with pharmacological treatments has not been investigated (Trautmann et al, 2006 **Level I**).

Menstruation-related migraine

Management of acute migraine during menstruation does not differ from treatment at other times of the menstrual cycle, but prophylaxis is based on significant oestrogen and progesterone fluctuations with appropriate hormone replacement, usually oestrodiol (Evers et al, 2006). NsNSAIDs and triptans were effective in the treatment and prophylaxis of menstruation-related headaches (Evers et al, 2006). Menstruation-related migraine was effectively treated with an OTC combination of paracetamol, aspirin, and caffeine (Silberstein et al, 1999 **Level II**).

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 the patient may become headache-free later in pregnancy. Approximately 60% to 70% of migraineurs improve during pregnancy. The true incidence of migraine in pregnancy is uncertain and most cases are of migraine with aura (Silberstein, 2001).

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, although aspirin, nsNSAIDs or coxibs may be of concern, especially during the third trimester (Evers et al, 2006) (see Section 11.1 and Tables 11.1 and 11.2).

Ergot alkaloids and triptans are contraindicated in pregnancy (Steiner et al, 2007; Evers et al, 2006). In one study, the use of sumatriptan in early pregnancy did not result in a large increase in teratogenic risk, but the possibility of a moderate increase in risk for a specific birth defect was not excluded. Among sixteen infants who had major malformations, nine had been exposed to sumatriptan; 1.3% of infants exposed to sumatriptan alone and 2.8% of infants exposed to other drugs for migraine had such malformations (Kallen & Lygner, 2001). Ergot alkaloids during pregnancy may disrupt feto-placental blood supply and cause uterine contraction, which can result in fetal injury or loss. Birth defects and stillbirths due to vascular spasm have been reported. On the basis of current data, all ergotamines are contraindicated in pregnancy and are category X (see Table 11.1).

Ibuprofen, diclofenac, metoclopramide or paracetamol are considered safe for the treatment of migraine in mothers who are breastfeeding. There is no clear consensus on the safety of triptans. Although the transfer of eletriptan or sumatriptan to breast milk is considered 'negligible', the manufacturers of most triptans recommend avoiding breastfeeding for at least 24 hours postadministration (Steiner et al, 2007) (see Table 11.3).

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.

Consensus guidelines for the treatment of cluster headache attacks recommended high-flow oxygen therapy or SC sumatriptan as therapies of first choice (May et al, 2006; Steiner et al, 2007). Acute steroid prophylaxis is recommended at the start of every cluster period (see below), either with prednisolone (Steiner et al, 2007) or methylprednisolone (orally or intravenously) (May et al, 2006), tapered over days to weeks.

Oxygen

Oxygen therapy may be useful in patients with cluster headache who have either a contraindication to sumatriptan or experience several cluster attacks per day (Dahlof, 2002). Although oxygen is recommended as a first-line treatment (May et al, 2006; Steiner et al, 2007), such recommendations are only supported by evidence from two small trials and clinical case reports (Bennett et al, 2008 **Level I**). High-flow oxygen provided symptomatic relief in approximately 50% of patients with acute cluster headache (Fogan, 1985 **Level II**) (NNT 2; CI 1 to 5); approximately 76% of patients responded to normobaric oxygen therapy (Bennett et al, 2008 **Level I**). The presence of nausea/vomiting and 'restlessness' was predictive of a poor response to oxygen (Schurks et al, 2007 **Level IV**).

Hyperbaric oxygen was no more effective than sham hyperbaric treatment in reducing the frequency or duration of cluster headaches (Bennett et al, 2008 **Level I**); however, 83% of patients with episodic cluster headache improved significantly with either treatment, suggesting either a placebo effect or therapeutic benefit from the hyperbaric process itself (Nilsson Remahl et al, 2002 **Level II**).

Triptans

SC sumatriptan injection (Ekbom, 1995 **Level II**) or IN sumatripan spray (van Vliet et al, 2003 **Level II**) were effective first-line treatments for cluster headache attacks, with SC administration providing faster onset and greater reliability of analgesia (Hardebo & Dahlof, 1998 **Level II**). IN zolmitriptan was rapidly effective (Cittadini et al, 2006 **Level II**; Rapoport et al, 2007 **Level II**) and oral zolmitriptan was effective in treating 'episodic' but not chronic cluster headache (Bahra et al, 2000 **Level II**). Increased age was associated with a reduced response to triptans (Schurks et al, 2007 **Level IV**).

Other treatments

There have been no RCTs of ergotamines in the treatment of cluster headache, although injectable or IN dihydroergotamine may be of benefit (its use has been superseded by sumatriptan) (Dodick et al, 2000). IN (Dahlof, 2002) or IV (May et al, 2006) lignocaine may be effective. A single suboccipital steroid injection with betamethasone completely suppressed cluster headache attacks in 80% of patients for weeks, compared with a placebo control injection (Ambrosini et al, 2005 **Level II**).

Bilateral occipital nerve stimulation has been used successfully to treat otherwise intractable cluster headaches (Burns et al, 2009 **Level IV**).

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 Subcommittee of the IHS, 2004), which is the suggested treatment of choice (May et al, 2006). There is no high-level evidence to guide the treatment of SUNCT, however consensus guidelines based on case-series data suggest that lamotrigine or possibly topiramate or gabapentin may be useful prophylactics (May et al, 2006).

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% to 50%, (Halpern & Preston, 1994 **Level I**; Gaiser, 2006); up to 90% of cases improve spontaneously within 10 days (Candido & Stevens, 2003).

PDPH is more common in patients under 50 years of age and parturients (Candido & Stevens, 2003), and following inadvertent dural puncture with an epidural needle. The odds of developing PDPH are significantly lower in males compared with (non-pregnant) females (Wu et al, 2006 **Level I**). A history of previous PDPH significantly increases the risk of developing a headache with subsequent spinal anaesthesia (Amorim & Valenca, 2008 **Level IV**). Children who undergo lumbar puncture may present a special group (Janssens et al, 2003).

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 (26 gauge or less [NNT: 3]) or a needle with a 'non-cutting' bevel (eg 'pencil point') (NNT: 27) (Halpern & Preston, 1994 **Level I**). The incidence of PDPH was also reduced by orientating the cutting bevel parallel to the spinal saggital plane (dural fibres) (Richman et al, 2006 **Level I**) or by replacing the stylette prior to withdrawing a non-cutting needle (Strupp et al, 1998 **Level II**); both of these techniques (presumably) reduced cerebrospinal fluid (CSF) loss.

Although the American Academy of Neurology determined that non-cutting needles (eg pencil point) clearly reduced PDPH following spinal anaesthesia, data for their effectiveness in diagnostic lumbar puncture were conflicting and inconclusive (Evans et al, 2000). Subsequent trials have demonstrated that, for diagnostic lumbar punctures, non-cutting (pencil point) needles significantly reduce the incidence of PDPH compared with cutting needles (eg Quincke) (Lavi et al, 2006 **Level II**; Strupp et al, 2001 **Level II**), leading to a recommendation to now use non-cutting needles routinely in neurology practice (Arendt et al, 2009).

The incidence of accidental dural puncture was not reduced by using an 18-gauge epidural Sprotte (pencil point) needle, compared with a 17-gauge epidural Tuohy needle, however the incidence of PDPH was significantly lower with the Sprotte needle (Morley-Forster et al, 2006 **Level II**).

Epidural blood patch

The use of an epidural blood patch (EBP) for the treatment of PDPH has been recommended as first-line therapy, especially in obstetric patients (Thew & Paech, 2008) and following inadvertent dural puncture with an epidural needle (Gaiser, 2006). However, further high quality trials are required to clearly determine the efficacy of EBP administration for the treatment of PDPH (Sudlow & Warlow, 2002a **Level I**). The potential risks, adverse effects, optimal timing and blood volume and other technical issues associated with EBP therapy remain unclear.

Compared with 'conventional treatment' (fluids, analgesia and caffeine), an EBP significantly reduced the intensity of PDPH (following spinal anaesthesia or diagnostic lumbar puncture) at 24 hours (Sandesc et al, 2005 **Level II**) and also reduced the incidence and severity of PDPH at 1 week, following lumbar puncture (van Kooten et al, 2008 **Level II**).

The most effective blood volume for EBP administration is not known. Significant relief of PDPH was obtained in 93% of patients who received a mean EBP volume of 23 (+/-5) mL, with 20 mL recommended as the 'optimal' target volume, beyond which there was a higher incidence of lumbar discomfort on injection (Safa-Tisseront et al, 2001 **Level IV**). EBP volumes in the range of 10 to 20 mL were effective in relieving PDPH in 98% of patients, following spinal or epidural anaesthesia (Wu et al, 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 et al, 1993 **Level III-1**). In parturients, there was no difference in the severity of PDPH to 3 days 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 et al, 2007 **Level II**).

EBP is sometimes performed prophylactically to prevent PDPH after an inadvertent dural puncture (by an epidural needle). However, there is conflicting evidence of benefit with prophylactic EBP administration. One study demonstrated a reduced incidence of PDPH (Colonna-Romano & Shapiro, 1989 **Level II**); another reported no reduction in the incidence of PDPH or subsequent blood patch requirements in parturients, but headache duration was shorter (Scavone et al, 2004 **Level II**).

The use of autologous blood patch may be contraindicated in patients with leukaemia, coagulopathy or infection including HIV.

Bed rest and hydration

There was no evidence of benefit with bed rest in the treatment or prevention of PDPH (Sudlow & Warlow, 2002b **Level I**). However, patients with PDPH may have difficulty in mobilising and the headache subsides with bed rest. The role of fluid therapy (hydration) in the prevention of PDPH remains unclear (Sudlow & Warlow, 2002b **Level I**).

Other treatments

Although caffeine is often prescribed to prevent or treat PDPH, evidence for its efficacy is limited and conflicting (Halker et al, 2007). Administration of caffeine combined with paracetamol for 3 days following spinal anaesthesia did not reduce the incidence of PDPH (or associated symptoms such as nausea and photohobia) compared with placebo (Esmaoglu et al, 2005 **Level II**). IV caffeine administered during spinal anaesthesia reduced pain scores, analgesia requirements and the incidence of moderate-to-severe PDPH for up to 5 days (Yucel et al, 1999 **Level II**). IV theophylline also reduced the severity of PDPH (Ergun et al, 2008 **Level II**). Oral caffeine reduced the severity PDPH at 4 hours (Camann et al, 1990 **Level II**) but did not reduce the rate of EBP administration (Candido & Stevens, 2003; Halker et al, 2007).

The addition of IV hydrocortisone to conventional therapy (bed rest and analgesia) for 48 hours decreased the intensity of PDPH following spinal anaesthesia for Caesarean section (Rucklidge et al, 2004 **Level II**). There was no evidence to support the efficacy of adrenocorticotrophic hormone in PDPH (Candido & Stevens, 2003).

There was no evidence to support the efficacy of sumatriptan (Connelly et al, 2000 **Level II**) in PDPH, although in open-label studies other triptans have been reported to have sufficient benefit to warrant further evaluation (Bussone et al, 2007).

There was no evidence to support the use of epidurally administered saline, dextran or fibrin glue or neuraxial opioids in the treatment of PDPH (Turnbull & Shepherd, 2003), however prophylactic epidural morphine in saline significantly reduced the incidence of PDPH and EBP compared with epidural saline alone following inadvertent dural puncture in parturients (Al-metwalli, 2008 **Level II**).

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). The treatment of giant cell arteritis is with high-dose steroids, but there are no evidence-based guidelines.

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 and may include cessation of analgesics, IV hydration, steroids, nsNSAIDs, antiemetics and benzodiazepines (Trucco et al, 2005). Evidence for the benefit of steroids is mixed. One study showed that administration of prednisone led to a significant reduction in the duration of severe headache compared with placebo (Pageler et al, 2008 **Level II**). However, another found that prednisolone did not have a significant effect on 'rebound headache' outcomes during the withdrawal phase (Boe et al, 2007 **Level II**).

A 12-week open-label study of a single daily dose of tizanidine in combination with a single morning dose of NSAID, resolved chronic daily headache in 62% of patients (Smith, 2002 **Level III-3**).

Complementary and alternative medicines and therapies

There is no high-level evidence of efficacy for acupuncture, hypnotherapy, chiropractic, spinal manipulation or homeopathy in the treatment of migraine (Vernon et al, 1999 **Level I**; Astin & Ernst, 2002 **Level I**; Melchart et al, 2001 **Level I**). However, acupuncture is an effective non-pharmacological intervention in TTH (Linde et al, 2009 **Level I**).

Opioids and acute headache

Although opioids are commonly used for the emergency treatment of headache (Vinson, 2002), they cannot be recommended for use on a regular basis because of the risk of dependency and other opioid-related adverse effects. The Australian Association of Neurologists recommended that opioids should not be used for migraine unless the patient is unresponsive to all other measures or where the use of ergot agents and triptans is contraindicated (Lance et al, 1997). Pethidine in particular should be avoided in the treatment of headache, due to evidence of poor efficacy compared with other migraine treatments (Friedman et al, 2008 **Level I**) and a higher risk of opioid dependency.

Key messages

Tension-type headache

1. Acupuncture is effective in the treatment of tension-type heachache (**N**) (**Level I** [Cochrane Review]).
2. The addition of caffeine to aspirin or paracetamol improves analgesia in the treatment of episodic tension-type heachache (**U**) (**Level I**).
3. Simple analgesics such as aspirin, paracetamol or NSAIDs, either alone or in combination, are effective in the treatment of episodic tension-type heachache (**U**) (**Level II**).

Migraine

4. Triptans are effective in the treatment of severe migraine (**U**) (**Level I**).
5. Aspirin-metoclopramide is effective in the treatment of mild-to-moderate migraine (**U**) (**Level I**).
6. Parenteral metoclopramide is effective in the treatment of migraine (**U**) (**Level I**).
7. Over-the-counter medications, including combined paracetamol-aspirin-caffeine preparations, are effective in the treatment of migraine with mild-to-moderate symptoms and disability (**N**) (**Level I**).
8. Effervescent aspirin, ibuprofen or dipyrone are effective in the treatment of migraine (**N**) (**Level I**).
9. In children or adolescents with migraine, ibuprofen or intranasal sumatriptan (over 12 years of age) are effective treatments (**N**) (**Level I**).
10. Pethidine is less effective than most other migraine treatments and should not be used (**N**) (**Level I**).
11. Parenteral prochlorperazine, chlorpromazine or droperidol are effective in the treatment of migraine, especially in the emergency department (**N**) (**Level II**).
12. Paracetamol is effective in the treatment of mild-to-moderate migraine (**U**) (**Level II**).
13. A 'stratified care strategy' is effective in treating migraine (**U**) (**Level II**).

Cluster headache

14. Parenteral triptans (sumatriptan or zolmitriptan) (**S**) or oxygen therapy (**U**), are effective treatments for cluster headache attacks (**Level II**).

Postdural puncture headache

15. There is no evidence that bed rest is beneficial in the treatment and prevention of postdural puncture headache (**U**) (**Level I** [Cochrane Review]).
16. The incidence of postdural puncture headache is reduced by using small-gauge spinal needles and/or a non-cutting bevel (**U**) (**Level I**).
17. Further high quality trials are required to determine the efficacy of epidural blood patch administration in the treatment of postdural puncture headache (**U**) (**Level I**), however benefit is likely (**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 (**U**).

☑ Frequent use of analgesics, triptans and ergot derivatives in the treatment of recurrent acute headache may lead to medication overuse headache (**U**).

9.6.6 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 dysfunction of the peripheral nervous system (PNS) (eg painful peripheral neuropathy) or the CNS (central pain, eg poststroke pain) (Loeser & Treede, 2008).

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.

Multiple sclerosis

Chronic pain is experienced by 49% to 73.5% of patients with multiple sclerosis (Osterberg et al, 2005; Hadjimichael et al, 2007; Khan & Pallant, 2007; Brochet et al, 2009) and the type of pain may vary. In one survey, central pain was reported in 27.5% of patients (17.3% of these had trigeminal neuralgia); another 20.9% had nociceptive pain and 2.2% described peripheral neuropathic pain (Osterberg et al, 2005). In another survey, of those patients with chronic pain, 60.7% had dysaesthetic pain and just 6.6% reported nociceptive pain (Khan & Pallant, 2007).

Pain related to trigeminal neuralgia responds to carbamazepine (Wiffen et al, 2005 **Level I**). Cannabinoids reduced the intensity of neuropathic pain associated with multiple sclerosis by approximately 1.5/10 (VAS or verbal numerical rating scale [VNRS]), compared with placebo; there were significant side effects, particularly dizziness (Iskedjian et al, 2007 **Level I**). Safety concerns regarding cannabinoid use need to be considered. There was no evidence to guide the use of antispasticity agents such as baclofen in the treatment of multiple sclerosis-related acute pain (Shakespeare et al, 2003 **Level I**). Nortriptyline was as effective as transcutaneous nerve stimulation in reducing pain intensity and/or sensory complaints in patients with multiple sclerosis (Chitsaz et al, 2009 **Level II**). Levetiracetam was effective in reducing pain in multiple sclerosis (Rossi et al, 2009 **Level II)**.

Central poststroke pain

Central pain develops in 8% to 35% of stroke patients; its pathophysiology and treatment options have been reviewed by Kumar et al (Kumar et al, 2009). Intravenous lignocaine (Attal et al, 2000 **Level II**) and IV propofol in subhypnotic doses (Canavero & Bonicalzi, 2004 **Level II**) may provide short-term relief in central poststroke pain, and amitriptyline was more effective than placebo and carbamazepine (which was not different from placebo) (Leijon & Boivie, 1989 **Level II**). Lamotrigine was moderately effective and well-tolerated in central poststroke pain (Vestergaard et al, 2001 **Level II**).

Trigeminal neuralgia

Excerbations of trigeminal neuralgia can present as acute neuropathic pain. Published guidelines identified insufficient evidence for the effectiveness of any IV medication in this setting (Cruccu et al, 2008 **Level I**). The same guidelines rate carbamazepine as effective and oxcarbazepine as probably effective in this condition and suggest that baclofen, lamotrigine, and pimozide may be considered if the first line medications are ineffective. Topical ophthalmic anaesthesia is described as probably ineffective.

Guillain-Barre syndrome

See Section 9.8.4.

Key message

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.

9.6.7 Orofacial pain

Acute orofacial pain may be caused by infective, traumatic, neuropathic, vascular, neoplastic or other pathologies (Zakrzewska & Harrison, 2003; Keith, 2004; Ward & Levin, 2004). Most commonly acute orofacial pain is due to dental or sinus disease but it may also be associated with chronic facial pain syndromes (eg trigeminal neuralgia) or be referred from adjacent regions such as the cervical spine and the thorax. A thorough history (including dental) and examination (particularly of the oral cavity and cranial nerves) are essential components of the assessment of orofacial pain. Recurrent or persistent orofacial pain requires a biopsychosocial assessment and appropriate multidisciplinary management (Vickers et al, 2000). Neuropathic orofacial pain (atypical odontalgia, phantom pain) may be exacerbated by repeated dental procedures (eg extraction of teeth, root canal therapy, sectioning of nerves), incorrect drug therapy or psychological factors (Vickers et al, 1998).

Acute postoperative dental pain

Acute pain after third molar extraction is the most extensively studied model for testing postoperative analgesics. Ibuprofen, paracetamol, aspirin (Barden et al, 2004 **Level I**) and celecoxib (Derry et al, 2008 **Level I**; Cheung et al, 2007 **Level II**) were found to be effective in this setting. Interestingly, the placebo response for analgesia was significantly lower in postdental extraction pain than in other acute pain models (Barden et al, 2004 **Level I**).

NsNSAIDs or coxibs were recommended as 'first-line' analgesics following third molar extraction (Barden et al, 2004 **Level I**), however paracetamol was also safe and effective (Weil et al, 2007 **Level I**), with a dose of 1000 mg providing better pain relief than lower doses (NNT 3; NNH 33) (Dodson, 2007 **Level I**). NsNSAIDs were more effective than paracetamol or codeine

(either alone or in combination) (Ahmad et al, 1997 **Level I**) and ketorolac provided better analgesia with fewer adverse effects than pethidine (Fricke et al, 1992 **Level II**) or tramadol (Ong & Tan, 2004 **Level II**). The combination of paracetamol 1000 mg with ketoprofen 100 mg was more effective than either drug given alone (Akural et al, 2009 **Level II**).

Coxibs were of similar efficacy to nsNSAIDs in acute postoperative dental pain (Chen et al, 2004 **Level I**; Cicconetti et al, 2004 **Level I**). A single dose of celecoxib 400 mg provided similar analgesia to ibuprofen 400 mg, however with a longer duration of action and increased time to rescue analgesia following dental surgery (Cheung et al, 2007 **Level II**). A combination of oxycodone 5 mg /ibuprofen 400 mg was more effective than various other combinations of paracetamol, ibuprofen, oxycodone or hydrocodone or placebo for analgesia following dental surgery (Litkowski et al, 2005 **Level II**). Tramadol 100 mg had a similar efficacy to aspirin/opioid or paracetamol/opioid combinations in treating acute dental pain (Moore & McQuay, 1997 **Level I**). A tramadol/paracetamol combination was superior to tramadol alone with fewer adverse effects (Edwards, McQuay et al, 2002 **Level I**; Fricke et al, 2004 **Level II**).

Perioperative steroid administration reduced swelling and trismus but not pain, following third molar extraction (Markiewicz et al, 2008 **Level I**) and reduced postoperative nausea (Baxendale et al, 1993 **Level II**; Schmelzeisen & Frolich, 1993 **Level II**).

Note: reversal of conclusion

This reverses the Level 1 conclusion in the previous edition of this document; an earlier meta-analysis reported an improvement in analgesia.

A single postoperative IM injection of prednisolone combined with diclofenac reduced pain for the first 7 hours postextraction and reduced swelling and trismus at various times up to 7 days, compared with placebo; prednisolone alone reduced pain at 7 hours and swelling on day 2 (Buyukkurt et al, 2006 **Level II**). A submucosal injection of either 4 mg or 8 mg of dexamethasone at the time of third molar extraction reduced facial swelling but not pain or trismus compared with placebo for up to 48 hours (Grossi et al, 2007 **Level II**); injection of methylprednisolone into the masseter muscle following extraction reduced pain, swelling and trismus (Vegas-Bustamante et al, 2008 **Level II**).

Cryotherapy (ice packs) following third molar extraction did not reduce trismus but may have reduced facial swelling and pain, although the results were conflicting (Laureano Filho et al, 2005 **Level II**; van der Westhuijzen et al, 2005 **Level II**). Facial compression reduced pain for up to 3 days, with no additional benefit from co-application of ice packs (Forouzanfar et al, 2008 **Level II**).

Acupuncture may be of benefit in reducing postprocedural dental pain but better quality trials are required (Ernst & Pittler, 1998 **Level I**).

NSAIDs and emergency pulpectomy (Sutherland & Matthews, 2003 **Level I**) but not antibiotics (Keenan et al, 2005 **Level I**) reduced pain in patients with acute apical periodontitis.

Acute pain associated with pharyngitis

Paracetamol, nsNSAIDs, coxibs and opioids, administered as monotherapy or in combination, were effective in the treatment of pain associated with acute pharyngitis (Thomas et al, 2000 **Level I**; Romsing et al, 2000 **Level II**). Aspirin (Thomas et al, 2000 **Level I**; Eccles et al, 2003 **Level II**) particularly when combined with caffeine (Schachtel et al, 1991 **Level II**) was also effective.

Topical analgesics such as benzydamine HCl 0.15% (as an anti-inflammatory spray) (Thomas et al, 2000 **Level I**) or flurbiprofen lozenges (Watson et al, 2000 **Level II**) provided effective analgesia in acute sore throat, with minimal side effects.

Steroids have been prescribed to reduce acute pain and swelling in severe pharyngitis. They provide symptomatic relief of pain, in particular in patients with severe or exudative sore throat (Hayward et al, 2009 **Level I**). In particular, steroids in combination with analgesics and antibiotics increased the likelihood of complete resolution of pain and the time to onset of pain relief. Oral dexamethasone (Olympia et al, 2005 **Level II**; Niland et al, 2006 **Level II**) or IM betamethasone (Marvez-Valls et al, 1998 **Level II**) significantly reduced dysphagia and the duration of symptoms in patients with severe streptococcal pharyngitis, although a study in children failed to find any benefit with oral dexamethasone (Bulloch et al, 2003 **Level II**). Following drainage and antibiotics for peritonsillar abscess, a single dose of IV steroid reduced pain, trismus and fever (Ozbek et al, 2004 **Level II**).

Antibiotics for sore throat reduced pain, headache and fever by 50% on day 3 and shortened the duration of symptoms by approximately one day. The NNT to prevent a sore throat at day 3 was approximately 6 (95% CI 4.9 to 7.0) and at day 7, 21 (95% CI 13.2 to 47.9) (Del Mar et al, 2006 **Level I**).

Acute pain associated with sinusitis and otitis media

There is no evidence to guide the choice of analgesia for acute pain associated with sinusitis or otitis media. It may be appropriate to use nsNSAIDs, coxibs, paracetamol, weak opioids or tramadol, based on evidence for treatment of dental pain. Nasal irrigation with physiological saline may provide symptomatic relief (Clement et al, 1998; Low et al, 1997). Administration of penicillin V decreased pain scores over 3 days in patients with severe sinus pain (Hansen et al, 2000 **Level II**). Local anaesthetic eardrops reduced pain in otitis media (Bolt et al, 2008 **Level II**); however the overall effectiveness of eardrops in this condition was unclear (Foxlee et al, 2006 **Level I**).

Acute post-tonsillectomy pain

(Also see Sections 10.5.1, 10.5.2 & 10.5.5)

Peritonsillar infiltration or topical application of local anaesthetics produced a modest reduction in post-tonsillectomy pain (7 to 19 mm on a 100 mm VAS) for up to 24 hours, with topical application and infiltration being equally effective (Grainger & Saravanappa, 2008 **Level I**).

Note: reversal of conclusion

This reverses the Level 1 conclusion in the previous edition of this document; an earlier meta-analysis had reported no improvement in analgesia.

Injection of local anaesthesics in the tonsillar fossa improved pain scores, and reduced time to first oral intake and the incidence of referred ear pain (Naja et al, 2005 **Level II**; Somdas et al, 2004 **Level II**). Ropivacaine 1.0% with adrenaline resulted in better pain relief for up to 3 days after tonsillectomy than bupivacaine 0.25% with adrenaline or placebo (Arikan et al, 2008 **Level II**). The addition of magnesium to levobupivacaine reduced analgesic requirements compared with levobupivacaine alone or saline control (Karaaslan et al, 2008 **Level II**) and bupivacaine 0.25% with pethidine reduced analgesic requirements at rest, but did not affect other pain outcomes compared with saline, following tonsillectomy in children (Nikandish et al, 2008 **Level II**).

Infiltration of the tonsillar bed with tramadol may reduce pain and analgesic requirements in the first few hours after tonsillectomy (Atef & Fawaz, 2008a **Level II**), although infiltration may be no more effective than an equivalent IM dose (Ugur et al, 2008 **Level II**). Peritonsillar infiltration of ketamine reduced pain and analgesic requirements for up to 24 hours post-tonsillectomy in

children (Honarmand et al, 2008 **Level II**; Erhan et al, 2007 **Level II**) although the effects of ketamine infiltration were not significantly different to an equivalent IV dose (Dal et al, 2007 **Level II**).

A systematic review of analgesia for tonsillectomy in children was unable to generate clear conclusions due to heterogeneity of the trials; however no single prophylactic dose of an analgesic provided adequate pain relief for the entire first postoperative day; orally administered paracetamol was more effective than rectal, and prophylactic NSAIDs were at least as effective as opioids in reducing post-tonsillectomy pain (Hamunen & Kontinen, 2005 **Level I**).

In meta-analyses of tonsillectomy in both adult and paediatric patients, nsNSAIDs were found to increase the risk of reoperation for bleeding (NNH 29 to 60) (Marret et al, 2003 **Level I**; Moiniche et al, 2003 **Level I**) but surgical blood loss was not significantly increased (Moiniche et al, 2003 **Level I**) (see also Section 4.2.2). Looking at studies in children only, there was no increase in the risk of reoperation for bleeding after tonsillectomy (Cardwell et al, 2005 **Level I**). Aspirin, which irreversibly inhibits platelet aggregation, increased the risk of post-tonsillectomy haemorrhage (Krishna et al, 2003 **Level I**).

Diclofenac (Romsing et al, 2000 **Level II**; Schmidt et al, 2001 **Level II**) or ketorolac (Rusy et al, 1995 **Level II)** were no more effective than paracetamol in providing analgesia in children post-tonsillectomy. Rofecoxib provided effective analgesia for up to 24 hours after surgery, and led to decreased nausea but no increased blood loss (Joshi et al, 2003 **Level II**). IV paracetamol administered 6-hourly for the first postoperative day reduced pain and rescue analgesia requirements in adults following tonsillectomy (Atef & Fawaz, 2008b **Level II**).

Gabapentin may reduce analgesia requirements for up to 48 hours and pain on swallowing for up to 4 hours, following tonsillectomy in adults (Jeon et al, 2008 **Level II**; Mikkelsen et al, 2006 **Level II**).

In children, dexamethasone produced a significant but clinically moderate reduction in post-tonsillectomy pain on the first postoperative day (Afman et al, 2006 **Level I**). There was a reduced risk of postoperative nausea and vomiting and reduced use of ibuprofen but also an increased risk of bleeding (Czarnetzki et al, 2008 **Level II**).

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 (eutectic mixture of lignocaine and prilocaine) and 5% lignocaine (Vickers & Punnia-Moorthy, 1992 **Level II**).

Mucositis may also be due to side effects of chemoradiotherapy for solid and blood malignancies and may be complicated by opportunistic infections including HSV and candidiasis. Quality of life and nutrition can be greatly impaired.

In treating the pain of cancer-related acute mucositis, 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 et al, 2007 **Level I**).

There was weak evidence that allopurinol mouthwash, granulocyte macrophage-colony stimulating factor (GM-CSF), immunoglobulin or human placental extract improved or eradicated mucositis; benzydamine HCl, sucralfate, tetrachlorodecaoxide, chlorhexidine, lignocaine solution, diphenhydramine hydrochloride and aluminum hydroxide suspensions were ineffective (Clarkson et al, 2007 **Level I**).

Polymyxin E, tobramycin and amphotericin B (PTA), GM-CSF, oral cooling and amifostine, significantly reduced the incidence and severity of oral mucositis (Stokman et al, 2006 **Level I**).

Povidone-iodine mouthwash also significantly reduced the severity of oral mucositis compared with sterile water, however chlorhexidine was ineffective (Potting et al, 2006 **Level I**). Preventive strategies for mucositis such as palifermin or oral cryotherapy, may be effective in specific circumstances (Bensinger et al, 2008).

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 side-effects profile but no better than placebo for analgesia in radiation-induced mucositis (Shaiova et al, 2004 **Level II**). Topical morphine (Cerchietti et al, 2003 **Level III-I**), doxepin (Epstein et al, 2006 **Level II**) and ketamine (Slatkin & Rhiner, 2003) may also provide analgesia, and IV ketamine 'burst therapy' may be effective in mucositis pain that is refractory to opioid analgesia (Jackson et al, 2005) (see Sections 9.7, 10.8).

Oral laser light therapy reduced mucositis pain and progression (Abramoff et al, 2008 **Level II**; Arora et al, 2008 **Level II**).

Clinical practice guidelines for the prevention and treatment of mucositis in cancer patients have been published by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (Keefe et al, 2007).

Key messages

Dental extraction

1. Paracetamol 1000 mg provides safe and effective analgesia with minimal adverse effects, following dental extraction (**N**) (**Level I** [Cochrane Review]).
2. Non-selective NSAIDs, coxibs, paracetamol, opioids or tramadol provide effective analgesia after dental extraction (**U**) (**Level I**).
3. Non-selective NSAIDs or coxibs provide better analgesia with fewer adverse effects, than paracetamol, paracetamol/opioid, paracetamol/tramadol, tramadol or weaker opioids, following dental extraction (**U**) (**Level I**).
4. Perioperative steroid administration reduces swelling (**S**) but not pain (**R**) (**Level I**) and reduces postoperative nausea (**U**) (**Level II**), following third molar extraction.
5. The combination of paracetamol with a non-selective NSAID provides analgesia that is superior to each drug given alone following third molar extraction (**N**) (**Level II**).

Tonsillectomy

6. Aspirin and some NSAIDs increase the risk of perioperative bleeding after tonsillectomy (**U**) except in children (**N**) (**Level I** [Cochrane Review]).
7. Peritonsillar infiltration or topical application of local anaesthetics produces a modest reduction in acute post-tonsillectomy pain (**R**) with topical application and infiltration being equally effective (**N**) (**Level I**).
8. Intraoperative dexamethasone administration reduces acute pain (**S**) (**Level I**), nausea and vomiting (**U**) (**Level I**) post-tonsillectomy, although there may be an increased bleeding risk (**N**) (**Level II**).
9. Peritonsillar infiltration with tramadol or ketamine may reduce post-tonsillectomy pain and analgesia requirements, but was no more effective than equivalent doses administered parenterally (**N**) (**Level II**).

Mucositis

10. Opioids, via PCA or a continuous infusion, provide effective analgesia in mucositis, however PCA is associated with reduced opioid requirements and pain duration (**U**) (**Level I** [Cochrane Review]).
11. Topical treatments, including oral cooling or povidone-iodine solution, provide effective analgesia in mucositis (**N**) (**Level I**).
12. Oral laser light therapy reduces mucositis pain and progression (**N**) (**Level II**).

Pharyngitis

13. Steroids improve analgesia in sore throat, in particular in severe and exudative conditions (**N**) (**Level I**).
14. Paracetamol, nsNSAIDs or coxibs and opioids, administered as monotherapy or in combination, are effective analgesics in acute pharyngitis (**N**) (**Level I**).
15. Steroids may reduce acute pain associated with severe pharyngitis or peritonsillar abscess (following drainage and antibiotics) (**N**) (**Level II**).

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

☑ Recurrent or persistent orofacial pain requires biopsychosocial assessment and appropriate multidisciplinary approaches. Neuropathic orofacial pain (atypical odontalgia, phantom pain) may be exacerbated by repeated dental procedures, incorrect drug therapy or psychological factors (**U**).

9.6.8 Acute pain in patients with HIV infection

Pain is a common problem in people infected with HIV, particularly when they develop the AIDS. Pain may be due to the effects of the virus, which is neurotropic, or an infective or neoplastic process associated with immunodeficiency. Pain may also be a side effect of treatment or related to debilitation (in patients with end-stage AIDS) or may be due to an unrelated comorbidity (O'Neill & Sherrard, 1993; Glare, 2001).

In patients with HIV/AIDS, pain is progressive, affecting approximately 25% with early stage disease, 50% to 75% with AIDS and almost all patients in the terminal phase (Singer et al, 1993 **Level IV**; Breitbart, McDonald et al, 1996; Kimball & McCormick, 1996). CD4+ T-cell count does not predict number of symptoms or severity of distress (Vogl et al, 1999 **Level IV**).

Pain occurs at multiple sites with the number of pains reported per patient increasing throughout the course of AIDS. The most frequent neurological diagnosis is a distal symmetrical polyneuropathy (DSP), found in 38% or patients. Common clinical features of DSP include non-painful paresthesias (71%), abnormalities of pain and temperature perception (71%), and reduced or absent ankle reflexes (66%). Increased age, immunosuppression, poor nutritional status and the presence of chronic disease all contribute to distal peripheral nerve dysfunction associated with HIV infection (Tagliati et al, 1999 **Level IV**).

Pain associated with HIV/AIDS is often undertreated due to patient and clinician-related barriers (Breitbart, Rosenfeld et al, 1996; **Level IV**; Larue et al, 1997; Breitbart et al, 1998; Breitbart et al, 1999; Frich & Borgbjerg, 2000). Therefore patients cite poorly treated pain as one of the most common reasons to use complementary or alternative medicines (Tsao et al, 2005 **Level IV**). Undertreatment is more common in certain patient groups — non-Caucasians, women, those with a substance abuse disorder, less educated individuals, and those with higher levels of psychosocial distress (Breitbart et al, 1998 **Level IV**). Physical and psychological symptoms

including pain had no impact on HIV-1 RNA levels in patients with stable suppression of viremia (Nettles et al, 2005 **Level IV**).

Disease-specific therapy, psychosocial interventions and physical modalities should accompany standard analgesic treatment (Jacox et al, 1994; Glare, 2001). Disease-specific therapy may need to be ceased prematurely if pain is a side effect (eg peripheral neuropathy caused by some antiretrovirals, in particular nucleoside reverse transcriptase inhibitors).

Treatment of HIV/AIDS-related pain

A significant reduction in pain intensity was achievable with CR opioids in a variety of painful conditions with limited or manageable side effects, supporting the usefulness of opioid analgesia for HIV-related severe pain (Kaplan et al, 1996; Kaplan et al, 2000 **Level IV**). Approximately 15% to 20% of patients need parenteral opioids in the terminal phase (Dixon & Higginson, 1991 **Level IV**; Kimball & McCormick, 1996 **Level IV**; Frich & Borgbjerg, 2000 **Level IV**). Transdermal fentanyl provided better pain relief and improvement in daily functioning in patients with severe AIDS-related pain who were previously taking oral opioids (Newshan & Lefkowitz, 2001 **Level IV**).

Painful peripheral neuropathy associated with HIV infection has been the subject of a number of treatment trials. Lamotrigine (Simpson et al, 2000 **Level II**) and gabapentin (La Spina et al, 2001 **Level IV**) were better than placebo. A single application of a high-concentration capsaicin patch was safe and provided at least 12 weeks of pain reduction in patients with HIV-associated distal sensory polyneuropathy, suggesting that such patches could have a role in the analgesic regimens of people with painful HIV neuropathy (Simpson et al, 2008 **Level II**).

Smoking cannabis was significantly more effective in reducing HIV-related neuropathic pain than smoking placebo cigarettes (Abrams et al, 2007 **Level II**); the rate of responders (30% reduction in pain) in one trial was 46% with cannabis and 18% with placebo (Ellis et al, 2009 **Level II**).

The use of nucleoside reverse transcriptase inhibitors (NRTIs) can lead to a toxic neuropathy with neuropathic pain. Acetyl-L-carnitine (ALCAR) can provide neurotrophic support of sensory neurones and therefore its use in the setting of NRTI therapy may encourage nerve regeneration and analgesia. IM or oral ALCAR use was safe and well-tolerated and resulted in a reduction of pain intensity compared to placebo (Youle & Osio, 2007 **Level II**).

TCAs (Kieburtz et al, 1998 **Level II**; Shlay et al, 1998 **Level II**), antiarrythymics (Kemper et al, 1998 **Level II**; Kieburtz et al, 1998 **Level II**), Peptide T (Simpson et al, 1996 **Level II**), vibratory counterstimulation (Paice et al, 2000 **Level III-1**) and acupuncture (Shlay et al, 1998 **Level II**) have not been shown to be effective.

Several complex drug interactions may occur between opioids and other medications taken by patients with HIV/AIDS; however the clinical relevance of most of these interactions is still unclear.

The HIV-1 protease inhibitor ritonavir inhibits the metabolism of methadone and buprenorphine (Iribarne et al, 1998) but this has no relevant clinical effect (McCance-Katz et al, 2003 **Level III-2**). However, ritonavir results in a clinically relevant inhibition of fentanyl metabolism (Olkkola et al, 1999 **Level II**) and leads to increased concentrations of the toxic metabolite norpethidine (normeperidine) if used in combination with pethidine (Piscitelli et al, 2000 **Level III-2**). Lopinavir induces metabolism of methadone leading to withdrawal symptoms in patients on maintenance doses (McCance-Katz et al, 2003 **Level III-2**). Rifampicin and rifabutin may increase opioid metabolism (particularly methadone) (Finch et al, 2002) and fluconazole may potentiate adverse effects of methadone (Tarumi et al, 2002). Zidovudine metabolism is

inhibited by methadone, thereby increasing its bioavailability and possibly toxicity (McCance-Katz et al, 1998 **Level III-3**).

Patients with a history of substance abuse

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 & Soto, 2009 **Level III-2**). Those with a history of substance abuse are also more likely to receive inadequate analgesia and suffer greater psychological distress (Breitbart et al, 1997 **Level III-2**). 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 non-problematic users (Tsao et al, 2007 **Level III-2**; Passik et al, 2006 **Level III-2**).

Patients in a methadone maintenance program, who also suffered from HIV/AIDS related pain, gained improved analgesia without adverse effects by use of additional methadone (Blinderman et al, 2009 **Level IV**).

The principles of pain management in these patients are outlined in Section 11.8.

Key messages

1. High concentration capsaicin patches, smoking cannabis and lamotrigine are effective in treating neuropathic pain in patients with HIV/AIDS (**N**) (**Level II**).
2. Nucleoside reverse transcriptase inhibitor (NRTIs)-induced neuropathic pain in HIV/AIDS patients is treatable with acetyl-L-carnitine (ALCAR) (**N**) (**Level II**).
3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use, but also more intense pain (**N**) (**Level III-2**).

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

☑ Neuropathic pain is common in patients with HIV/AIDS (**U**).

☑ In the absence of specific evidence, the treatment of pain in patients with HIV/AIDS should be based on similar principles to those for the management of cancer and chronic pain (**U**).

☑ Interaction between antiretroviral and antibiotic medications and opioids should be considered in this population (**U**).

9.7 Acute cancer pain

9.7.1 The scope 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.

Acute pain in the cancer patient requires urgent assessment and treatment. A thorough evaluation of the patient should include a full history and examination, and mechanism-based assessment of pain and, where indicated, appropriate investigations to determine the

presence of recurrent disease or serious complications of cancer that might require active intervention.

The European Association for Palliative Care recommends the use of standardised symptom assessment tools in the comprehensive assessment of cancer pain (Caraceni et al, 2002). Validated tools include the revised Edmonton Staging System (rESS) (Fainsinger et al, 2005; Nekolaichuk et al, 2005) and the McGill Pain Questionnaire and Brief Pain Inventory. All have been validated in different cultures (Uki et al, 1998; Aisyaturridha et al, 2006; Yesilbalkan et al, 2008). Pain assessment tools are available for non-verbal, cognitively impaired or dying patients.

Comprehensive consensus guidelines relating to cancer pain management have now been developed by several agencies worldwide (Hanks et al, 2001; Carr et al, 2002; Singapore Ministry of Health, 2003; NHS Quality Improvement Scotland, 2004; Broadfield et al, 2005; Miaskowski et al, 2005; SIGN, 2008; NCCN, 2009) all recommend best practice, but some sections are based on systematic reviews.

9.7.2 Principles of management of acute cancer pain

A pain crisis has been defined as 'an event in which the patient reports pain that is severe, uncontrolled, and causing distress for the patient, family members, or both' (Moryl et al, 2008). An acute pain crisis should be treated with a degree of urgency and a similar methodological approach as other medical crisis situations (Moryl et al, 2008).

In an acute pain crisis, rapid analgesic control may be achieved with a regular dose schedule of a parenteral opioid, with frequent reassessment and dose adjustment, or use of PCA technique. One clinical practical guideline for the administration of short-acting opioids, including IV morphine, in response to severe, moderate or increased pain has been published by the United States National Comprehensive Cancer Network (NCCN, 2009).

9.7.3 Breakthrough pain

The term breakthrough pain typically refers to a transitory flare of pain in the setting of chronic cancer pain managed with opioid drugs (Portenoy & Hagen, 1990). Despite stable therapy, exacerbations of pain are common, frequently severe or excruciating, often paroxysmal, occur a median 4 times daily and last from seconds to hours (Portenoy & Hagen, 1990 **Level IV**). Breakthrough pain may relate to waning opioid action prior to the next maintenance opioid dose (end-of-dose failure), be predictably precipitated by some movement or action (incident pain) or occur with some other random precipitant.

Consensus guidelines for management of breakthrough pain in adults have been based on limited evidence (Zeppetella & Ribeiro, 2006 **Level I**; Zeppetella, 2008 **Level IV**; Davies et al, 2009 **Level IV**). Medications used should ideally have a pharmacokinetic profile that mirrors the time-course of the breakthrough pain, with rapid onset, high potency and fast offset (SIGN, 2008). Dose requirements are subject to enormous interindividual variability and breakthrough medication doses should be titrated for each patient according to their response to these doses and separate from the background medication (Hagen et al, 2007 **Level II**). Conventional management guidelines dictate 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 (MEDD) (Hanks et al, 2001).

Oral transmucosal fentanyl citrate (OTFC) was effective for the management of breakthrough pain (Zeppetella & Ribeiro, 2006 **Level I**). The effective dose was determined by upward titration and found to be independent of the daily opioid dose (Portenoy et al, 1999 **Level II**). Analysis of

three RCTs of OTFC confirmed that the optimal OTFC dose correlated poorly with scheduled or previous breakthrough opioid doses. The only clinical indicator of breakthrough dose was age; the average final OTFC dose significantly decreased with increasing age (Hagen et al, 2007 **Level II**). In one trial, where patients were titrated to a successful dose of OTFC (69% patients), OTFC was more successful than morphine in relieving breakthrough pain and patients preferred OTFC (Coluzzi et al, 2001 **Level II**). A comparative study of OTFC and IV morphine for breakthrough pain demonstrated analgesic superiority of IV morphine at 15 minutes but not 30 minutes and comparable adverse effects (Mercadante et al, 2007 **Level III-1**).

A buccal tablet formulation of fentanyl was superior to OTFC with respect to bioavailability and time to peak plasma concentration (Darwish et al, 2007 **Level II**), and provided relief from breakthrough pain within 10 minutes (Slatkin et al, 2007 **Level II**).

9.7.4 Postoperative and procedural pain

Many of the issues relating to postoperative pain discussed in Sections 1.3 and 9.1 are particularly pertinent in the patient with cancer. Cancer patients represent a high proportion of patients undergoing thoracotomy, breast surgery, lymph node dissection from axillary, inguinal or cervical regions, and limb amputation, all associated with persistent pain syndromes that may respond to various interventions in the postoperative period. In addition, cancer patients often will undergo radio- or chemotherapy after surgery; both are risk factors for chronic postsurgical pain as outlined in Section 1.3. Chemotherapy has also been considered a risk factor for phantom limb pain, contributing to the higher incidence of phantom limb pain in children with cancer than with trauma (Smith & Thompson, 1995 **Level IV**), but no prospective trials have confirmed this association.

Identification of prior use and tolerance to opioids is essential to ensure adequate analgesia in the postoperative period, as discussed in Section 11.7.

The impact of analgesic techniques on immune response, and implications for cancer progression, are new areas of research. A review of patients undergoing radical prostatectomy, comparing outcomes after general anaesthesia plus epidural analgesia and regional anaesthesia plus opioid therapy, suggested a 57% (95% CI 17% to 78%) lower risk of cancer recurrence after the use of epidural analgesia (Biki et al, 2008 **Level IV**). Pre-emptive epidural analgesia with lignocaine and morphine, established prior to radical hysterectomy for cervical cancer, significantly reduced postoperative pain and modulated the immune response to surgery to a greater extent than epidural established after peritoneal closure; interleukin-6 rise was lowered and the duration of interleukin-2 suppression was shortened (Hong & Lim, 2008 **Level II**). Similarly, different analgesics may have different effects on postoperative immune suppression; in animals (Sacerdote et al, 1997) and in humans (Sacerdote et al, 2000 **Level II**) tramadol resulted in reduced immune suppression compared with morphine. The clinical implications of this effect have not yet been evaluated.

Patients with cancer may undergo multiple painful procedures and attention to adequate analgesia and anxiolysis is imperative, to reduce anticipatory stress prior to repeat interventions. Simple techniques include use of topical local anaesthetic, premedication or administration of breakthrough analgesia in advance, and administration of sedation by trained personnel. Few trials have evaluated procedural pain in adult patients with cancer. A review of interventions to decrease pain during mammography identified seven RCTs, but conclusions were few and based on single studies due to inability to combine data from different studies (Miller et al, 2008 **Level I**). The provision of prior information about the procedure, increasing self-control over the degree of breast compression, and the use of breast cushions all decreased pain, whereas paracetamol did not.

9.7.5 Acute cancer pain due to bone involvement

Primary cancers in bone and bone metastases are an important and common cause of acute and chronic cancer pain. Whereas some bone metastases are painless, others are associated with persistent pain with acute exacerbations precipitated by movement or mobilisation (incident pain), pathological fractures or compression of nerves or spinal cord. Hypercalcaemia may be a complication of bone malignancy that further heightens the pain experience.

In addition to pharmacological therapeutic options including opioids, NSAIDs, bisphosphonates and possibly calcitonin, patients require assessment to determine whether radiation therapy, tumour-targeting cytotoxic or hormonal therapy, or, in the case of imminent or actual pathological fracture or cord compression, surgical intervention may be of benefit.

Radiotherapy

Radiotherapy effectively reduces malignant bone pain and may reduce complications of bone cancer. At 1 month after radiation therapy around 25% patients experience complete pain relief, and 41% experience 50% pain relief (NNT for complete pain relief at one month 4.2; 95% CI 3.7 to 4.9) (McQuay et al, 2000 **Level I**).

One area of controversy has been the optimal fractionation schedule for radiotherapy. A systematic review and meta-analysis of single-fraction versus multi-fraction radiation therapy considered 11 trials (3435 patients) (Sze et al, 2004 **Level I**). Single-fraction treatment was as effective as multi-fraction radiation treatment in terms of overall pain response rates (60% vs 59%; OR 1.03; 95% CI 0.89 to 1.19), and complete pain relief (34% vs 32%; OR 1.11; 95% CI 0.94 to 0.13); however, the definition of a pain response (reduction by at least one category in a 4- or 5-point scale), and the time of pain assessment varied between studies. Despite equivalent pain relief outcomes, the incidence of retreatment and the pathological fracture rate were higher after single-dose therapy. The optimal treatment regimen must consider the clinical scenario and patient's life expectancy (Sze et al, 2004).

For patients with widespread bone metastases, radioisotopes had similar analgesic efficacy but were associated with increased risk of leukocytopenia and thrombocytopenia (McQuay et al, 2000 **Level I**).

Bisphosphonates

Evidence supports the use of bisphosphonates where analgesics and radiotherapy have provided inadequate pain relief (Wong & Wiffen, 2002 **Level I**). In multiple myeloma, bisphosphonates lowered the risk of vertebral pathological fracture (OR 0.59; 95% CI 0.45 to 0.78) and decreased pain (OR 0.59; 95% CI 0.46 to 0.76) (Djulbegovic et al, 2002 **Level I**). Similarly, in breast cancer, bisphosphonates reduce skeletal events (median reduction 28%, range 14% to 48%); pain was significantly better after bisphosphonates in five of eleven studies (Pavlakis et al, 2005 **Level I**). Bisphosphonates for prostatic bone metastases improved pain, but not analgesic consumption (Yuen et al, 2006 **Level I**).

A prospective study indicated the incidence of osteonecrosis of the jaw after bisphosphonates to be 6.7% (17 of 252 patients); incidence may increase with time of exposure, a history of dental exposure and type of bisphosphonate (Bamias et al, 2005 **Level IV**).

Although calcitonin is used to reduce metastatic bone pain and skeletal events, there is limited evidence to support the practice. Of only two RCTS considered in a recent systematic review, calcitonin provided no analgesic benefit relative to placebo in one trial, a non-significant benefit in the other, and, overall, was associated with a higher rate of adverse events (Martinez-Zapata et al, 2006 **Level I**).

Percutaneous vertebroplasty

Where other measures fail, percutaneous vertebroplasty is a minimally invasive procedure that aims to stabilise vertebral compression fractures by the injection of bone cement (polymethylmethacrylate) and achieve rapid pain relief. Two systematic reviews suggested that both vertebroplasty and kyphoplasty procedures for osteoporotic vertebral lesions were effective and safe (Hulme et al, 2006 **Level I;** McGirt et al, 2009 **Level I**). However results of more recent randomised-controlled trials found no benefit from these procedures compared with conservative management (Buchbinder et al, 2009 **Level II**; Kallmes et al, 2009 **Level II**).

Data to support these procedures for malignant bone lesions relies on low level evidence (Cheung et al, 2006 **Level IV**; Pflugmacher et al, 2006 **Level IV**; Ramos et al, 2006 **Level IV** Anselmetti et al, 2007 **Level IV**; Brodano et al, 2007 **Level IV**; Calmels et al, 2007 **Level IV**; Chi & Gokaslan, 2008 **Level IV**; Masala et al, 2008 **Level IV**). All suggest a role for vertebroplasty for rapid relief of intractable pain and restoration of function in vertebral malignancy, and a low complication rate with experienced operators. An adverse event rate of 6.8% has been reported, including haematoma, radicular pain, and pulmonary embolism of cement (Barragan-Campos et al, 2006 **Level IV**).

Cementoplasty procedures for intractable pain also extend to percutaneous injection of bone cement under fluoroscopic guidance into pelvic bone malignancies, including metastases or sarcoma involving acetabulum, superior and inferior pubic rami, ischium and sacrum (Weill et al, 1998 **Level IV**; Marcy et al, 2000; Kelekis et al, 2005 **Level IV**; Harris et al, 2007 **Level IV**).

9.7.6 Other acute cancer pain syndromes

Other acute pain syndromes in patients with cancer include malignant bowel obstruction and mucositis.

Malignant bowel obstruction

Malignant bowel obstruction may present with generalised abdominal pain or visceral colicky pain. Very little trial data exists to guide choices between best medical care, surgery or endoscopic interventions.

Pharmacological management is based on analgesic, antiemetic and antisecretory agents. Acute pain in malignant bowel obstruction is best managed with parenteral opioids, which also reduce colicky pain by reducing bowel motility (Anthony et al, 2007). The parenteral route is utilised due to the unpredictability of absorption of oral medications. For exacerbations of colic, the antispasmodic hyoscine butylbromide is of benefit and less sedating than hyoscine hydrobromide (Anthony et al, 2007; Ripamonti et al, 2008 **Level IV**). Decompression and reduction in secretions may also assist with pain. In patients with inoperable malignant bowel obstruction and decompressive nasogastric tube, both hyoscine butylbromide and the somatostatin analog octreotide reduced both continuous and colicky pain intensity (Ripamonti et al, 2000 **Level III-1**). A Cochrane Database systematic review revealed a trend for improvement in bowel obstruction after dexamethasone (Feuer & Broadley, 2000 **Level I**). For malignant bowel obstruction with peritoneal carcinomatosis, treatment according to a staged protocol with analgesic, antiemetic, anticholinergic and corticosteroid as initial therapy (Stage 1), followed by a somatostatin analog for persistent vomiting (Stage 2) and then venting gastrostomy (Stage 3) was highly effective in relieving symptoms and avoiding permanent nasogastric tube, in one hospital centre (Laval et al, 2006 **Level IV**).

Whereas laparotomy may not always be an appropriate treatment option, endoscopic stenting may offer effective and safe palliation or act as a bridging step before surgery; analysis of many retrospective case series, single case reports and reviews indicated a wide variation in

symptom control from 42% to over 80% of patients (Khot et al, 2002 **Level IV**) and complications including perforation (3.76%), stent migration (11.81%) and reobstruction (7.34%) (Sebastian et al, 2004 **Level IV**).

Mucositis

Mucositis may be due to side effects of chemoradiotherapy for solid and blood malignancies. For management see Section 9.6.7.

9.7.7 Interventional therapies for acute cancer pain

Although pain is adequately controlled in the majority of patients with advanced cancer, those with an acute exacerbation of pain or prolonged intractable pain may benefit from an interventional procedure, including local anaesthetic nerve blocks, neuraxial infusions, neurolytic or neurosurgical procedures (Chambers, 2008).

A systematic review of the comparative efficacy of epidural, subarachnoid and intracerebroventricular (ICV) opioid infusions for cancer pain found no controlled trials, so conclusions were drawn from uncontrolled trials and case series of patients with ICV, epidural, or subarachnoid opioid infusions (Ballantyne & Carwood, 2005 **Level IV**). Excellent analgesia was reported in 73%, 72% and 62% of patients after ICV, epidural and subarachnoid opioids, respectively, and there were few treatment failures in all groups. Adverse effects more common with epidural and subarachnoid infusions were persistent nausea, urinary retention, pruritus and constipation, whereas respiratory depression, sedation and confusion were more common with ICV therapy.

Currently, intrathecal infusions of several classes of agents by a variety of drug delivery systems may provide effective analgesia to cancer patients with previously refractory pain, poor tolerance of oral or systemic analgesia and poor performance status. Consensus guidelines have been established for the use of intrathecal opioids, local anaesthetics, clonidine, baclofen and other medications in cancer patients (Stearns et al, 2005).

The issue of analgesia for breakthrough pain in patients with intrathecal analgesia was addressed in a small case series, where either an intrathecal local anaesthetic bolus or sublingual ketamine was used successfully (Mercadante et al, 2005 **Level IV**).

Key messages

1. Oral transmucosal fentanyl is effective in treating acute breakthrough pain in cancer patients (**S**) (**Level I** [Cochrane Review]).
2. Radiotherapy and bisphosphonates are effective treatments of acute cancer pain due to bone metastases (**N**) (**Level I** [Cochrane Review]).
3. Opioid doses for individual patients with cancer pain should be titrated to achieve maximum analgesic benefit with minimal adverse effects (**S**) (**Level II**).
4. Analgesic medications prescribed for cancer pain should be adjusted to alterations of pain intensity (**U**) (**Level III**).

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**).
- ☑ Cancer patients receiving controlled-release opioids need access to immediate-release opioids for breakthrough pain; if the response is insufficient after 30 to 60 minutes, administration should be repeated (**U**).
- ☑ Breakthrough analgesia should be one-sixth of the total regular daily opioid dose in patients with cancer pain (except when methadone is used, because of its long and variable half life) (**U**).
- ☑ If nausea and vomiting accompany acute cancer pain, parenteral opioids are needed (**U**).

9.8 Acute pain management in intensive care

The management of pain in the intensive care unit (ICU) requires the application of many principles detailed elsewhere in these guidelines. Analgesia may be required for a range of painful conditions, for example after 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 (Hawryluck et al, 2002).

Consensus guidelines have been published in the United States for the provision of analgesia and sedation in adult intensive care (Jacobi et al, 2002), but there remains a dearth of sufficient large-scale randomised ICU pain studies on which to base evidence-based guidelines. Some of the key consensus findings regarding IV analgesia and sedation in the ICU setting were (Jacobi et al, 2002):

- a therapeutic plan and goal of analgesia should be established and communicated to caregivers;
- assessment of pain and response to therapy should be performed regularly;
- the level of pain reported by the patient is the standard for assessment but subjective observation and physiological indicators may be used when the patient cannot communicate; and
- sedation of agitated critically ill patients should only be started after providing adequate analgesia and treating reversible physiological causes.

It is difficult to separate pain management from sedation in this context and intensive care sedation algorithms usually address both aspects. There has been a recent change in emphasis from sedative-based sedation (Soliman et al, 2001) to analgesia-based sedation (Park et al, 2007 **Level III-3**; Fraser & Riker, 2007). Although these measures have been widely recommended, they have not yet been universally incorporated into routine practice. This is despite the fact that the use of such protocols to preserve consciousness while treating pain appropriately has been demonstrated to produce a 57.3% decrease in the median duration of mechanical ventilation in one study (De Jonghe et al, 2005).

Probably 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 et al, 2000 **Level II**), but does not cause adverse

psychological outcomes and reduces symptoms of post-traumatic stress disorder (Kress et al, 2003 **Level III-2**). Contrary to initial concerns, DIS is not associated with an increased risk of myocardial ischemia even in high-risk patients (Kress et al, 2007 **Level III-1**).

9.8.1 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 et al, 1995 **Level IV**).

Traditional subjective scales including the VAS or numerical rating scale (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 et al, 1997 **Level IV**; Puntillo et al, 2002 **Level IV**; Chong & Burchett, 2003).

A new behavioural pain scale has been described and validated for the evaluation of pain in sedated, mechanically ventilated, unresponsive patients (Aissaoui et al, 2005 **Level III-1**; Payen et al, 2001 **Level III-1**). A 'critical-care pain observation tool' that is based upon the response to noxious stimuli has undergone validation in diverse critically ill patient subgroups (Gelinas et al, 2009 **Level III-2**).

The available data support self-rating where possible, and where not, a nurse-administered NRS combined with the Behavioural Pain Scale (Ahlers et al, 2008 **Level III-3**).

The use of formal pain/ agitation assessment and subsequent treatment decreased the incidence overall of pain (63% vs 42%) and agitation (29% vs 12%). These findings were associated with a decrease in the duration of mechanical ventilation (Chanques et al, 2006 **Level III-1**). 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 et al, 2008 **Level III-3**).

9.8.2 Non-pharmacological measures

Much of the discomfort associated with a prolonged admission to intensive care 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 et al, 1996; Chong & Burchett, 2003 **Level IV**; Puntillo et al, 2004 **Level III-3**). Maintenance of a day/night routine (lighting and activity) is thought to aid sleep quality (Horsburgh, 1995). 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.

9.8.3 Pharmacological treatment

The mainstay of treatment of acute pain in the ICU remains parenteral opioid analgesia (Shapiro et al, 1995; Hawryluck et al, 2002). 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 drugs (eg tramadol, monoamine oxidase

inhibitors [MAOIs] and SSRIs). Fentanyl is emerging as a useful alternative to morphine, with a lesser tendency to cause haemodynamic instability (Shapiro et al, 1995). It 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 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 et al, 1997 **Level II**). Remifentanil exhibits rapid clearance that is independent of renal function (Cohen & Royston, 2001; Breen et al, 2004) while remifentanil acid, a weak active metabolite, may accumulate in the presence of renal impairment (Pitsiu et al, 2004 **Level IV**). This has no clinical consequences (Breen et al, 2004 **Level IV**). When titrated carefully against a sedation scale, remifentanil did not reduce the need for supplementary sedation or the time to extubation after cessation compared with fentanyl (Muellejans et al, 2004 **Level II**). The use of remifentanil in postsurgical ICU patients provided superior analgesia and an accelerated extubation time compared with morphine (Dahaba et al, 2004 **Level II**). The combination of morphine and remifentanil provided better analgesia and sedation than morphine alone, with a lower incidence of side effects and a similar haemodynamic profile and patient satisfaction (Carrer et al, 2007 **Level II**). In a comparison between a remifentanil-based sedation regimen titrated to response before the addition of midazolam for further sedation, or a midazolam-based sedation regimen with fentanyl or morphine added for analgesia, remifentanil-based sedation reduced the duration of mechanical ventilation, improved the weaning process, and decreased overall sedative doses required in ICU patients requiring long-term ventilation (Breen et al, 2005 **Level II**).

Dexmedetomidine is a highly selective alpha-2 agonist sedative, with anxiolytic and analgesic properties. It has the advantage of providing titratable sedation with minimal respiratory depression (Martin et al, 2003 **Level II**). 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 intensive care practice as an aid to increase tolerance of intubation and mechanical ventilation and to smooth the transition to spontaneous respiration and extubation. After coronary artery surgery, dexmedetomidine was associated with similar ventilation times to propofol-based sedation but significantly lower morphine requirements and fewer ventricular arrhythmias (Herr et al, 2003 **Level II**). These findings were contradicted by a retrospective review in general ICU patients, where adjunctive dexmedetomidine reduced sedative requirements but did not alter analgesic requirements. (MacLaren et al, 2007 **Level III-2**).

In ventilated patients, the spread of thoracic epidural block increased with positive pressure ventilation (Visser et al, 2006 **Level II**).

9.8.4 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 (Khatri & Pearlstein, 1997).

Early treatment of pain with carbamazepine improved analgesia and reduced requirements for pethidine and sedation in patients with Guillain-Barre syndrome (Tripathi & Kaushik, 2000 **Level II**). Gabapentin (Pandey et al, 2002 **Level II**) and ketamine infusions (Parisod, 2002) also improved pain relief. Gabapentin was more effective than carbamazepine for the treatment of pain in patients with Guillain-Barre syndrome admitted to ICU for mechanical ventilation

(Pandey et al, 2005 **Level II**). IV lignocaine 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 et al, 1998 **Level I**).

Plasma exchange in acute Guillain-Barre syndrome was associated with a shortened duration of disease and improved outcomes, including pain (Guillain-Barre Syndrome Study Group, 1985 **Level II**).

While steroid therapy is not advocated as primary management in postinfectious polyneuropathy, it may provide rapid resolution of the severe backache associated with the acute phase of the neuropathy (Kabore et al, 2004 **Level IV**).

9.8.5 Procedure-related pain

There is often an assumption that patients who are intubated and sedated in intensive care 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 et al, 2007 **Level III-1**). Patients who have memories of ICU, recall discomfort in 54% and overt pain in 12% (Payen et al, 2007 **Level IV**). Endotracheal tube suctioning and other medical interventions are consistently reported as being uncomfortable or painful.

In conclusion, adequate local and/or parenteral anaesthesia should be provided during any noxious procedure (Puntillo et al, 2004).

Key messages

1. 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 (**N**) (**Level III-1**).
2. Gabapentin is more effective than carbamazepine in reducing the pain associated with Guillain-Barre syndrome (**S**) (**Level II**).
3. Remifentanil or remifentanil with morphine provides better analgesia than morphine alone in ventilated intensive care unit patients (**N**) (**Level II**).
4. The use of formal pain and agitation assessment and subsequent treatment in ventilated intensive care unit patients decreases the incidence of pain and duration of ventilation (**N**) (**Level III-1**).

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

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

☑ Patients should be provided with appropriate sedation and analgesia during potentially painful procedures (**U**).

9.9 Acute pain management in emergency departments

Pain is the most common reason for presentation to the emergency department and many patients will self-medicate for pain before attending (Kelly & Gunn, 2008). There is evidence that, as in many other areas of health care, patients in emergency departments around the world receive suboptimal pain management (Todd et al, 2007). Although 70% of patients presenting to an emergency department 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**).

In the emergency department setting, analgesia should be simple to administer, condition-specific and where possible based on local-regional rather than systemic techniques. Systems should be adopted to ensure adequate pain assessment, timely and appropriate analgesia, frequent monitoring and reassessment of pain and additional analgesia as required. For example, the introduction of a protocol based fentanyl titration regimen improved timely and effective delivery of analgesia in the emergency department (Curtis et al, 2007 **Level II**).

9.9.1 Systemic analgesics

Opioids

In the emergency department, opioids are frequently prescribed for the treatment of severe pain and should preferably be administered via the IV route, given the wide interindividual variability in dose response and the delayed absorption via the IM or SC routes. However, IV and intraosseous morphine demonstrated similar pharmacokinetic profiles in adults (Von Hoff et al, 2008 **Level II**). Doses should be adjusted for age (see Section 4.1) and titrated to effect. Patients require close observation for sedation, respiratory depression and occasionally hypotension (Coman & Kelly, 1999 **Level IV**).

There is no clear consensus on what constitutes the most effective IV opioid or dosing regimen for analgesia in the emergency department. There was no difference between IV bolus dose fentanyl or morphine in providing effective analgesia for up to 30 minutes during prehospital care (Galinski et al, 2005 **Level II**). Similarly, in elderly patients attending an emergency department there were no differences in effects or adverse effects between IV bolus doses of morphine or hydromorphone (Chang, Bijur, Baccelieri et al, 2009 **Level II**). The addition of ultra-low-dose naloxone to bolus dose morphine failed to improve analgesia or reduce opioid adverse effects (Bijur et al, 2006 **Level II**).

Titrating (relatively) high doses of opioid frequently to clinical effect provides the best chance of delivering rapid and effective analgesia. Significantly more patients attained effective analgesia at 10 minutes with the administration of 0.1 mg/kg morphine, followed by 0.05 mg/kg, 5 minutely, compared with those who received half these doses; however there was no difference in analgesia outcomes at 30 minutes (Bounes et al, 2008 **Level II**). In non-elderly adults, a bolus dose of 2 mg hydromorphone IV provided good analgesia, but caused oxygen desaturation in one third of patients (Chang, Bijur, Napolitano et al, 2009 **Level III-3**); use of a 1 mg bolus dose was slightly less effective but caused oxygen desaturation in just 5% of patients (Chang, Bijur, Campbell et al, 2009 **Level III-3**). IV opioid PCA was as effective as nurse-administered IV bolus dosing in the emergency department (Evans et al, 2005 **Level II**).

In children requiring analgesia in the emergency department, IN (Borland et al, 2007 **Level II**), inhaled (nebulised) (Miner et al, 2007 **Level II**), or oral transmucosal (Mahar et al, 2007 **Level II**) fentanyl provided effective analgesia (see Sections 6.6.1 and 10.4.4 for details). IN fentanyl

and IV morphine were equally effective in reducing acute cardiac chest pain during prehospital transfer (Rickard et al, 2007 **Level II**). In a study of patients with post-traumatic thoracic pain, there was no difference in analgesia between nebulised morphine and morphine PCA (Fulda et al, 2005 **Level II**).

Opioid-tolerant patients pose a special challenge in the emergency department and their management is discussed in Section 11.7.

Tramadol

In the management of severe trauma pain, IV tramadol had similar analgesic efficacy to morphine (Vergnion et al, 2001 **Level II**). In patients with right lower quadrant pain, presumably due to appendicitis, parenteral tramadol reduced the mean VAS by only 7.7/100 mm compared with placebo, and did not affect the clinical examination (Mahadevan & Graff, 2000 **Level II**). For renal colic, tramadol was as effective as parenteral ketorolac (Nicolas Torralba et al, 1999 **Level II**) but less effective than pethidine (Eray et al, 2002 **Level II**). For acute musculoskeletal pain, IM tramadol was similar to ketorolac in efficacy and side effects, when both were combined with oral paracetamol (Lee et al, 2008 **Level II**).

Non-steroidal anti-inflammatory drugs

NSAIDs are useful for treating mild-to-moderate trauma pain, musculoskeletal pain, renal and biliary colic and some acute headaches, as discussed elsewhere in this document (see Section 4.2).

Inhalational analgesics

N_2O in oxygen (see Section 4.3.1) provided effective analgesia and anxiolysis for minor procedures in both adults and children (Gamis et al, 1989 **Level II**; Gregory & Sullivan, 1996 **Level II**; Burton et al, 1998 **Level II**; Gerhardt et al, 2001 **Level II**; Burnweit et al, 2004 **Level IV**) 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 4.3) is used to provide analgesia, most commonly in prehospital emergency care (see Section 9.10.1).

Ketamine

Ketamine-midazolam was more effective and had fewer adverse effects than fentanyl-midazolam or fentanyl-propofol, for paediatric fracture reduction in the emergency department (Migita et al, 2006 **Level I**) (for more information see Section 10.4.4).

IV ketamine boluses produced a significant morphine-sparing effect (without a change in pain scores) when used to treat severe trauma pain in the emergency department (Galinski et al, 2007 **Level II**). 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, compared with intermittent SC morphine injections (Gurnani et al, 1996 **Level II**). IN ketamine provided effective pain relief (within 15 minutes); adverse effects were mild and transient (Christensen et al, 2007 **Level II**).

For further information on ketamine, see Section 4.3.2.

9.9.2 Analgesia in specific conditions

Abdominal pain

Patients and physicians differ in their assessment of the intensity of acute abdominal pain in the emergency department. Physician's VAS estimates of abdominal pain were significantly lower than the patient's 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 emergency department with abdominal pain were satisfied with their analgesia on discharge (Marinsek et al, 2007 **Level IV**).

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 does not interfere with the diagnostic process in acute abdominal pain in adults (Ranji et al, 2006 **Level I**; Manterola et al, 2007 **Level I**) or in children (Kim et al, 2002 **Level II**; Green et al, 2005 **Level II**).

If pain is severe, opioids may be required. 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 evidence to support this position (see Section 9.6.1).

Renal colic

See Section 9.6.1.

Biliary colic and acute pancreatitis

See Section 9.6.1.

Acute cardiac chest pain

See Section 9.6.3.

Acute pain and sickle cell disease

See Section 9.6.4.

Migraine

Most migraine headaches are successfully managed by the patient and his or her family doctor. However a small number of patients fail to respond and present for treatment at the emergency department. Approximately 80% of patients have tried their usual medications (simple analgesics and triptans) before presentation (Larkin & Prescott, 1992; Shrestha et al, 1996).

Table 9.4 lists some of the drugs that have been shown to be effective agents for treating acute migraine in the emergency department. See Section 9.6.5 for a more detailed review of the treatment of migraine and other acute headache syndromes.

Table 9.4 Pooled effectiveness data from emergency department studies of the treatment of migraine

Agent	No. of studies	Total patients	Clinical success rate	NNT: Clinical success# (95% CI)	Level of evidence
Chlorpromazine	6	171	85%	1.7 (1.5, 2.0)	II
Droperidol IM	3	233	83%	1.7 (1.5, 2.0)	II
Prochlorperazine	4	113	79%	1.9 (1.5,2.3)	II
Sumatriptan	5	659	69%	2.3 (2.1,2.6)	II
Ketorolac IM	6	155	66%	2.5 (2.0, 3.3)	II
Tramadol [IM or IV]	3	191	60%	2.9 (2.3, 3.9)	II
Metoclopramide	6	374	57%	3.1 (2.6, 3.9)	I

Notes: Only agents used in an aggregate of 50 patients or more have been included.
= assumes placebo success rate of 25% * = As defined by study authors
Source: Adapted and updated from Kelly & Gunn (Kelly & Gunn, 2008).

Fractured neck of femur

In patients with a fractured neck of femur in the emergency department, a '3 in 1' femoral nerve block with bupivacaine, combined with IV morphine was more effective than IV morphine alone, with a faster onset of analgesia (Fletcher et al, 2003 **Level II**). A facia iliaca block with mepivacaine, significantly improved pain scores and reduced IV morphine requirements and sedation, compared with IM morphine (Foss et al, 2007 **Level II**). For safety reasons, ropivacaine or levobupivacaine may be the preferred local anaesthetics (see Section 5.1).

Wounds

Local anaesthesia is frequently required for the treatment of wounds in the emergency department. Agents most commonly used for needle infiltration are lignocaine or longer acting agents such as 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 et al, 1998 **Level II**; Kelly et al, 1994 **Level III-1**). There are conflicting data on whether buffering of lignocaine reduces the pain of infiltration (Boyd, 2001 **Level II**).

Digital nerve block with 0.75 % ropivacaine, significantly prolonged analgesia and reduced rescue analgesia requirements to 24 hours, without a clinically significant increase in time to block onset, compared with 2% lignocaine (Keramidas & Rodopoulou, 2007 **Level II**).

Topical local anaesthesic 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 analgesia in the emergency department (Eidelman et al, 2005 **Level I**). Topical anaesthetic preparations such as mixtures of adrenaline, lignocaine and amethocaine are effective alternatives to infiltration with local anaesthesia for simple lacerations (Smith et al, 1997 **Level II**; Singer & Stark, 2000 **Level II**) and reduced the pain of infiltration when injecting local anaesthetics (Singer & Stark, 2000 **Level II**). 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 et al, 2007 **Level II**). A topical gel dressing containing morphine was no more effective than other gel dressings in reducing burns injury pain in the emergency department (Welling, 2007 **Level II**).

9.9.3 Non-pharmacological management of pain

Although analgesic agents may be required to treat pain in the emergency department setting, the importance of non-pharmacological 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 8.1 and 9.3.2).

Deep breathing exercises did not provide effective pain relief to patients in emergency departments (Downey & Zun, 2009 **Level II**).

Key messages

Abdominal pain (see Section 9.6.1)

Migraine (also see Section 9.6.5)

1. Triptans or phenothiazines (prochlorperazine, chlorpromazine) are effective in at least 75% of patients presenting to the emergency department with migraine (**U**) (**Level II**).

Local anaesthesia

2. Topical local anaesthetic agents (including those in liposomal formulations) (**N**) (**Level I**) or topical local anaesthetic-adrenaline agents (**N**) (**Level II**) provide effective analgesia for wound care in the emergency department.
3. 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 (**S**) (**Level II**).

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 and appropriate analgesia, frequent monitoring and reassessment of pain (**U**).

9.10 Prehospital analgesia

The above section (9.9) considered management of acute pain in patients admitted to emergency departments. 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 and that moderate or severe pain is present in at least 20% of patients (McLean et al, 2002), nearly one-third of all injured patients and over 80% of those with extremity fractures (Thomas & Shewakramani, 2008). Yet the proportion of patients given analgesics (opioid or inhalational) prior to transfer to an emergency department varies significantly. 'Unnecessary pain' was the second most common type of injury in 56 of 272 claims against ambulance trusts in the United Kingdom between 1995 and 2005 (Dobbie & Cooke, 2008).

One survey of 1073 adult patients with suspected extremity fractures showed that just 18 were given any analgesia and only 2 received morphine (White et al, 2000 **Level IV**). A later survey showed that only 12.5% of patients with isolated extremity injuries received any prehospital parenteral pain relief (Abbuhl & Reed, 2003 **Level IV**). Another study reported prehospital opioid administration in 18.3% of patients with lower extremity fractures; however older patients and those with a hip fractures were less likely to be given analgesia prior to arrival in the emergency department (McEachin et al, 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 6% received morphine (Vassiliadis et al, 2002 **Level IV**). Similarly, in a 2005 survey from Australia, 55% of patients in pain received analgesia by paramedics (Lord et al, 2009 **Level IV**).

Prehospital use of opioids may be increasing; in two surveys of 2005, 29% of patients with isolated extremity injuries (Michael et al, 2007 **Level IV**) and 13% of females and 17% of males in pain (Lord et al, 2009 **Level IV**) had been given morphine.

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 drugs (Rogovik & Goldman, 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 years, but not to any child aged less that 5 years; a greater proportion of this younger group (70% vs 54%) were given opioid analgesia once in the emergency department (Watkins, 2006 **Level IV**).

Despite such studies showing that pain relief prior to arrival in an emergency department 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 randomised controlled studies 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.

9.10.1 Assessment of pain in the prehospital environment

As in other settings, pain intensity is best assessed using patient self-report measures such as VASs (Galinski et al, 2005; Kober et al, 2002), VNRSs (McLean et al, 2004; Woollard et al, 2004; Rickard et al, 2007; Bounes et al, 2008), VDSs (McLean et al, 2004; Vergnion et al, 2001), faces pain scales (Rogovik & Goldman, 2007) (see Section 2). A ruler incorporating both visual analogue and faces pain scales (Lord & Parsell, 2003 **Level IV**) has also been used to measure pain in patients prior to arrival at hospital.

However, 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 10.3), elderly patients (see Section 11.2.3), 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.

9.10.2 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 (Alonso-Serra & Wesley, 2003) so that it can be repeated as often as necessary and titrated to effect for each patient. Consideration should be given to both choice of analgesic drug and route of administration.

Opioids and tramadol

The administration of systemic opioids as an effective prehospital analgesic is widespread. Their application is influenced by not only the knowledge and judgment required to use them, but also by the different drugs of dependence legislation found in most 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. Occasionally morphine is given intramuscularly in the

prehospital environment, but this is not encouraged because of the unpredictable impact upon the pharmacokinetics in a poorly perfused patient.

Both morphine and fentanyl are commonly used for prehospital analgesia. Morphine (Bruns et al, 1992 **Level IV**; Fullerton-Gleason et al, 2002 **Level IV**) and fentanyl (Kanowitz et al, 2006 **Level IV**), as well as tramadol (Ward et al, 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 et al, 2005 **Level IV**; Krauss et al, 2009 **Level IV**).

Morphine doses of 0.1 mg/kg IV followed by 0.05 mg/kg every 5 mins as needed provided more rapid pain relief and patient satisfaction than doses that were 50% lower (Bounes et al, 2008 **Level II**).

In a comparison of IV fentanyl and morphine bolus doses given every 5 minutes as needed for prehospital analgesia, no difference was found in pain relief or incidence of side effects (Galinski et al, 2005 **Level II**). Similarly, there was no difference in pain relief or adverse effects reported in a comparison of IV tramadol and morphine (Vergnion et al, 2001 **Level II**).

When used to treat acute cardiac chest pain during prehospital transfer, IV alfentanil provided more rapid relief than IV morphine (Silfvast & Saarnivaara, 2001 **Level II**). IN fentanyl and IV morphine were equally effective for patients with cardiac and non-cardiac acute pain (Rickard et al, 2007 **Level II**).

A comparison of 5 mg and 10 mg nalbuphine doses given IV and repeated at 3-minute 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 et al, 2004 **Level II**).

Inhalational agents

Inhalational analgesics can provide early pain relief in the prehospital environment and are used before opioids in many situations. 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 et al, 2000), whereas in another series N_2O was not used (Rogovik & Goldman, 2007). Methoxyflurane is not available in many countries, but in Australia it has replaced N_2O in most prehospital settings. Provision of N_2O in ambulances is hampered by difficulties providing a scavenger system that minimises occupational exposure and the bulk/logistical issues associated with managing cylinders of oxygen and nitrous oxide (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 under 5 year (Watkins, 2006). There have been no RCTs of methoxyflurane (Grindlay & Babl, 2009) or N_2O (Faddy & Garlick, 2005), and no large case series comparing efficacy with other analgesic agents in the prehospital setting.

Methoxyflurane reduced pain scores (mean 2.47±0.24 on NRS 0 to 10) in adults, the majority of whom had musculoskeletal pain. The incidence of nausea was 8%, and 11% had increased drowsiness (Buntine et al, 2007 **Level IV**). When graded by the paramedic, methoxyflurane also reduced pain scores in children (Babl et al, 2006 **Level IV**). The overall incidence of drowsiness was 27%, but the risk of deep sedation was significantly higher in younger children. In both of these studies, methoxyflurane was delivered by a Penthrox® inhaler which contains 3 mL of methoxyflurane and lasts for 25 to 30 minutes (Medical Developments International, 2001). There have been no reports of toxicity with analgesic use if doses are limited to 3 mL repeated once with a maximum of 15 mL per week, or a maximum of 0.5% for one hour (Grindlay & Babl, 2009) (see also Section 4.3.1).

N_2O is included in prehospital management protocols for manipulation, splinting and transfer of patients with lower limb fracture (Lee & Porter, 2005 **Level IV**) and as a second-line in burns patients if opioids are not available (Allison & Porter, 2004 **Level IV**). Although N_2O has been reported to provide pain relief in over 80% of patients requiring prehospital analgesia (Thomas & Shewakramani, 2008 **Level IV**), this is not based on RCTs (Faddy & Garlick, 2005) 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 emergency department, 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 contra-indications (such as pneumothorax and decreased consciousness) may be particularly relevant in this patient group (Faddy & Garlick, 2005) (see Section 4.3.1 for further details).

Ketamine

Ketamine has been administered by physicians for prehospital procedural analgesia and sedation in both adults (Porter, 2004 **Level IV**; Svenson & Abernathy, 2007 **Level IV**; Bredmose, Lockey et al, 2009 **Level IV**) and children (Bredmose, Grier et al, 2009 **Level IV**) with good safety profile.

Non-steroidal anti-inflammatory drugs and paracetamol

The use of parenterally administered NSAIDs has been suggested for prehospital analgesia (Alonso-Serra & Wesley, 2003; McManus & Sallee, 2005) but the slower onset of effect as well as the risk of adverse effects (eg bleeding, renal impairment [see Section 4.2]), 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 acute prehospital setting.

9.10.2 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 & Sallee, 2005). However, there are no studies looking at efficacy and safety. It should be remembered that their 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 & Sallee, 2005).

9.10.3 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 emergency department (Lopez et al, 2003 **Level IV**).

9.10.4 Non-pharmacological management of pain

Although analgesic agents are often used to treat pain in the prehospital setting, the importance of non-pharmacological treatments should not be forgotten. These include ice, elevation and splinting for injuries. The role of reassurance in the management of acute pain in an anxious patient is often undervalued.

TENS applied over the painful flank during prehospital transport reduced pain scores, anxiety and nausea in patients with renal colic (Mora et al, 2006 **Level II**).

Acupressure performed by during prehospital transport using 'true points' led to better pain relief and less anxiety than acupressure using 'sham points' (Kober et al, 2002 **Level II**; Barker et al, 2006 **Level II**; Lang et al, 2007 **Level II**) or no acupressure (Kober et al, 2002 **Level II**).

Local active warming resulted in significant analgesia for females in pelvic pain during prehospital transport (Bertalanffy et al, 2006 **Level II**).

9.10.5 Analgesia in specific conditions

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 & Braunwald, 2008; Cannon, 2008) and nitroglycerine (Henrikson et al, 2003 **Level IV**). Opioid analgesia may also be required (see Section 9.6.3).

Abdominal pain

As noted in Section 9.6, administration of opioid drugs does not interfere with the diagnostic process in acute abdominal pain.

Patients with a head injury

Caution is often expressed about the use of opioids for pain relief in patients with a head injury (Thomas & Shewakramani, 2008). 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 opioid-induced respiratory depression will lead to hypercarbia and increased intracranial pressure (Nemergut et al, 2007). 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 9.1.5).

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 (**N**) (**Level IV**).
3. Methoxyflurane, in low concentrations, may be an effective analgesia in the hospital and prehospital setting (**N**) (**Level IV**).
4. Ketamine provides effective analgesia in the prehospital setting (**N**) (**Level IV**)**.**
5. Moderate to severe pain is common in both adult and paediatric patients in the prehospital setting (**N**) (**Level IV**).

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

☑ The ideal prehospital analgesic agent should be simple to use, safe, 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. Consideration should be given to both choice of analgesic drug and route of administration (**N**).

☑ Non-pharmacological measures are effective in providing pain relief and should always be considered and used if practical (**N**).

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10. THE PAEDIATRIC PATIENT

10.1 DEVELOPMENTAL NEUROBIOLOGY OF PAIN

Following birth, the neural pathways required for nociception are functional and cortical responses to noxious stimuli such as blood tests can be demonstrated in even the most premature neonate (Slater et al, 2006). However, as significant functional and structural changes occur in nociceptive pathways during the postnatal period, pain does not evoke the same pattern of activity in the infant and adult central nervous system (Fitzgerald & Walker, 2009). 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).

Although C-fibre polymodal nociceptors are mature in their pattern of firing at birth and are capable of being activated in the periphery by exogenous stimuli, 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 was 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). 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 et al, 1988 **Level IV**) and infants following abdominal surgery (Andrews & Fitzgerald, 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. 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 et al, 2004; Palmer et al, 2008; Prins et al, 2008). In addition, changes in nociceptive processing may have significant effects on the pharmacodynamic response to analgesics in early life (Walker, 2008). Therefore, developmental age and not just weight should be considered when calculating analgesic dosing. Laboratory studies have demonstrated postnatal changes in the mechanism of action, analgesic efficacy, and side-effect profile of analgesics that can inform subsequent clinical trials (Nandi & Fitzgerald, 2005; Walker, 2008; Fitzgerald & Walker, 2009). 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 (Mellon et al, 2007), although the clinical significance of these findings requires further research.

10.2 Long-term consequences of early pain and injury

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 & Walker, 2009).

In clinical studies, neonatal intensive care and surgery have been associated with: alterations in pain-related behaviour (Grunau et al, 2006 **Level IV**); enhanced response to future noxious stimuli (Taddio & Katz, 2005 **Level III-2**); increased perioperative analgesic requirements when subsequent surgery is performed (Peters, Koot, de Boer et al, 2003 **Level III-2**); and long-term changes in sensory processing (Hermann et al, 2006; Walker et al, 2009 **Level III-2**). In laboratory studies, the degree of long-term change varies with the type and severity of injury (Fitzgerald & Walker, 2009). Inflammation, full thickness skin wounds, and skin incision produce prolonged alterations in sensitivity and in 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 et al, 2005; Moss et al, 2007). 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 that experienced by older children and adults.

Importantly, analgesia at the time of the initial painful stimulus may modulate long-term effects. Male neonates circumcised without analgesia showed an increased behavioural pain response to immunisation several months later, but this was reduced if local anaesthetic was used prior to the procedure (Taddio et al, 1995 **Level III-2**). Infants who had undergone surgery in the neonatal period with perioperative morphine did not show any increase in later response to immunisation when compared with infants without significant previous pain experience (Peters, Koot, de Boer et al, 2003 **Level III-2**). Further research is required to determine the most developmentally appropriate and effective analgesic regimen for modulating the effects of early pain and injury.

Key messages

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

- ☑ Following birth, even the most premature neonate responds to nociceptive stimuli (**U**).
- ☑ In early development more generalised reflex nociceptive responses occur in response to lower intensity stimuli (**U**).
- ☑ Due to the increased plasticity of the developing nervous system, pain and injury in early life may have adverse long-term consequences (**U**).

10.3 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 et al, 2008). However, pain in hospitalised children is often assessed infrequently (Johnston et al, 2007; Twycross, 2007; Taylor et al, 2008). Improvements in pain management and in patient, parent and staff satisfaction have been associated with regular assessment and measurement of pain (Treadwell

et al, 2002). Adoption of written guidelines or algorithms for pain management improved both assessment and management of pain in neonates and children (Falanga et al, 2006 **Level IV**; Gharavi et al, 2007). 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 et al, 2007) should be incorporated into overall assessment. Clinical trials have focussed on assessment of pain intensity and further evaluation and validation of tools for measuring global satisfaction, adverse effects and physical recovery following paediatric acute pain are required (McGrath et al, 2008).

Verbal self-report is considered to be the best measure of pain in adults. Although self-report should be used in children whenever possible, it is not always possible as a child's understanding of pain and their ability to describe it changes with age. Therefore measurement tools must be appropriate to the different stages of their development. Examples of acute pain measurement tools are listed in Tables 10.1, 10.2 and 10.3.

10.3.1 Pain assessment in neonates

A large number of 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 the age of the infant, the stimulus (eg procedural or postoperative pain) and the purpose of the measurement (eg clinical care or research).

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 carbon dioxide tension and vagal tone (Sweet & McGrath 1998). As these changes are reduced by analgesia, they are useful surrogate outcome measures of pain, but as their sensitivity and specificity will also be influenced by concurrent clinical conditions (eg increased heart rate due to sepsis) and other factors (eg distress, environment, movement), they should be used in conjunction with other behavioural measures (Howard et al, 2008 **Level IV**). Cortical pain responses to noxious stimuli can be demonstrated in premature neonates (Bartocci et al, 2006 **Level III-3**; Slater et al, 2006 **Level III-3**). This technique is currently utilised solely as a research tool, but the level of cortical activity has been shown to correlate with the premature infant pain profile (PIPP) score (Slater et al, 2008 **Level IV**).

Behavioural measures

Noxious stimuli produce a series of behavioural responses in neonates and infants that can be used as surrogate measures of pain (McGrath, 1998; Gaffney et al, 2003) 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 and amplitude or pitch.

The reliability and validity of behavioural measures is best established for short sharp pain associated with procedural interventions such as heel stick. The specificity and sensitivity of the response can be influenced by previous interventions and handling (Holsti et al, 2006), motor development, and manifestations of other states of distress (eg hunger and fatigue), particularly in neonates requiring intensive care (Ranger et al, 2007).

Ten facial actions are included in the Neonatal Facial Coding Scale (NFCS), which was originally validated for procedural pain in neonates and infants (see Table 10.1) (Grunau & Craig, 1987).

A reduced scale with five items (brow bulge, eye squeeze, nasolabial furrow, horizontal mouth stretch and taut tongue) has been found to be a sensitive and valid measure of postoperative pain in infants ages 0 to 18 months (Peters, Koot, Grunau et al, 2003). In neonatal intensive care, facial actions were found to be more reliable than physiological measures for evaluating pain responses (Stevens, Franck et al, 2007), but may be dampened in preterm neonates (Holsti & Grunau, 2007) in whom cortical responses to pain have been demonstrated in the absence of a change in facial expression (Slater et al, 2008).

Many neonatal pain assessment tools have not been rigorously evaluated, but the following are widely used (McNair et al, 2004; Howard et al, 2008) (see Table 10.1 and 10.2):

- acute procedural pain — PIPP, Cries, Requires oxygen, Increased vital signs, Expression, Sleeplessness (CRIES), NFCS;
- postoperative pain — PIPP, CRIES; and
- intensive care — COMFORT.

10.3.2 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 et al, 2000). Some examples are included in Table 10.2 but a wider range of measures, their strengths and limitations, and issues of testing reliability and validity have been reviewed (Johnston et al, 2002; von Baeyer & Spagrud, 2007; McGrath et al, 2008). In infants and young children, behavioural items that predicted analgesic demand in the postoperative period were crying, facial expression, posture of the trunk, posture of the legs and motor restlessness (Buttner & Finke, 2000).

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 versus research reliability). Based on current data the following observational / behavioural measurement tools were recommended for pain measurement in infants 1 year and above (McGrath et al, 2008 **Level I**), children and adolescents (von Baeyer & Spagrud, 2007 **Level I**) (see Table 10.2).

- acute procedural pain — Face Legs Activity Cry and Consolability (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.

10.3.3 Self-report in children and adolescents

Self-report of pain is preferred when feasible, and is usually possible by 4 years of age, but this will depend on the cognitive and emotional maturity of the child. Scales for self-report need to consider the child's age, ability to differentiate levels of intensity, and to separate the emotional from the physical components of pain. 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. At 4 to 5 years of age, children can differentiate 'more', 'less' or 'the same', and can use a Faces Pain Scale (Figure 10.1) if it is explained appropriately and is a relatively simple scale 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

(Hicks et al, 2001). In scales anchored with smiling or tearful faces, pain may be confused with other emotional states such as happiness, sadness or anxiety (Champion et al, 1998).

Between 7 and 10 years of age 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 et al, 2003). It is not until 10 to 12 years of age that children can clearly discriminate the sensory intensity and the affective emotional components of pain and report them independently (McGrath et al, 1996). Verbally competent children aged 12 years and above can understand and use the McGill Pain Questionnaire (Gaffney et al, 2003).

Six self-report tools have well-established evidence of reliability and validity (Pieces of Hurt tool; Faces Pain Scale and Faces Pain Scale-Revised; Oucher; Wong-Baker Faces; visual analogue scale [VAS]) for acute pain assessment in children (over 3 years) and adolescents (Stinson et al, 2006 **Level I**; McGrath et al, 2008 **Level I**). Although chronological age may not always be an accurate indicator of developmental stage, the following general age ranges are suggested (see also Howard et al, 2008):

- 3 to 4 years — Pieces of Hurt (Poker Chip) tool;
- 4 to 12 years — Faces Pain Scale-Revised; and
- over 8 years — 0 to 100 VAS.

10.3.4 Children with cognitive impairment

In children with cognitive impairment and/or communication problems, assessment of pain is difficult and can contribute to inadequate analgesia. Neonates at risk for neurological impairment required more procedural interventions in intensive care, but received less analgesia (Stevens et al, 2003) and may be perceived as being less responsive to painful stimuli (Breau et al, 2006; Stevens, McGrath et al, 2007). A retrospective chart review of children who had undergone spine fusion surgery, found that pain was assessed less frequently in cognitively impaired children and that they received less analgesia (Malviya et al, 2001 **Level IV**). Another group found that while cognitively impaired children received less analgesia during surgery, they received comparable amounts and types of analgesics as cognitively intact children in the postoperative period (Koh et al, 2004 **Level III-2**).

Specific tools have been developed for cognitively impaired children (Howard et al, 2008). 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) (Breau, McGrath et al, 2002), which also has a postoperative version (NCCPC-PV) (Breau, Finley et al, 2002). The Paediatric Pain Profile (PPP) also rates 20 behaviours to assess pain in children with severe neurological disability (Hunt et al, 2004). A revised FLACC scale, which incorporates specific descriptors and parent-identified behaviours for individual children, has also been developed for cognitively impaired children (Malviya et al, 2006).

Key messages

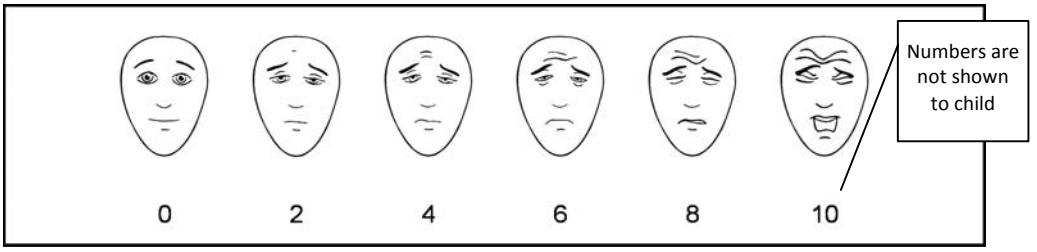
The following tick boxes ☑ represent conclusions based on clinical experience and expert opinion.

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

☑ Pain measurement tools are available for children of all ages (**U**).

☑ Pain measurement tools must be matched to the age and development of the child, be appropriate for the clinical context and be explained and used consistently (**U**).

Figure 10.1 Faces Pain Scale — Revised



Note: The full-size version of the Faces Pain Scale (FPS-R), together with instructions for administration (available in many languages), are freely available for non-commercial clinical and research use from www.painsourcebook.ca.

Source: FPS-R; Hicks et al 2001; adapted from Bieri et al (1990).

Table 10.1 Acute pain intensity measurement tools — neonates

Scale	Indicators	Score	Utility
Premature Infant Pain Profile (PIPP) (Stevens et al 1996)	gestational age behavioural state heart rate oxygen saturation brow bulge eye squeeze nasolabial furrow	each scored on 4-point scale (0,1,2,3); total score 0–21; 6 or less = minimal pain; >12 = moderate to severe pain	preterm and term neonates; procedural pain; postoperative pain in term neonates
Neonatal Infant Pain Scale (NIPS) (Lawrence et al 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

Scale	Indicators	Score	Utility
Neonatal Facial Coding Scale (NFCS) (Grunau & Craig 1987; Johnston et al 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; total score 0–10	preterm to 4 months; procedural pain
Children's Revised Impact of Event Scale (CRIES) (Krechel & Bildner 1995)	cries requires oxygen increased vital signs (heart rate/blood pressure) expression sleeplessness	each scored 3-point scale (0,1,2); total score 0–10	preterm and term neonates; postoperative pain

Further details available in Howard et al, 2008 and Bandstra & Chambers, 2008

Table 10.2 Composite scales for infants and children

Scale	Indicators	Score	Utility
Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (McGrath et al 1985)	cry facial expression verbal expression torso position touch leg position	each scored as 0, 1, 2 or 3; total score 4–18	1–7 years; postoperative pain procedural pain
Face Legs Activity Cry and Consolability (FLACC) (Merkel et al 1997)	face legs activity cry consolability	each scored on 3-point scale (0,1,2); total score 0–10	young children; postoperative pain
COMFORT scale (Ambuel et al 1992)	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 year olds (Van Dijk et al 2000)

Further details available in Howard et al, 2008 and Bandstra & Chambers, 2008.

Table 10.3 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 years
Faces Pain Scale - Revised (Hicks et al 2001)	6 line drawn faces	graded faces with neutral anchors (ie no smiling or tears)	> 4 years
Wong-Baker Faces Pain Rating Scale (Wong & Baker 1988)	6 cartoon faces	faces graded from smiling to tears	3–8 years; postoperative and procedural pain
Coloured Analogue Scale (McGrath et al, 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 years and above

Further details available in Howard et al, 2008 and Bandstra & Chambers, 2008.

10.4 Management of procedural pain

Procedure-related pain is a frequent and distressing component of medical care for children, their families and hospital staff (Cummings et al, 1996 **Level IV**; Ljungman et al, 1996 **Level IV**; Gale et al, 2004 **Level III-2**). Repeated interventions are often required and the level of pain and memory of the first procedure affect the pain (Weisman et al, 1998) and distress (Chen et al, 2000) associated with subsequent procedures.

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 non-pharmacological 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 et al, 2003). 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 the Association of Paediatric Anaesthetists (Howard et al, 2008), Royal Australasian College of Physicians (Royal Australasian College of Physicians, 2005) and the Italian Society of Neonatology (Lago et al, 2009).

10.4.1 Procedural pain in the neonate

Blood sampling and intravenous cannulation

Neonates in intensive care often require frequent blood sampling. Heel lance produced more pain than venipuncture (Shah & Ohlsson, 2007 **Level I**), but fewer attempts were required and less pain behaviour was exhibited with spring loaded automated devices for heel lance (Shah et al, 2003 **Level II**). Topical local anaesthesia reduced the physiological and behavioural response to venipuncture (Taddio et al, 1998 **Level I**). Sucrose (Stevens et al, 2004 **Level I**) and breastfeeding (Shah et al, 2006 **Level I**) reduced pain responses to venipuncture. The optimal dose of sucrose, its efficacy and the safety of repeated doses have not been determined. Background morphine infusions in ventilated neonates had limited efficacy for acute procedural interventions in intensive care (Bellu et al, 2008 **Level I**). IV morphine bolus with topical amethocaine provided more effective analgesia than morphine or amethocaine alone for peripheral central venous line placement in preterm neonates (Taddio et al, 2006 **Level II**).

Lumbar puncture

EMLA® (eutectic mixture of lignocaine and prilocaine) reduced the physiological and behavioural response with needle insertion for lumbar puncture in preterm and term neonates (Kaur et al, 2003 **Level II**).

Urine sampling

EMLA® reduced pain scores in neonates and young infants undergoing suprapubic aspiration (Nahum et al, 2007 **Level II**). Transurethral catheterisation after the urethral application of 2% lignocaine (lidocaine) was less painful than suprapubic aspiration after the topical application of EMLA® (Kozer et al, 2006 **Level II**). Sucrose reduced pain scores during transurethral catheterisation in neonates (Rogers et al, 2006 **Level III-2**).

Ocular examination for retinopathy of prematurity

Screening for retinopathy of prematurity in neonates is painful (Belda et al, 2004 **Level IV**). Topical local anaesthesia reduced pain scores (Marsh et al, 2005 **Level II**), and sucrose in addition to topical local anaesthetic had a greater effect (Gal et al, 2005 **Level II,** Mitchell et al, 2004 **Level II**).

10.4.2 Procedural pain in infants and older children

Venipuncture and intravenous cannulation

Venipuncture causes pain and significant distress in many children (Humphrey et al, 1992 **Level IV**). Topical local anaesthesia reduced pain associated with IV cannulation, but amethocaine was more effective than EMLA® and had more rapid onset (Lander et al, 2006 **Level I**). Lignocaine administered by iontophoresis (Zempsky et al, 2004 **Level II**) or liposomal lignocaine 4% cream (Eidelman, Weiss, Lau et al, 2005 **Level I**) had a more rapid onset and was as effective as EMLA® for venipuncture and IV cannulation. A needleless device that delivers 1% buffered lignocaine under high pressure from a compressed carbon dioxide gas cartridge was effective within 3 minutes, and produced more effective skin anaesthesia than EMLA® (Jimenez et al, 2006 **Level II**).

Vapocoolant sprays have variably been reported to be ineffective (Costello et al, 2006 **Level II**) or reduce pain (Farion et al, 2008 **Level II**) associated with IV cannulation, and to be as effective as topical amethocaine in children undergoing venipuncture (Davies & Molloy, 2006 **Level III-1**).

Nitrous oxide (N_2O) reduced pain and anxiety associated with IV cannulation (Henderson et al, 1990 **Level II**). Use of 70% N_2O in oxygen was more effective that 50% (Furuya et al, 2009 **Level II**). The combination of N_2O and topical EMLA® for IV cannulation was more effective in reducing

pain scores and increased satisfaction when compared with either method alone (Hee et al, 2003 **Level III-2**; Ekbom et al, 2005 **Level III-2**).

Non-pharmacological strategies such as distraction, hypnosis and combined cognitive-behavioural interventions reduced needle-related pain and distress in children and adolescents (Uman et al, 2006 **Level 1**). Positioning the child vertically and being held by a parent reduced distress in children during IV cannulation (Sparks et al, 2007 **Level II**). Combination of hypnosis with EMLA® reduced pain, anxiety and distress associated with venipuncture, and was more effective than either intervention alone (Liossi et al, 2009 **Level II**).

Lumbar puncture and bone marrow aspiration

Addition of fentanyl to propofol sedation improved analgesia (Nagel et al, 2008 **Level II**) and satisfaction (Cechvala et al, 2008 **Level II**) in children with leukaemia undergoing bone marrow aspirations and lumbar punctures. Oral transmucosal fentanyl reduced pain scores (Schechter et al, 1995 **Level IV**). Oral or IV ketamine was associated with less distress during lumbar puncture and /or bone marrow aspiration in children with cancer (Tobias et al, 1992 **Level III-3**; Evans et al, 2005 **Level IV**). For some patients, general anaesthesia is preferred to sedation, and has been associated with less distress and pain for children requiring multiple procedures (Crock et al, 2003 **Level III-3**) (see also 10.1.8). Topical anaesthesia with EMLA® was effective for lumbar puncture (Juarez Gimenez et al, 1996 **Level II**). Anticipatory and procedure-related anxiety and pain was reduced when hypnosis was combined with EMLA® (Liossi et al, 2006 **Level II**).

Urethral catheterisation and micturating cystourethrogram

Local anaesthetic lubricant reduced pain when administered 10 minutes (Gerard et al, 2003 **Level II**) but not 2 to 3 minutes (Vaughan et al, 2005 **Level II**) prior to urethral catheterisation.

N_2O reduced pain and distress in children undergoing urethral catheterisation for micturating cystourethrogram investigation (Zier et al, 2007 **Level III-2**). Preparing the child for the procedure using a story booklet or play preparation reduced distress (Phillips et al, 1998 **Level III-2**; Butler et al, 2005 **Level II**), as did hypnosis (Butler et al, 2005 **Level II**).

Chest drain removal

IV morphine, topical anaesthesia with EMLA®, and N_2O reduced pain but did not provide adequate analgesia for chest drain removal in children (Rosen et al, 2000 **Level III-2**; Bruce et al, 2006 **Level III-2**).

Nasogastric tube insertion

Nasogastric tube insertion causes pain and distress in children (Juhl & Conners, 2005 **Level IV**). In adults, topical anaesthesia of the nose and pharynx reduced pain associated with nasogastric tube insertion (Singer & Konia, 1999 **Level II**; Wolfe et al, 2000 **Level II**) and nebulised lignocaine after intranasal (IN) lignocaine gel was more effective than sprayed lignocaine (Spektor et al, 2000 **Level II**). In children aged 1 to 5 years a benefit of nebulised lignocaine could not be confirmed, but the study was terminated early due to the distress associated with nebulisation (Babl et al, 2009 **Level II**).

Burns dressings

Children who have sustained burn injuries often require repeated, painful and distressing dressing changes. Considerable interindividual variation occurs and analgesia needs to be titrated to effect as requirements differ according to the surface area involved, the location, and the child's previous experiences. It is important to consider that one-third will have post-traumatic stress disorder (Stoddard et al, 2006 **Level IV**).

Opioids are frequently required, and in the early phases general anaesthesia may be preferred. Oral transmucosal (Robert et al, 2003 **Level II**) or IN fentanyl (Borland et al, 2005

Level II), oral hydromorphone, morphine and oxycodone reduced pain associated with dressing changes (Sharar et al, 1998 **Level II**; Sharar et al, 2002 **Level II**).

Non-pharmacological strategies such as distraction, preparation, parental presence and hypnosis may be effective. Music (Fratianne et al, 2001 **Level II**), virtual reality games (Das et al, 2005 **Level II**) and massage therapy (Hernandez-Reif et al, 2001 **Level IV**) reduced self-reported pain scores associated with burn dressing changes.

10.4.3 Immunisation pain in infants and children

Procedure modifications, such as rapid injection and needle withdrawal (Ipp et al, 2007 **Level II**) and using a longer needle (Schechter et al, 2007 **Level I**) reduced pain associated with immunisations. Parental responses during injection such as excessive reassurance, criticism or apology increase distress, whereas humour and distraction tend to decrease distress (Schechter et al, 2007 **Level I**).

Oral sucrose in infants aged 2 to 4 months or breastfeeding in neonates reduced the duration of pain behaviour after but not during immunisation (Efe & Ozer, 2007 **Level II**; Hatfield, 2008 **Level II**). Combining sucrose, oral tactile stimulation and parental holding reduced the duration of crying in infants receiving multiple vaccinations (Reis et al, 2003 **Level II**). Combination of EMLA® and oral glucose reduced the behavioural and physiologic response to immunisation (Lindh et al, 2003 **Level II**).

Selective use of topical local anaesthetic has been recommended in older children (Schechter et al, 2007 **Level I**) and the combination of topical EMLA®, preparation, parental presence and distraction reduced pain scores during immunisation in 4 to 12 year old children (Boivin et al, 2008 **Level III-1**).

10.4.4 Procedural pain management in the emergency department

Laceration repair

Topical anaesthesia for wound closure can avoid the distress caused by intradermal injection of local anaesthetic, but cocaine-containing preparations are no longer recommended (Eidelman, Weiss, Enu et al, 2005). Topical anaesthetics, such as lignocaine-adrenaline-amethocaine solutions were safe and effective in children (Schilling et al, 1995 **Level II**; Smith et al, 1997 **Level II**; White et al, 2004 **Level III-1**), and had equivalent or superior efficacy when compared with intradermal administration (Eidelman, Weiss, Enu et al, 2005 **Level I**). Application of topical anaesthetic solution to wounds at triage reduced treatment time (31 minutes less than controls) (Priestley et al, 2003 **Level II**) and reduced pain associated with subsequent intradermal injection of lignocaine (Singer & Stark, 2000 **Level II**). Topical anaesthesia reduced the requirement for procedural sedation for wound management (Pierluisi & Terndrup, 1989 **Level III-3**).

Tissue adhesives (Farion et al, 2003 **Level I**) and hair apposition for scalp lacerations (Hock et al, 2002 **Level III-1**) were as effective as suturing for simple lacerations but produced less pain and may be more acceptable to children.

Inhaled 50% N_2O / 50% oxygen reduced pain and anxiety during laceration repair (Burton et al, 1998 **Level II**; Luhmann et al, 2001 **Level II**) in children.

Fracture pain and reduction

In order to provide analgesia rapidly, opioids are increasingly being administered at triage in children with suspected fractures. To avoid the distress associated with IV access or IM injections, alternative routes of opioid delivery have been investigated in the emergency department. IN diamorphine (Kendall et al, 2001 **Level III-1**) and fentanyl via IN (Borland et al,

2007 **Level II**), transmucosal (Mahar et al, 2007 **Level III-1**), and inhaled routes (Miner et al, 2007 **Level III-2**; Furyk et al, 2009 **Level III-2**) provided comparable analgesia to IM or IV morphine, with a similar side-effect profile. Oral oxycodone was more effective and produced less itching than codeine, but early administration at triage was required as having Xrays, rather than examination or casting, was identified as the most painful period (Charney et al, 2008 **Level II**).

Although no longer used as an anaesthetic, methoxyflurane is available as a self-administered 'Penthrox®' inhaler that dispenses 0.2 to 0.7% methoxyflurane (Medical Developments International, 2001). Use of the Penthrox® inhaler in children reduced pain associated with extremity injuries (Babl et al, 2006 **Level IV**) but did not provide adequate analgesia for subsequent fracture manipulation (Babl et al, 2007 **Level IV**). Side effects included hallucinations, vomiting, confusion and dizziness, and sedation/drowsiness was common (26%) in children (Babl et al, 2006 **Level IV**; Buntine et al, 2007).

Closed fracture reduction is a major procedure, which may be performed in emergency departments with a variety of analgesic techniques (Kennedy et al, 2004). IV regional block with local anaesthetic was safe and effective in 90% to 98% of cases (Murat et al, 2003 **Level I**), but complications may arise with faulty equipment, inappropriate use of local anaesthetic, or inadequate monitoring and training of staff. Inhalation of N_2O was as effective as IV regional anaesthesia using lignocaine (Gregory & Sullivan, 1996 **Level III-1**) and better than IM analgesia and sedation with pethidine (meperidine) and promethazine (Evans et al, 1995 **Level III-1**), although N_2O has recently been reported to have limited efficacy as a sole agent for fracture manipulation (Babl et al, 2008 **Level IV**). N_2O and a haematoma block with lignocaine produced similar analgesia but fewer side-effects and more rapid recovery than IV ketamine and midazolam (Luhmann et al, 2006 **Level III-1**). Ketamine-midazolam reduced distress during fracture manipulation and fewer paediatric patients required airway interventions than those receiving fentanyl-midazolam and propofol-fentanyl (Migita et al, 2006 **Level I**). As there is the potential for complications and a high incidence of side effects with sedative agents, particularly when given in combination (Cote et al, 2000; Cote, 2008) or in children with comorbidities (Morton, 2008), fully monitored general anaesthesia may be more appropriate than sedation or local anaesthesia in some clinical settings (Murat et al, 2003).

Additional paediatric guidelines for procedural sedation, as opposed to analgesia, have been produced by the American Academy of Pediatrics (Cote & Wilson, 2006) and the Scottish Intercollegiate Guidelines Network (Scottish Intercollegiate Guidelines Network, 2004).

Psychological interventions

In addition to pharmacological interventions, the planning of procedures for children in the emergency department should include age-appropriate psychological interventions, such as distraction techniques. Distraction reduced self-reported pain following needle-related procedural pain (Uman et al, 2006 **Level I**). Age-appropriate distraction techniques reduced situational anxiety in older children and lowered parental perception of distress in younger children undergoing laceration repair (Sinha et al, 2006 **Level II**).

Key messages

1. Sucrose reduces the behavioural response to heel-stick blood sampling in neonates (**U**) (**Level I** [Cochrane Review]).
2. Breastfeeding or breast milk reduces measures of distress in neonates undergoing a single painful procedure compared to positioning or no intervention (**U**) (**Level I** [Cochrane Review]).
3. Distraction, hypnosis, and combined cognitive-behavioural interventions reduce pain and distress associated with needle-related procedures in children and adolescents (**S**) (**Level I** [Cochrane Review]).
4. EMLA® is an effective topical anaesthetic for children, but amethocaine is superior for reducing needle insertion pain (**N**) (**Level I** [Cochrane Review]).
5. Topical local anaesthetic application, inhalation of nitrous oxide (50%) or the combination of both provides effective and safe analgesia for minor procedures (**U**) (**Level I**).
6. Combinations of hypnotic and analgesic agents are effective for procedures of moderate severity (**U**) (**Level II**).

The following tick box ☑ represents 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 drug combinations has been associated with major adverse outcomes during procedural analgesia and sedation (**U**).

10.5 Analgesic agents

10.5.1 Paracetamol

Paracetamol (acetaminophen) is effective for mild pain in children (Anderson, 2008), but the dose required for analgesia is greater than for an antipyretic effect (Anderson, 2004). It has similar efficacy to non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs), and may be a useful adjunct to other treatments for more severe pain. Supplemental opioid requirements were reduced after day case surgery by 40 mg/kg but not 20 mg/kg rectal paracetamol (Korpela et al, 1999 **Level II**) and after tonsillectomy by 40 mg/kg oral paracetamol (Anderson et al, 1996 **Level II**). Rectal paracetamol did not reduce morphine requirements in infants following major surgery (van der Marel et al, 2007 **Level II**).

Pharmacokinetics and pharmacodynamics

Paracetamol's bioavailability is dependent on the route of administration. Oral doses are subject to first pass hepatic metabolism of 10% to 40% and peak plasma concentrations are reached in 30 minutes (Arana et al, 2001). Rectal administration is associated with slower and more erratic absorption and loading doses of 30 to 40 mg/kg paracetamol may be required to achieve therapeutic plasma concentrations (Anderson et al, 1996 **Level II**; Howell & Patel, 2003 **Level II**). An IV formulation of paracetamol increased dosing accuracy with less pharmacokinetic variability attributable to absorption, but also had more rapid offset than a rectal preparation (Capici et al, 2008 **Level II**).

Dose regimens that target a steady state plasma concentration of 10 to 20 mg/L have been determined. There is some evidence for analgesic efficacy at this concentration in children (Anderson et al, 2001 **Level III-3**) but a relationship between plasma concentration and analgesia

has not been confirmed (Palmer et al, 2008 **Level III-3**). The volume of distribution of paracetamol decreases and clearance increases from 28 weeks postconceptional age resulting in a gradual fall in elimination half-life. Suggested maximum oral or rectal doses are: 25 mg/kg/day at 30 weeks postconceptional age; 45 mg/kg/day at 34 weeks postconceptional age; 60 mg/kg/day in term neonates and infants; and 90 mg/kg/day in children aged between 6 months and 12 years. These doses are suitable for acute administration for 2 to 3 days (Anderson et al, 2002 **Level III-3**). Following IV dosing in neonates aged 28 to 45 weeks postmentrual age, volume of distribution was similar to the adult value, suggesting higher IV doses may be tolerated in neonates (Palmer et al, 2008 **Level III-3**), but current recommended maximum doses of IV paracetamol are 30 mg/kg/day in neonates and infants, and 40 to 60 mg/kg/day in infants and children (Palmer et al, 2007; Howard et al, 2008).

Adverse effects

Paracetamol is metabolised in the liver, predominantly via glucuronidation and sulphation. Increased production of a reactive oxidative product N-acetyl-p-benzoquinoneimine 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 et al, 2008), but as overall clearance is reduced a lower dose is appropriate. Risk factors for paracetamol hepatoxicity may include fasting, vomiting, dehydration, systemic sepsis, pre-existing liver disease and prior paracetamol intake, however the situation remains unclear (Kaplowitz, 2004).

10.5.2 Non-selective non-steroidal anti-inflammatory drugs

NsNSAIDs are effective analgesic agents for mild to moderate pain. Although the product information states that safety in children less than 2 years is not established, nsNSAIDs have been studied and used in all age groups including infants (Eustace & O'Hare, 2007 **Level IV**). The choice between ibuprofen, diclofenac and ketorolac mainly depends on the available formulation and convenience of administration.

Clinical studies suggest similar efficacy of nsNSAIDs and paracetamol (Tay & Tan, 2002 **Level II**; Hiller et al, 2006 **Level II**; Riad & Moussa, 2007 **Level II**), as long as equieffective doses are being given. Combining nsNSAIDs and paracetamol has been shown to improve analgesia and/or decrease the need for additional analgesia after adenoidectomy (Viitanen et al, 2003 **Level II**), tonsillectomy (Pickering et al, 2002 **Level II**), inguinal surgery (Riad & Moussa, 2007 **Level II**), multiple dental extractions (Gazal & Mackie, 2007 **Level II**), and orthopaedic surgery (Hiller et al, 2006 **Level II**). As a component of multimodal analgesia, nsNSAIDs decrease opioid consumption (Antila et al, 2006 **Level II**; Rugyte & Kokki, 2007 **Level II**). A combination of individually titrated intraoperative opioids and regularly administered perioperative mild analgesics (NSAID and/or paracetamol) is recommended for management of pain following tonsillectomy (Hamunen & Kontinen, 2005 **Level I**).

Pharmacokinetics and pharmacodynamics

The elimination half-life of ketorolac (Lynn et al, 2007), ibuprofen (Kyllonen et al, 2005) and diclofenac (Litalien & Jacqz-Aigrain, 2001) is longest in neonates, with the value in toddlers approaching that of adults. Rectal bioavailability of diclofenac is high in children (van der Marel et al, 2004). Ibuprofen plasma concentrations of 10 to 25 mg/L have been suggested post paediatric inguinal hernia repair (Kokki et al, 2007). Target analgesic concentrations for other NSAIDs, developmental changes in pharmacodynamics, and the impact of different stereoisomer forms on the differential pharmacokinetics, efficacy and side-effect profile of NSAIDs (Kyllonen et al, 2005) require further evaluation (Anderson & Palmer, 2006).

Adverse effects

In large series of children with febrile illnesses, the risk of serious adverse events following short-term use of ibuprofen was low, and similar to that following the use of paracetamol (Lesko & Mitchell, 1995 **Level II**; Lesko & Mitchell, 1999 **Level II**). 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).

NsNSAIDs should be avoided in children with a sensitivity reaction to aspirin or other nsNSAIDs. A subset of children with moderate to severe asthma and nasal disease/polyps are susceptible to NSAID-exacerbated respiratory disease (Palmer, 2005). NsNSAIDs may be safe in children with mild asthma as single dose diclofenac had no significant effect on respiratory function tests (spirometry) in children with asthma (Short et al, 2000 **Level III-3**) and short-term use of ibuprofen did not increase outpatient visits for asthma (Lesko et al, 2002 **Level II**). The use of nsNSAIDs in children undergoing tonsillectomy remains controversial (see Section 4.2.2). In a meta-analysis that included only paediatric trials, an increased risk of bleeding requiring either non-surgical (OR 1.23; 95% CI 0.44 to 3.43) or surgical intervention (OR 1.46; 95% CI 0.49 to 4.0) after tonsillectomy could not be confirmed (Cardwell et al, 2005 **Level I**). Although neither represented a statistically significant increase, risk of bleeding requiring surgical intervention tended to be higher following high dose ketorolac 1mg/kg (OR 3.1; 95%CI 0.53 to 18.4) than other nsNSAIDS (OR 0.91; 95% CI 0.22 to 3.71) (Cardwell et al, 2005 **Level I**).

Note: reversal of conclusions

This partially reverses the Level 1 conclusion in the previous edition of this document; earlier meta-analyses had reported an increased risk of reoperation for post-tonsillectomy bleeding in studies that included adults and children.

In a small trial, ketorolac did not increase the risk of bleeding complications after congenital cardiac surgery (Gupta et al, 2004 **Level II**).

NsNSAIDs affect renal blood flow, glomerular filtration and renal drug clearance (Allegaert, Vanhole et al, 2005). Renal failure in association with nsNSAID use has occurred in neonates (Andreoli, 2004) and older children (Taber & Mueller, 2006), usually in the setting of other haemodynamic compromise.

NsNSAID use for analgesia has been restricted in infants less than 3 months of age. Neonatal bolus and short-term use for patent ductus arteriosus closure can produce pulmonary hypertension and alterations in cerebral (Naulaers et al, 2005), gastrointestinal and renal blood flow (Allegaert, Vanhole et al, 2005; Aranda & Thomas, 2006). Relative effects of indomethacin (indometacin) and ibuprofen on the risk of intraventricular haemorrhage continue to be debated (Aranda et al, 1997; Ment et al, 2004).

10.5.3 Coxibs

Coxibs (COX-2 specific inhibitors) have been used off-license in children. Celecoxib was as effective as naproxen in children with juvenile rheumatoid arthritis (Foeldvari et al, 2008 **Level II**). Small-scale efficacy studies evaluated different perioperative doses of rofecoxib (prior to its withdrawal from the market): low dose (0.625 mg/kg) was inferior to ibuprofen (in combination with paracetamol) (Pickering et al, 2002 **Level II**); 1 mg/kg was superior to placebo (Joshi et al, 2003 **Level II**; Sheeran et al, 2004 **Level II**), and multi-day postoperative dosing provided superior analgesia to paracetamol (Vallee et al, 2007 **Level III-3**) or hydrocodone combined with paracetamol (Bean-Lijewski et al, 2007 **Level II**). The degree of COX-2 selectivity, pharmacokinetic

profile, adverse effects and use of parenteral forms (eg parecoxib) of coxibs have not been adequately studied in children.

10.5.4 Opioids and tramadol

As there are significant developmental changes in the pharmacokinetic handling (Bouwmeester et al, 2004) and pharmacodynamic response to opioids (Nandi & Fitzgerald, 2005), doses must be adjusted according to age and individual response. Routine and regular assessment of pain severity, the analgesic response, and the incidence of side effects (particularly nausea and vomiting and sedation) is essential, with titration of opioid treatment according to individual needs. As with adult patients, appropriate dose regimens, guidelines for monitoring, documentation, management of side effects, and education of staff and carers are required (Wrona et al, 2007 **Level IV**) (see Section 4).

Morphine

The clearance of morphine is reduced and half-life prolonged in neonates and infants (Bouwmeester et al, 2004; Anand et al, 2008). Within age groups, individual variability in kinetics results in 2 to 3-fold differences in plasma concentration with the same rate of infusion (Lynn et al, 1998). In neonates, infants and children to 3 years, age was the most important factor affecting morphine requirements and plasma morphine concentrations (Bouwmeester, van den Anker et al, 2003 **Level II**), and in older children average patient-controlled morphine requirements also change with age (Hansen et al, 1996 **Level IV**).

The risk of respiratory depression is reduced when infusions are targeted to plasma morphine concentrations less than 20 ng/mL. However, no minimum effective concentration for analgesia has been determined (Kart, Christrup et al, 1997). No clear relationship between plasma concentration and analgesia has been identified due to variability in individual requirements, the clinical state of the child, the type of surgery, the assessment measure used and the small sample size in many studies (Bouwmeester, Hop et al, 2003 **Level II**; Anand et al, 2008 **Level II**). Analysis of 35 paediatric RCTs of morphine, administered via IV, epidural, IM and intrathecal routes, reported analgesic efficacy in comparison with inactive controls, but with significantly increased vomiting and sedation. The majority of studies analysed compared single perioperative doses and only one study evaluated a postoperative infusion of morphine (Duedahl & Hansen, 2007 **Level II**).

Fentanyl

Fentanyl is a potent mu-opioid agonist and highly lipophilic. Rapid redistribution contributes to offset of action, fentanyl is metabolised by CYP3A4 to inactive metabolites, and clearance is only 70-80% of adult levels in neonates but rapidly matures (Tibboel et al, 2005). Fentanyl has been administered by multiple routes for perioperative pain management in neonates (Simons & Anand, 2006) and children (Howard et al, 2008), including: IV infusion or PCA (Antila et al, 2006 **Level II**; Butkovic et al, 2007 **Level III-1**); intrathecal (Batra et al, 2008 **Level II**) injection; epidural infusion (Lerman et al, 2003 **Level II**) and patient-controlled epidural analgesia (PCEA) (Saudan et al, 2008 **Level III-3**). Prolonged IV infusion of fentanyl during neonatal intensive care has been associated with more rapid dose escalation than morphine, but both can produce opioid withdrawal symptoms following rapid cessation (Simons & Anand, 2006).

Due to its rapid onset and short duration of action, fentanyl can be used alone or in combination with sedatives, to control procedural pain (Tibboel et al, 2005), but opioid-related side effects, such as nausea and vomiting and respiratory complications may also be increased (Migita et al, 2006 **Level I**). Due to its high lipophilicity, fentanyl can also be administered via transmucosal, IN, and inhaled routes (Robert et al, 2003 **Level II**) (Borland et al, 2005 **Level II**). Transdermal fentanyl has approximately 30% of the IV bioavailability (Tibboel et al, 2005).

In children, the time to reach steady-state serum drug concentrations following transdermal application is longer, and the elimination half-life is shorter as clearance is enhanced, but there have been no randomised trials of efficacy (Zernikow et al, 2007).

Codeine

Codeine is a weak opioid and conversion to morphine (by CYP2D6) is required for analgesia. Intermediate or poor metabolisers — 46% of children undergoing tonsillectomy in a United Kingdom population (Williams et al, 2002) — may have reduced or minimal effect from codeine; while ultra metabolisers may attain high peak morphine levels and are at risk of sedation and respiratory depression (Kirchheiner et al, 2007 **Level III-3**; Voronov et al, 2007). Perceived advantages of codeine include less respiratory depression in neonates and reduced nausea and vomiting compared with morphine (Williams et al, 2002 **Level II**) but may relate to low levels of active metabolites and be associated with reduced efficacy (Williams et al, 2001).

Oral codeine has a similar time to peak effect but decreased total absorption compared with rectal and IM delivery (McEwan et al, 2000 **Level II**). IV administration should be avoided as severe hypotension may result (Shanahan et al, 1983 **Level IV**).

There are conflicting reports of efficacy for postoperative pain. Addition of codeine to paracetamol has been reported to improve analgesia (Pappas et al, 2003 **Level II**) or have no effect (Moir et al, 2000 **Level II**). Comparison of codeine and morphine for tonsillectomy has shown either no difference (Semple et al, 1999 **Level II**) or an increased requirement for rescue analgesia following codeine (Williams et al, 2002 **Level II**). Codeine was less effective than ibuprofen for acute musculoskeletal pain in children (Clark et al, 2007 **Level II**).

Oxycodone

Oxycodone is increasingly used in children, with efficacy shown in multiple settings: oral use in the emergency department for children with orthopaedic injuries (Charney et al, 2008 **Level II**; Koller et al, 2007 **Level II**); use of an oral controlled-release (CR) preparation as a step-down following PCA in adolescents after spinal fusion (Czarnecki et al, 2004 **Level IV**); IV bolus dose administration for postoperative rescue analgesia (Kokki, Laisalmi et al, 2006 **Level IV**); and IV PCA (in adolescents and adults) (Silvasti et al, 1999 **Level II**).

In infants over 6 months of age, the pharmacokinetic profile of oxycodone is similar to adults and dosing can be based on the weight of the child (El-Tahtawy et al, 2006). Similar absorption is seen following buccal and sublingual absorption (Kokki, Rasanen et al, 2006), but there is less interindividual variability following IV administration (Kokki et al, 2004). In neonates and infants, the half-life is prolonged and interindividual variability in kinetics is increased even following IV administration (Pokela et al, 2005).

Other opioids

A large number of opioid preparations have been utilised in children, but availability varies in different countries, and many have not been investigated in controlled trials. See Howard et al (Howard et al, 2008) for additional details. A review of paediatric and adult studies using hydromorphone found no clear advantage over other opioids in terms of analgesic efficacy or side-effect profile (Quigley, 2002 **Level I**). Several opioids are used as spinal analgesics in children, but the lack of comparative studies provide limited evidence for superiority of one agent (Williams & Howard, 2003 **Level IV**).

Tramadol

Evidence for the use of tramadol in paediatric acute pain is currently limited by studies of small sample size, difficulty determining comparative analgesic doses, and licensing only for 16 years and over. Dosing is the same in children as in adults (1 to 2 mg/kg 6 hourly), with some reporting use of a 2 to 3 mg/kg IV loading dose then infusion of 5 to 8 mg/kg/24hours

(Allegaert et al, 2008). A review of 20 studies (**Level II** to **Level III-3**) indicated efficacy following oral, rectal, and IV administration, but dose sparing and safety have not been demonstrated with spinal administration (Bozkurt, 2005). Many studies for post-tonsillectomy pain have low sensitivity (Hamunen & Kontinen, 2005) and tramadol has been variably reported to be more effective than low-dose paracetamol (Pendeville et al, 2000 **Level II**), have similar efficacy to morphine (Engelhardt et al, 2003 **Level II**), and be less effective than pure agonist opioids (Ozer et al, 2003 **Level II**; Ozalevli et al, 2005 **Level III-1**) or ketoprofen (Antila et al, 2006 **Level II**). Further controlled trials are required to determine the role and optimum dose of tramadol in children.

The side effects of tramadol are similar to opioids, with similar or reduced rates of nausea and vomiting (10% to 40%), sedation and fatigue, but less constipation and pruritus and no reports of respiratory depression in children (Bozkurt, 2005).

Pharmacokinetics

Oral administration is subject to extensive first-pass hepatic metabolism. Rectal bioavailability is good with low interindividual variability (Zwaveling et al, 2004). Maximum plasma concentrations post IV, oral and rectal dosing are achieved between 0.3 and 2.4 hours postadministration (Bozkurt, 2005). Analgesic efficacy is associated with a plasma concentration of tramadol of 100 ng/mL in adults and children and O-desmethyl tramadol (M1) of 15 ng/mL (Garrido et al, 2006).

The primary metabolite is 0-desmethyl tramadol (M1), formed by the enzyme CYP2D6. In addition to inter-individual variability in functional allele expression (resulting in poor, normal, extensive or ultra metabolisers), there are age-related changes in maturation of CYP2D6 (Allegaert, Van den Anker et al, 2005; Allegaert et al, 2008). Tramadol clearance is linked to weight and postmenstrual age (PMA): increasing rapidly from 25 weeks PMA to 80% of the adult value by 45 weeks PMA (Garrido et al, 2006; Allegaert et al, 2008).

10.5.5 Corticosteroids

Dexamethasone reduced vomiting and resulted in an earlier return to soft diet following tonsillectomy (Steward et al, 2003 **Level I**). A single dose of intraoperative dexamethasone (0.4 to 1 mg/kg; maximum 8 to 50 mg) reduced pain (by 1 on VAS scale 0 to 10 cm) on the first postoperative day (Afman et al, 2006 **Level I**). A reduction in postoperative analgesic requirements following tonsillectomy, and a dose-dependent reduction in postoperative nausea and vomiting following dexamethasone 0.05 mg/kg, 0.15 mg/kg or 0.5 mg/kg (maximum 20 mg) has recently been confirmed. However, the study was terminated after randomisation of 215 children as dexamethasone, but not postoperative use of ibuprofen, was associated with an increased risk of bleeding, which was highest after the largest dose (RR 6.8; 95% CI 1.8 to 16.5) (Czarnetzki et al, 2008 **Level II**).

10.5.6 Other pharmacological therapies

Acute otitis media is common in children. Analysis of four RCTs investigating topical local anaesthetic drops for pain associated with acute otitis media, found insufficient evidence to evaluate efficacy or adverse effects (Foxlee et al, 2006 **Level I**). Administration of lignocaine 2% as ear drops reduced pain at 10, but not 20 or 30 minutes (Bolt et al, 2008 **Level II**).

In children with acute migraine, ibuprofen and sumatriptan reduced headache (NNT 2.4 and 7.4 respectively) or completely relieved pain (NNT 4.9 and 6.9 respectively) (Silver et al, 2008 **Level I**). Paracetamol, zolmitriptan, rizatriptan and dihydroergotamine were not significantly better than placebo, but the number of RCTs in children was small.

Key messages

1. Non-selective NSAIDs do not increase the risk of reoperation for bleeding after tonsillectomy in paediatric patients (**R**) (**Level I** [Cochrane Review]).
2. Dexamethasone reduces post-tonsillectomy pain and postoperative nausea and vomiting (**N**) (**Level I**) but high doses may increase the risk of bleeding (**N**) (**Level II**).
3. Paracetamol and non-selective NSAIDs are effective for moderately severe pain and decrease opioid requirements after major surgery (**U**) (**Level II**).
4. The efficacy of oral codeine in children is variable, individual differences in the ability to generate active metabolites may reduce efficacy (**U**) (**Level II**) or increase side effects (**N**) (**Level IV**).

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**).

☑ Aspirin should be avoided in children, but serious adverse events after non-selective NSAIDs are rare in children over 6 months of age (**U**).

10.6 Opioid infusions and PCA

10.6.1 Opioid infusions

The safety and efficacy of IV opioid infusion for the management of acute postoperative pain are well established for children of all ages (van Dijk et al, 2002 **Level II**). Further procedure-specific evidence and dose recommendations are available (Howard et al, 2008). As intermittent IM injections are distressing for children, the IV route is preferred, but if peripheral perfusion is normal, the SC route can be used for continuous infusion (McNicol, 1993 **Level IV**) or for PCA, with similar safety and efficacy to the IV route (Doyle, Morton et al, 1994 **Level II**).

Differences between intermittent bolus doses and continuous infusions of opioid relate more to the total dose given than to the method of administration (Lynn et al, 2000 **Level III-2**). Comparison of the same total dose of morphine given via infusion (10 mcg/kg/hr) or bolus (30 mcg/kg every 3 hours) found no difference in pain scores (COMFORT scale and observer VAS) (van Dijk et al, 2002 **Level II**) or stress response to surgery (Bouwmeester et al, 2001 **Level II**) in neonates and young infants. However, these doses were inadequate in older children (1 to 3 years of age) who required additional bolus doses and the 3-hourly interval was less effective (possibly due to more rapid clearance) (van Dijk et al, 2002 **Level II**).

In ventilated preterm neonates, opioid infusions have limited efficacy for control of acute procedural pain (Bellu et al, 2008 **Level I**). Initial associations between routine morphine infusion and improved neurological outcome were not confirmed in a subsequent large multicentre study (Anand et al, 2004 **Level II**). A subsequent meta-analysis found no statistically significant differences in mortality, duration of ventilation, or improvements in short or long-term neurological outcomes with routine use of opioid infusions in ventilated neonates (Bellu et al, 2008 **Level I**). Prolonged sedation may have detrimental effects in preterm neonates (Anand et al, 1999 **Level II**), but no association with poor 5-year neurological outcome has also been reported (Roze et al, 2008 **Level II**), as studies vary in the degree and manner of correction for confounding factors.

10.6.2 Patient-controlled analgesia

PCA can provide safe and effective analgesia for children as young as 5 years old. Patient selection depends on the ability of the child and carers to understand the concepts of PCA and the availability of suitable equipment and trained staff. Recognition of potential complications of PCA use was enhanced by providing set instructions for monitoring, and by acute pain service (APS) support (Wrona et al, 2007 **Level III-2**).

Efficacy

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 side effects has varied, depending on the PCA dosing parameters (Bray et al, 1996 **Level III-2**; Peters et al, 1999 **Level II**).

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 non-sickle children (Crawford, Galton et al, 2006 **Level III-3**). Intraoperative remifentanil was associated with an increase in PCA morphine requirement in the 24 hours following scoliosis surgery (Crawford, Hickey et al, 2006 **Level II**), possibly due to acute opioid-induced hyperalgesia.

The PCA prescription

Morphine is the drug used most frequently in PCA. A bolus dose of morphine 20 mcg/kg is a suitable starting dose and improved pain scores during movement when compared with 10 mcg/kg (Doyle, Mottart et al, 1994 **Level II**). The addition of a background infusion is more common in children than adults, and 4 mcg/kg/hour is often recommended as doses of 10 mcg/kg/hour and above increased side effects (Howard et al, 2008). 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 degree of surgery (Kelly et al, 2006 **Level IV**).

Fentanyl is a useful alternative opioid, particularly for patients with renal impairment or those experiencing morphine-related side effects (Tobias & Baker, 1992 **Level IV**). Fentanyl PCA has been used safely and effectively following neurosurgery (Chiaretti et al, 2008 **Level IV**), thoracic surgery (Butkovic et al, 2007 **Level III-1**) and tonsillectomy (Antila et al, 2006 **Level II**), and for acute cancer-related pain (Ruggiero et al, 2007 **Level IV**). In comparison with morphine, tramadol PCA provided minor improvements in time to extubation post cardiac surgery (Chu et al, 2006 **Level II**) and reduced nausea post-tonsillectomy but at the cost of higher pain scores (Ozalevli et al, 2005 **Level II**). Pethidine does not have any advantage over other opioids and neurotoxicity from norpethidine (normeperidine) accumulation has been reported in a healthy adolescent (Kussman & Sethna, 1998).

Nausea and vomiting occurs in 30% to 45% of children using morphine PCA and can be reduced by prophylactic antiemetics (Carr et al, 2009 **Level I**). Adding antiemetics directly to PCA solutions for children was not effective (Munro et al, 2002 **Level II**). Addition of a low-dose naloxone infusion did not impair analgesia, but decreased pruritus and nausea in postoperative children treated with PCA (Maxwell et al, 2005 **Level II**) and also decreased pruritus in children requiring morphine infusions during a sickle cell crisis (Koch et al, 2008 **Level IV**).

10.6.3 Nurse-controlled analgesia

In younger children and infants, 'PCA' pumps have been used for nurses to administer intermittent bolus doses with or without a background infusion (ie nurse-controlled analgesia or NCA). This technique may increase ease of administration particularly prior to movement or

procedural interventions, increase dose flexibility, and improve parent and nurse satisfaction – see Howard et al (Howard et al, 2008) for dose recommendations. The incidence of adverse events was similar (24 or 22%) in children self-administering conventional PCA and those receiving NCA (administered by nurses or physicians). Rescue events (requiring naloxone, airway management or admission to high dependency unit or ICU) were more common in the NCA group, but this group was also younger and had a higher prevalence of comorbidities. Cognitive impairment and high opioid dose requirements on day 1 were associated with increased adverse events (Voepel-Lewis et al, 2008 **Level III-2**).

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 et al, 1993 **Level III-2**).

Administration by a nurse trained in pain assessment, rather than parents, is recommended in most centres (Howard, 2003). 'PCA by proxy' has also been used to describe administration by nurses and/or parents. In a prospective series of PCA by proxy (parents or health care providers), effective analgesia was achieved in 81% to 95% of children under 6 years of age, 25% required supplemental oxygen, and 4% required naloxone for respiratory depression (Monitto et al, 2000 **Level IV**). In a retrospective series, PCA by proxy resulted in low pain scores in children with developmental delay, and somnolence or respiratory depression requiring naloxone occurred in 2.8% of patients (Czarnecki et al, 2008 **Level IV**). PCA by proxy in children with cancer pain was associated with comparable complication rates as conventional PCA in this specific patient group (Anghelescu et al, 2005 **Level III-3**).

Key messages

1. Routine morphine infusion does not improve neurological outcome in ventilated preterm neonates (**N**) (**Level I** [Cochrane Review]).
2. Postoperative intravenous opioid requirements vary with age in neonates, infants and children (**N**) (**Level II**).
3. 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 (**U**) (**Level II**).
4. Intermittent intramuscular injections are distressing for children and are less effective for pain control than intravenous infusions (**U**) (**Level III-1**).

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

☑ Intravenous opioids can be used safely and effectively in children of all ages (**U**).

☑ 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**).

10.7 Regional analgesia

10.7.1 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 et al, 1996 **Level IV**). As placebos are rarely used in children, many current studies compare two active treatments. 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).

The use of ultrasound guidance has been has been shown to improve the accuracy, success rate and quality of blockade as well as reduce the volume of local anaesthetic required (Willschke et al, 2005 **Level IV**; Weintraud et al, 2008 **Level IV**). The efficacy of different local anaesthetic techniques has been compared for common paediatric surgical conditions. Additional procedure-specific data are available (Howard et al, 2008).

The use of peripheral nerve catheters and plexus techniques in children has increased (Ganesh et al, 2007; **Level IV** Rochette et al, 2007 **Level IV**). Descriptive studies of the efficacy and safety of continuous peripheral nerve block infusions in children are encouraging (Fisher et al, 2006 **Level IV**) but further controlled comparisons with other analgesic techniques are required.

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 et al, 2001 **Level IV**), and psoas compartment block may be a useful alternative to neuraxial techniques for unilateral hip and lower limb surgery (Dadure et al, 2004 **Level IV**; Schuepfer & Johr, 2005 **Level IV**). For children undergoing major foot and ankle surgery, continuous popliteal nerve block with 0.2% ropivacaine produced comparable analgesia but fewer adverse events (postoperative nausea and vomiting [PONV], early discontinuation) than continuous epidural infusion (Dadure et al, 2006 **Level II**).

Axillary brachial plexus blocks provided satisfactory analgesia for hand and forearm surgery in 75% to 94% of cases (Fisher et al, 1999 **Level IV**). The use of ultrasound guidance has led to new approaches to plexus anaesthesia in children (Fleischmann et al, 2003 **Level III-1**; Ponde, 2008 **Level IV**) with improved success rates (De Jose Maria et al, 2008 **Level III-1**).

Continuous paravertebral extrapleural infusions provided effective analgesia in infants following thoracotomy (Fisher et al, 1999 **Level IV**). Single-shot paravertebral injection provided effective analgesia after renal surgery (Berta et al, 2008 **Level IV**) and inguinal hernia repair (Naja et al, 2005 **Level I**V).

Specific procedures

Circumcision

A dorsal penile nerve block provided similar analgesia to a caudal block (Cyna & Middleton, 2008 **Level I**) and a longer duration of effect than application of a topical local anaesthetic cream, EMLA® (Choi et al, 2003 **Level II**). Caudal analgesia reduced the need for early rescue analgesia when compared with parenteral analgesia (Allan et al, 2003 **Level I**).

Policy statements from the Royal Australasian College of Physicians (Royal Australasian College of Physicians, 2004) and British Association of Paediatric Urologists (BAPU, 2007) emphasise the need for adequate analgesia for neonatal circumcision. 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 et al, 2004 **Level I**).

Inguinal surgery

Similar analgesic efficacy following inguinal hernia repair has been found with wound infiltration, ilioinguinal / iliohypogastric nerve block or caudal analgesia (Splinter et al, 1995 **Level II**; Machotta et al, 2003 **Level II**). Ilioinguinal block is inherently safe, but ultrasound guidance may improve safety and efficacy (Willschke et al, 2005 **Level II**; Weintraud et al, 2008 **Level IV**). In a small study following umbilical surgery, rectus sheath block offered no benefits

compared with infiltration of local anaesthetic (Isaac et al, 2006 **Level II**). Addition of clonidine to bupivacaine for ilioinguinal block did not improve duration or quality of analgesia (Kaabachi et al, 2005 **Level II**).

Tonsillectomy

Local anaesthetic by topical application or infiltration produced moderate reductions in pain (mean reduction 7 to 19 mm on 0 to 100 mm VAS) following tonsillectomy (Grainger & Saravanappa, 2008 **Level I**). Peritonsillar infiltration of ketamine 0.5 mg/kg reduced pain following tonsillectomy (Honarmand et al, 2008 **Level II**) but was no more effective than the same dose given systemically (Dal et al, 2007 **Level II**).

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) reduced pain following neurosurgery (Pardey et al, 2008 **Level IV**).

Greater auricular nerve block provided similar analgesia with reduced PONV compared with morphine following mastoidectomy (Suresh et al, 2004 **Level II**). Combined with a lesser occipital nerve block, it was also effective following otoplasty (Pardey et al, 2008 **Level II**). Infraorbital nerve block was superior to IV fentanyl following cleft lip repair (Rajamani et al, 2007 **Level II**). Compared with intraoperative opioids, peribulbar and subtenon blocks reduced intraoperative oculocardiac reflexes and PONV following strabismus surgery, but effects on postoperative analgesic requirements were variable (Chhabra et al, 2005 **Level III-1**; Steib et al, 2005 **Level II**; Gupta et al, 2007 **Level II**); and relative risks of the procedures have not been fully evaluated. Following cataract surgery, fewer children required rescue analgesia when subtenon block was compared with intravenous fentanyl (Ghai et al, 2009 **Level II**).

Local anaesthetic infiltration reduced pain following dental extractions (Anand et al, 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 et al, 2008 **Level II**).

10.7.2 Central neural blockade

The use of regional analgesia in children is well established but patient selection, technique, choice of drugs, availability of experienced staff for performing blocks, APS resources and adequacy of follow-up vary in different centres (Williams & Howard, 2003).

Caudal analgesia

Single-shot caudal analgesia is one of the most widely used regional techniques in children, and provides intra- and postoperative analgesia for surgery on the lower abdomen, perineum and lower limbs (Howard et al, 2008). Large series have reported a high success rate (particularly in children under 7 years of age), and a low incidence of serious complications (Giaufre et al, 1996 **Level IV**; Royal College of Anaesthetists, 2009 **Level IV**).

Caudal bupivacaine, levobupivacaine and ropivacaine, produced similar times to onset of block and quality of postoperative analgesia (Breschan et al, 2005 **Level II**; Ivani et al, 2005 **Level II**; Frawley et al, 2006 **Level II**; Ingelmo et al, 2006 **Level II**). Concentration-dependent differences have been noted; ropivacaine 0.175% was superior to lower concentrations, and was as effective as a 0.2% solution but produced less motor block (Khalil et al, 2006 **Level II**). Addition of adrenaline to bupivacaine has minimal effect on the duration of analgesia, particularly in older children (Ansermino et al, 2003 **Level I**).

Opioid and non-opioid adjuvants have been added to caudal local anaesthetic with the aim of improving the efficacy or duration of analgesia. Addition of morphine to caudal local anaesthetic prolonged analgesia, but dose-related side effects were relatively common (Bozkurt et al, 1997 **Level IV**; Cesur et al, 2007 **Level II**). Clinically significant respiratory depression has been reported, particularly with higher doses and in younger patients (de Beer & Thomas, 2003). Side effects are potentially less with lipid soluble opioids, but while fentanyl may prolong caudal analgesia slightly (Constant et al, 1998 **Level II**), others have shown no benefit (Kawaraguchi et al, 2006 **Level II**). Supplementing general anaesthesia with caudal blockade (bupivacaine with morphine) reduced time to extubation and the period of mechanical ventilation following cardiac surgery, but there was no difference in hospital stay or pain relief (Leyvi et al, 2005 **Level III-2**).

Addition of clonidine (1 to 2 mcg/kg) to caudal local anaesthetic prolonged analgesia (Ansermino et al, 2003 **Level I**). Effects on analgesic efficacy could not be assessed by meta-analysis due to variability in study design and outcome measures. Clinically important sedation occurred with higher doses (5 mcg/kg) (Ansermino et al, 2003 **Level I**). Clonidine 1 mcg/kg with ropivacaine 0.2% has been shown to have a longer duration than either ketamine 0.5% with ropivacaine or plain ropivacaine (Akbas et al, 2005 **Level II**).

Preservative-free ketamine 0.25 to 0.5 mg/kg prolonged analgesia without significant side effects, but higher doses (1 mg/kg) increased behavioural side effects (Ansermino et al, 2003 **Level I**). Levobupivacaine 0.175% with ketamine 0.5 mg/kg appears more effective than levobupivacaine 0.2% alone (Locatelli et al, 2008 **Level II**). Other adjuncts such as neostigmine and midazolam, while extending block duration offered little if any advantage over clonidine or preservative-free ketamine (Kumar et al, 2005 **Level II**). In addition, neostigmine was associated with a high incidence of dose-related vomiting when used as an adjunct (Batra et al, 2003 **Level II**).

The neurotoxicity of non-opioid spinal additives has not been systematically evaluated in neonates and children (Howard et al, 2008).

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 ultrasound, nerve stimulation and ECG guidance (Tsui & Finucane, 2002 **Level IV**; Tsui, 2004 **Level IV**; Willschke et al, 2006 **Level IV**). 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 appropriate size equipment (Giaufre et al, 1996 **Level IV**; Llewellyn & Moriarty, 2007 **Level IV**).

Continuous epidural infusions of bupivacaine are effective and safe in children (Llewellyn & Moriarty, 2007 **Level IV**) and can provide similar levels of analgesia to systemic opioids (Wolf & Hughes, 1993 **Level II**). In children 7 to 12 years of age, PCEA provided analgesia similar to a continuous infusion. Total local anaesthetic dose was reduced with PCEA but no differences in side effects were detected (Antok et al, 2003 **Level III-1**). 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 to 48 hours in neonates (Larsson et al, 1997 **Level IV**). Postnatal age and weight influence the pharmacokinetic profile of levobupivacaine, with slower absorption and clearance in neonates and infants (Chalkiadis & Anderson, 2006 **Level IV**). Although plasma concentrations increased, they remained low after 24 hours of epidural levobupivacaine infusion in children aged over 6 months (Lerman et al, 2003 **Level II**). Epidural

infusions of ropivacaine were effective and safe in neonates (Bosenberg et al, 2005 **Level IV**) and children (Berde et al, 2008 **Level IV**) with minimal drug accumulation.

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 et al, 2004 **Level II**). Epidural fentanyl alone was less effective than both levobupivacaine alone and a combination of local anaesthetic and fentanyl (Lerman et al, 2003 **Level II**). Bolus doses of epidural morphine were less effective than epidural infusions of fentanyl and local anaesthetic (Kart, Walther-Larsen et al, 1997 **Level II**; Reinoso-Barbero et al, 2002 **Level II**). Ketoprofen improved analgesia when given in conjunction with epidural sufentanil (Kokki et al, 1999 **Level II**).

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. Both improvements in analgesia (Lovstad & Stoen, 2001 **Level II**) and no change (Lerman et al, 2003 **Level II**) have been shown with addition of fentanyl to local anaesthetic infusions. Addition of fentanyl to bupivacaine or bupivacaine plus clonidine epidural infusions provided similar analgesia but increased side effects (Cucchiaro et al, 2006 **Level II**). Addition of morphine to an epidural local anaesthetic infusion was more effective than clonidine (Cucchiaro et al, 2003 **Level II**), but higher doses of clonidine improved analgesia when added to epidural ropivacaine infusions (De Negri et al, 2001 **Level II**).

Outcomes

Perioperative regional analgesia modifies the stress response to surgery in children (Wolf et al, 1998 **Level II**; Humphreys et al, 2005 **Level II**). 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 side effects or toxicity must be balanced against any potential benefit (Wolf et al, 1998 **Level II**). 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 et al, 2006 **Level II**).

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 & Hughes, 1993 **Level II**). Case series report improvements in respiratory function and/or a reduced need for mechanical ventilation with regional analgesia techniques (McNeely et al, 1997 **Level IV**; Hodgson et al, 2000 **Level IV**; Aspirot et al, 2008 **Level IV**; Raghavan & Montgomerie, 2008 **Level IV**). A meta-analysis of spinal versus 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 et al, 2003 **Level I**).

Epidural rather than systemic analgesia reduced hospital stay following fundoplication (McNeely et al, 1997 **Level IV**) and ligation of patent ductus arteriosus in infants (Lin et al, 1999 **Level IV**).

Complications

Accidental intravascular injection remains the most life-threatening complication of caudal and epidural analgesia. As the sacrum is largely cartilaginous during infancy and early childhood, there is an increased risk of injecting local anaesthetic into the highly vascular medullary space of the sacrum (Veyckemans et al, 1992 **Level IV**). Sevoflurane attenuated cardiovascular (CV) responses to adrenaline 0.5 mcg/kg less than halothane, and may be a better agent to facilitate detection (Kozek-Langenecker et al, 2000 **Level III-2**). 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 et al, 2008).

Lipid emulsion infusion has been shown to be of value in managing acute CV toxicity due to accidental intravascular injection of local anaesthetics (Ludot et al, 2008) and is recommended as an early intervention. See Section 5.1.

Neurological damage attributable to paediatric regional analgesia is rare, and the benefit of ensuring a cooperative and immobile infant or child may outweigh the risk of performing regional anaesthesia under general anaesthesia in children (Bernards et al, 2008). Prolonged blockade and immobility may result in nerve compression accompanied by neurological deficit or neuropathic pain (Symons & Palmer, 2008). A retrospective review of 24 005 cases of regional block revealed five serious adverse outcomes, including three deaths, associated with difficult epidural insertions in young infants (Flandin-Blety & Barrier, 1995 **Level IV**). A prospective study including 15 013 central blocks (predominantly caudal blocks) reported 1.5 minor complications per 1000 (Giaufre et al, 1996 **Level IV**). An audit of 10 633 paediatric epidurals performed in the United Kingdom and Ireland reported five serious incidents: two epidural abscesses, and one each of meningism, severe postdural puncture headache requiring autologous blood patch, and a drug volume error resulting in cauda equina syndrome (which was the only case associated with residual symptoms at 12 months). Peripheral or nerve root damage was reported in six cases: three resolved spontaneously, two required chronic pain referral and gabapentin but resolved by 12 months, and one had residual symptoms at 1 year. Compartment syndrome was reported in four children, but symptoms were not masked by the epidural infusion (Llewellyn & Moriarty, 2007 **Level IV**).

Bacterial colonisation of catheters is more commonly associated with caudal than lumbar catheters (Kost-Byerly et al, 1998 **Level IV**), but epidural space infection is rare in the absence of prolonged or repeated insertion or immunodeficiency syndromes (Strafford et al, 1995 **Level IV**).

Intrathecal opioids

Following cardiac surgery, intrathecal 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 et al, 2004 **Level II**). Addition of intrathecal tetracaine and morphine to IV remifentanil decreased pain scores and analgesic requirements after early extubation (Hammer et al, 2005 **Level II**).

In infants undergoing lower abdominal and urological surgery, addition of fentanyl 1 mcg/kg (but not lower doses) to intrathecal local anaesthetic prolonged the duration of analgesia and reduced supplemental analgesic requirements (Batra et al, 2008 **Level II**).

Spinal fusion

Low-dose intrathecal opioids given preoperatively, reduced blood loss and provided good analgesia in the immediate perioperative period (Eschertzhuber et al, 2008 **Level II**). Epidural infusion of local anaesthetic and opioid via a catheter placed prior to wound closure provided comparable (Cassady et al, 2000 **Level II**; O'Hara et al, 2004 **Level II**) or improved analgesia (Sucato et al, 2005 **Level IV**) compared with morphine PCA. Dual catheter techniques improved dermatomal spread and may be more effective (Ekatodramis et al, 2002 **Level IV**), improving analgesia at rest and on movement (Blumenthal et al, 2005 **Level II**; Blumenthal et al, 2006 **Level II**). PCEA was effective with a high level of patient satisfaction in selected cases (Saudan et al, 2008 **Level IV**).

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 (**U**) (**Level I** [Cochrane Review]).
3. Clonidine prolongs analgesia when added to caudal local anaesthetic blocks (**U**) (**Level I**) and improves analgesia when added to epidural local anaesthetic infusions (**U**) (**Level II**).
4. Wound infiltration, peripheral nerve blocks, and caudal local anaesthetic provide effective analgesia after day-case inguinal surgery (**U**) (**Level II**).
5. Epidural infusions of local anaesthetic and systemic opioids provide similar levels of analgesia (**U**) (**Level II**).
6. Epidural opioids alone are less effective than local anaesthetic or combinations of local anaesthetic and opioid (**U**) (**Level II**).
7. Intrathecal opioids provide prolonged analgesia after surgery (**N**) (**Level II**) and reduce blood loss during spinal fusion (**N**) (**Level II**).

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

☑ Caudal local anaesthetic blocks provide effective analgesia for lower abdominal, perineal and lower limb surgery and have a low incidence of serious complications (**U**).

☑ Continuous epidural infusions provide effective postoperative analgesia in children of all ages and are safe if appropriate doses and equipment are used by experienced practitioners, with adequate monitoring and management of complications (**U**).

10.8 Acute pain in children with cancer

Pain is a common symptom in children with cancer and is associated with significant fear and distress (Ljungman et al, 1999 **Level IV**). Compared with adults, the pattern and sources of acute pain differ significantly in children with cancer.

10.8.1 Cancer-related pain

Pain due to tumour is present at diagnosis in the majority of children (Miser et al, 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 et al, 2007 **Level IV**). Pain and opioid requirements may escalate in terminal stages of cancer, and benefit has been reported with use of PCA opioids to allow rapid dose titration (Schiessl et al, 2008 **Level IV**) and with addition of ketamine (Finkel et al, 2007 **Level IV**).

10.8.2 Procedure-related pain

Children, their parents, and physicians and nurses all rate pain due to procedural interventions and treatment as a significant source of pain (Ljungman et al, 1996; Ljungman et al, 1999). Multiple diagnostic and therapeutic interventions (eg lumbar punctures, bone marrow aspirations, blood samples) are required during the course of treatment and require analgesia matched to the type of procedure and needs of the child (see Section 10.4). EMLA® was evaluated as superior to placebo for pain relief during central venous port access in children

with cancer (Miser et al, 1994 **Level II**). Outcomes for second and subsequent procedures were improved if adequate analgesia was provided for the first procedure (Weisman et al, 1998 **Level III-2**).

10.8.3 Treatment-related pain

Pain related to side effects of chemotherapy and radiotherapy is a source of high distress to children with cancer (Collins et al, 2000 **Level IV**; Ljungman et al, 2000 **Level IV**). Mucositis is a common side effect of many chemotherapeutic regimens (Cella et al, 2003), can be difficult to assess (Tomlinson et al, 2008), and is a frequent indication for IV opioid therapy.

Opioid requirements are often high and escalate with the severity of mucositis (Dunbar et al, 1995 **Level IV**; Coda et al, 1997 **Level II**). In patients aged 12 to 18 years, morphine by PCA or continuous infusion provided similar analgesia, but morphine intake and opioid-related side effects were lower in the PCA group (Mackie et al, 1991 **Level II**). A systematic review (which included this study and additional adult studies) found no difference in pain control between PCA and continuous infusion, but reduced hourly opioid requirement and shorter duration of pain with PCA (Clarkson et al, 2007 **Level I**).

PCA morphine and hydromorphone had similar efficacy (Collins et al, 1996 **Level II**) but sufentanil was less effective (Coda et al, 1997 **Level II**). Prolonged administration is often required (6 to 74 days) (Dunbar et al, 1995 **Level IV**). If excessive or dose-limiting side 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 et al, 2004 **Level IV**). 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. 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 & Ljungman, 2003 **Level IV**). In children with cancer, supplemental IV opioid boluses (either nurse-administered or via PCA) were safely combined with epidural bupivacaine and fentanyl infusion to control postoperative pain. One of 117 patients developed respiratory depression (due to a drug-dose error), but patients were closely monitored and had pre-existing tolerance to opioids (Anghelescu et al, 2008 **Level IV**).

For management of acute cancer pain in general see Section 9.7; for the management of acute mucositis pain see Section 9.6.7.

Key messages

1. PCA and continuous opioid infusions are equally effective in the treatment of pain in mucositis, but opioid consumption is less with PCA (**U**) (**Level I**).
2. PCA morphine and hydromorphone are equally effective for the control of pain associated with oral mucositis (**U**) (**Level II**).

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11. OTHER SPECIFIC PATIENT GROUPS

11.1 THE PREGNANT PATIENT

11.1.1 Management of acute pain during pregnancy

Pregnant women with pain that is severe enough to warrant drug treatment (self-administered or prescribed by attendants) represent a problematic cohort in that drugs given to them almost always cross the placenta. While most drugs are safe there are particular times of concern, notably the period of organogenesis (weeks 4 to 10) and just before delivery. Where possible, non-pharmacological treatment options should be considered before analgesic medications are used and ongoing analgesic use requires close liaison between the obstetrician and the medical practitioner managing the pain.

Drugs used in pregnancy

Drugs that might be prescribed during pregnancy have been categorised according to foetal risk by the Australian Drug Evaluation Committee (ADEC). The categories used are listed in Table 11.1 and the classification of some of the drugs that might be used in pain management is summarised in Table 11.2. A list of these drugs, including regular updates is available from the Therapeutic Goods Administration (TGA, 1999).

Paracetamol

Paracetamol is regarded as the analgesic of choice during pregnancy (Niederhoff & Zahradnik, 1983), although it has been suggested that prostaglandin actions may have adverse effects in women at high risk of pre-eclampsia (Zelop, 2008 **Level IV**). A large Danish cohort study suggested an increase risk of preterm birth in mothers with pre-eclampsia (Rebordosa et al, 2009 **Level III-3**) following paracetamol exposure in early pregnancy; no increased prevalence of congenital anomalies (Rebordosa, Kogevinas, Horvath-Puho et al, 2008 **Level III-3**); but a slight increase in asthma in infants (Rebordosa, Kogevinas, Sorensen et al, 2008 **Level III-3**). A smaller study reported an increased risk of wheeze in offspring if exposure to paracetamol occurred in mid to late pregnancy (Persky et al, 2008 **Level IV**).

Non-selective non-steroidal anti-inflammatory drugs

Non-selective non-steroidal anti-inflammatory drugs (NsNSAIDs) are Category C drugs. Use of nsNSAIDs during pregnancy was associated with increased risk of miscarriage (Li et al, 2003 **Level III-2**; Nielsen et al, 2004 **Level III-2**). While relatively safe in early and mid pregnancy, they 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 the 32nd gestational week (Ostensen & Skomsvoll, 2004). Fetal exposure to nsNSAIDs has been associated with persistent pulmonary hypertension in the neonate (Alano et al, 2001 **Level III-2**) and an increased risk of premature closure of the ductus arteriosus (Koren et al, 2006 **Level I**).

Opioids

Most opioids are Category C drugs. Much of the information about the effects of opioids on neonates comes from pregnant patients who abuse opioids or who are on maintenance programs for drug dependence. Maternal opioid use can have significant developmental effects in the fetus, although social and environmental factors (eg other drugs, smoking) may also have an impact (Farid et al, 2008; Winklbaur et al, 2008). Neonatal abstinence syndrome

(NAS) requiring treatment occurs in over 60% to 90% of infants exposed to opioids *in utero* (Farid et al, 2008) and there is no clear relationship between maternal dose and the likelihood or duration of NAS (Bakstad et al, 2009 **Level III-2**). Outcomes tend to be better in mothers on maintenance therapy rather than heroin (Farid et al, 2008 **Level IV**), and although initial studies suggested an advantage of buprenorphine over methadone (Farid et al, 2008 **Level IV**), a recent trial (Bakstad et al, 2009 **Level III-2**) and a meta-analysis (Minozzi et al, 2008 **Level I**) reported no difference in maternal or neonatal outcome with methadone, buprenorphine or oral morphine. 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 & Kuschel, 2004 **Level III-2**). Overall, the short-term use of opioids to treat pain in pregnancy appears safe (Wunsch et al, 2003), but minimising use of opioid therapy for chronic pain during pregnancy has been recommended (Chou et al, 2009).

Musculoskeletal pain syndromes

Low back pain and/or pelvic girdle pain are common during pregnancy (Gutke et al, 2008; Borg-Stein & Dugan, 2007) and although low back pain may persist, pelvic girdle pain tends to resolve following delivery (Elden et al, 2008; Vleeming et al, 2008). Epidural techniques in labour did not increase the risk of long-term backache (RR 1.0; 95%CI 0.89 to 1.12) (Anim-Somuah et al, 2005 **Level I**), headache or migraine (Orlikowski et al, 2006 **Level II**).

Pregnancy-specific back support garments reduced movement pain and analgesic use (Kalus et al, 2008 **Level III-2**) but strengthening exercises reduced back pain (Pennick & Young, 2007 **Level I**), and exercise rather than a pelvic belt was recommended for pelvic girdle pain during pregnancy (Vleeming et al, 2008 **Level I**). Weak evidence for improvements with acupuncture (Pennick & Young, 2007 **Level I**; Ee et al, 2008 **Level I**; Vleeming et al, 2008 **Level I**) and chiropractic care (Stuber & Smith, 2008 **Level I**) has been found in systematic reviews, but studies included were of low quality. Oral magnesium therapy did not reduce the frequency or severity of painful leg cramps during pregnancy (Nygaard et al, 2008 **Level II**).

Meralgia paresthetica

This variable condition comprising some or all of the sensations of pain, tingling and numbness in the lateral thigh affects pregnant women in particular, with an increased odds ratio of 12 in comparison with a non-pregnant population (van Slobbe et al, 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, transcutaneous electrical nerve stimulation (TENS), drug therapy (eg tricyclic antidepressants [TCAs], antiepileptics) and surgical intervention (Van Diver & Camann, 1995 **Level IV**; Harney & Patijn, 2007 **Level IV**). Other compressive neuropathies, such as carpal tunnel syndrome and Bell's palsy also occur more commonly during pregnancy (Sax & Rosenbaum, 2006 **Level IV**).

Symphysial diastasis

This occasionally disabling disorder (sometimes called osteitis pubis) involving separation of the symphysis pubis during pregnancy or immediately after delivery, has a quoted incidence of 1:600 (Taylor & Sonson, 1986 **Level IV**) and can produce persistent pain, but there are limited data to inform management (Aslan & Fynes, 2007).

Key messages

1. Exercises reduce back and pelvic pain during pregnancy. There is weak evidence for improvements with acupuncture and chiropractic care (**N**) (**Level I**).
2. Use of NSAIDs during pregnancy is associated with an increased risk of miscarriage (**U**) (**Level III-2**).

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

☑ For pain management in pregnancy non-pharmacological 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 obstetrician and the medical practitioner managing the pain (**U**).

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

Table 11.1 ADEC drug categorisation according to fetal risk

A	Drugs that 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	Drugs that 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	Drugs that 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	Drugs that 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	Drugs that, 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	Drugs that have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Drugs that 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 drugs 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. Drugs 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, sponsor 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 booklet due to the process of ongoing document revision.

Source: ADEC (1999). © Commonwealth of Australia. Reproduced with permission (see notes on verso page).

Table 11.2 Categorisation of drugs used in pain management

Drug	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 infant. Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs.
codeine, dihydrocodeine	A	Prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate
Paracetamol	A	
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 infant and in the mother because of its antiplatelet effects. Products containing aspirin should be avoided in the last trimester. Low-dose aspirin (100 mg/day) 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), mepivacaine, prilocaine	A	
etidocaine, ropivacaine	B1	
procaine hydrochloride	B2	
levobupivacaine	B3	
Antidepressants		
SSRIs: citalopram, fluoxetine, fluvoxamine, sertraline	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 infant.
paroxetine	D	Category changed Sept 2005

Drug	Cat	Comments
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 drugs.
Other antidepressants:		
mirtazapine, moclobemide, nefazodone venlafaxine	B3 B2	
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 infant, which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.
phenytoin sodium	D	This drug 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 infant, which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.
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 mid-trimester morphology ultrasound for prenatal diagnosis of such abnormalities.
lamotrigine	D	Category changed June 2006
clonazepam	C	Clonazepam is a benzodiazepine. These drugs may cause hypotonia, respiratory depression and hypothermia in the newborn infant if used in high doses during labour. Withdrawal symptoms in newborn infants have been reported with this class of drugs.
gabapentin	B1	
tiagabine, topiramate, pregabalin	B3	
lamotrigine	D	

Drug	Cat	Comments
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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11.1.2 Management of pain during delivery

Pain during labour and delivery 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 relief does not necessarily equate with a high level of satisfaction and no difference in satisfaction was reported following epidural or non-epidural analgesia (Anim-Somuah et al, 2005 **Level I**). Severe pain during labour is one of several factors associated with post-traumatic stress symptoms following childbirth (Slade, 2006 **Level IV**). Consistent with pain experience in other settings, high scores on a pain catastrophising scale have been associated with increased report of intense labour pain (Flink et al, 2009 **Level IV**).

Women should have access to safe and appropriate maternity services, including anaesthesia and analgesia (RANZCOG et al, March 2009). Guidelines from the American Society of Anesthesiologists (ASA) Taskforce on Obstetric Anesthesia include recommendations for analgesia during labour and delivery (ASA, 2007).

Systemic analgesia in labour pain

Systemic opioid analgesics continue to be used in labour although practice varies, as there are insufficient data to evaluate the comparative efficacy and safety of different opioids (Tuckey et al, 2008 **Level IV**). IM tramadol provided similar pain relief to pethidine in the first stage of labour, but pain scores remained high in both groups and side effects were more common following tramadol (Khooshideh & Shahriari, 2009 **Level II**). IV administration has greater efficacy than equivalent IM dosing (Isenor & Penny-MacGillivray, 1993 **Level II**).

In comparison with epidural analgesia, systemic opioids provided less analgesia and increased the need for additional pain relief methods, although with no measurable difference in maternal satisfaction (Anim-Somuah et al, 2005 **Level I**). Their use also worsened fetal acid-base balance (Reynolds et al, 2002 **Level I**).

A quantitative assessment of the efficacy of nitrous oxide (N_2O) inhalational analgesia is currently not possible. However, although it is not a potent labour analgesic, it is safe (Rosen, 2002 **Level I**). In cross-over comparisons with N_2O, self-administration of low-concentration sevoflurane (0.8%) (Yeo et al, 2007 **Level III-2**) and IV PCA remifentanil (Volmanen et al, 2005 **Level II**) reduced pain to a greater degree, but also increased sedation. Although, IV PCA remifentanil can reduce pain, particularly in early labour, it had less effect on pain scores and

produced greater maternal sedation when compared with epidural analgesia (Volmanen et al, 2008 **Level II**). In addition, PCA remifentanil has been associated with maternal apnoea and there is currently no consensus on the optimal dosing regimen (Hill, 2008 **Level IV**).

Epidural and combined spinal-epidural analgesia for labour pain

Epidural analgesia provided better pain relief than non-epidural analgesia (weighted mean difference [WMD] -2.6; CI -3.82 to -1.38; VAS 0 to 10). Although associated with an increased use of oxytocin (RR 1.18; CI 1.03 to 1.34) and longer second stage of labour (WMD 15.6 minutes; CI 7.5 to 23.6), there was no increase in the incidence of low neonatal 5-minute Apgar Scores (RR 1.18; CI 0.92 to 1.5) (Anim-Somuah et al, 2005 **Level I**). Epidural analgesia increased the risk of instrumental vaginal birth (RR 1.38; CI 1.24 to 1.53), but did not increase the rate of Caesarean section (RR 1.07; CI 0.93 to 1.23) (Anim-Somuah et al, 2005 **Level I**). Although almost 90% of women can achieve optimal analgesia with epidural techniques, suboptimal analgesia has been associated with an increased risk of second-stage outcomes (Caesarean section, mid-pelvic procedures and severe perineal tears) (Abenhaim & Fraser, 2008 **Level III-2**).

The timing of neuraxial analgesia is based on the degree of cervical dilatation in some centres. In nulliparous women, on-demand administration of neuraxial analgesia from early labour (<4 cm cervical dilation) provided more effective pain relief and did not increase the rate of Caesarean section or instrumental vaginal delivery when compared with commencement of epidural analgesia later in labour (Marucci et al, 2007 **Level I**; Wong et al, 2009 **Level II**). By contrast, women receiving early systemic opioid analgesia before late epidural analgesia had a higher incidence of instrumental vaginal delivery. Infants of mothers receiving early neuraxial analgesia had improved neonatal acid-base status, a reduced requirement for naloxone, but no measurable difference in Apgar scores when compared with infants of mothers receiving parenteral opioid analgesia (Marucci et al, 2007 **Level I**). However, it was also noted that many of the included studies did not score highly for quality, and a lack of blinding may produce bias.

Combined spinal-epidural (CSE) analgesia in labour had a faster onset of analgesia than epidural analgesia (Goodman et al, 2009 **Level II**; Simmons et al, 2007 **Level I**). Foetal heart rate abnormalities have been reported following CSE: this has also been associated with increased uterine hypotonus (Abrao et al, 2009 **Level II**), high maternal pain scores and older maternal age (Nicolet et al, 2008 **Level IV**). As CSE does not improve satisfaction or mobilisation, and increases the risk of pruritus, clinical advantages over epidural analgesia (either traditional or low dose) are limited (Simmons et al, 2007 **Level I**).

Note: reversal of conclusion

This reverses the Level 1 conclusion in the previous edition of this document, which concluded that maternal satisfaction was increased.

Low dose (0.1%) bupivacaine/opioid infusions in comparison with 0.25% bupivacaine bolus dose injection reduced motor block and instrumental vaginal delivery rate (Comparative Obstetric Mobile Epidural Trial (COMET) Study Group, 2001 **Level II**). There was no significant difference in any outcome between the use of bupivacaine and ropivacaine (Halpern & Walsh, 2003 **Level I**).

Combination of epidural fentanyl with levobupivacaine 0.125%, bupivacaine 0.125% or ropivacaine 0.2% produced effective analgesia, although pain scores were higher in the levobupivacaine group and motor block was greater with bupivacaine (Atienzar et al, 2008

Level II). Respiratory depression related to epidural or intrathecal opioids during labour was rare (Carvalho, 2008 **Level IV**).

Patient-controlled epidural analgesia (PCEA) can provide effective analgesia but the optimal settings are not clear (Leo & Sia, 2008 **Level IV**; Halpern & Carvalho, 2009 **Level I**). A systematic review concluded that dilute concentrations of bupivacaine or ropivacaine provide acceptable analgesia, and that use of large bolus doses and background infusions with PCEA may improve analgesia (Halpern & Carvalho, 2009 **Level I**). A comparison of demand dose-only PCEA, PCEA with a continuous infusion, and a continuous epidural infusion only during labour, showed that dose-only PCEA resulted in less total epidural dose compared with the other modalities; no differences were noted with respect to pain scores, motor block, duration of labour, number of staff interventions, delivery outcome, and maternal satisfaction score (Vallejo et al, 2007 **Level II**). However, a later systematic review of PCEA in labour analgesia concluded that the use of a continuous background epidural infusion combined with PCEA resulted in improved maternal analgesia and reduced unscheduled clinician interventions (Halpern & Carvalho 2009, **Level I**).

Single-injection intrathecal opioids were as effective as epidural local anaesthetics for the management of pain in early labour; there was increased pruritus but no effect on nausea or mode of delivery (Bucklin et al, 2002 **Level I**). Intrathecal opioids increased the risk of fetal bradycardia (NNH 28) and maternal pruritus (NNH 1.7) in comparison with non-intrathecal opioid analgesia (Mardirosoff et al, 2002 **Level I**). Continuous intrathecal infusion improved early analgesia with no differences in neonatal or obstetric outcomes, but more technical difficulties when compared with epidural administration (Arkoosh et al, 2008 **Level II**).

Other regional techniques in labour pain

Paracervical block was more effective than IM opioids (Jensen et al, 1984 **Level II**) but required supplementation more frequently than epidural analgesia (Manninen et al, 2000 **Level II**) and was less effective than single-shot intrathecal analgesia (Junttila et al, 2009 **Level III-2**). Serious fetal complications may occur (Shnider et al, 1970), although this technique may have a role in hospitals without obstetric anaesthesia services (Levy et al, 1999 **Level III-2**) or in patients with contraindications for spinal techniques (Junttila et al, 2009 **Level III-2**).

Complementary and other methods of pain relief in labour

Continuous or one-to-one support by a midwife or trained layperson during labour reduced analgesic use, operative delivery and dissatisfaction, especially if the support person was not a member of the hospital staff, was present from early labour, or if an epidural analgesia service was not available (Hodnett et al, 2007 **Level I**).

Non-pharmacological or complementary therapies may be used during labour. Acupuncture decreased the need for pain relief (RR 0.7; CI 0.49 to 1.0) and women taught self-hypnosis had reduced pharmacological requirements (RR 0.53; CI 0.36 to 0.79), a slight decrease in need for epidural analgesia (RR 0.30, CI 0.22 to 0.40), and increased satisfaction compared with controls (Smith et al, 2006 **Level I**). The efficacy of acupressure, aromatherapy, audio analgesia, relaxation or massage has not been established (Smith et al, 2006 **Level I**). TENS reduced reports of severe pain during labour, but a consistent reduction in pain scores or in requirements for other analgesia could not be confirmed (Dowswell et al, 2009 **Level I**). Few complementary therapies have been carefully studied in well-designed trials with clinically relevant outcomes, and sample sizes have been small (Smith et al, 2006 **Level I**).

Pain after Caesarean section

After Caesarean section utilising epidural anaesthesia, epidural opioids were more effective than intermittent injections of parenteral opioids (ASA, 2007 **Level I**). Single-dose epidural morphine (particularly a slow-release formulation) (Carvalho et al, 2007 **Level II**) or intrathecal morphine (Girgin et al, 2008 **Level II**) reduced post Caesarean section analgesic requirements. The addition of clonidine to intrathecal hyperbaric bupivacaine improved early analgesia after Caesarean section, but did not reduce morphine consumption during the first 24 hours (van Tuijl et al, 2006 **Level II**).

Following Caesarean section under general anaesthesia, local anaesthetic wound infiltration reduced postoperative opioid requirements (Bamigboye & Justus, 2008 **Level II**), and bolus doses of local anaesthetic via an incisional catheter were as effective as epidural bolus doses (Ranta et al, 2006 **Level II**). Following Caesarean section under spinal anaesthesia, local anaesthetic transversus abdominus block reduced postoperative opioid requirements (McDonnell et al, 2008 **Level II**), but addition of a coxib had no advantage over intrathecal morphine alone (Carvalho et al, 2006 **Level II**). Local anaesthetic techniques (wound infiltration or catheter, ilio-inguinal/ilio-hypogatsric block, transversus abdominus plane block) reduce opioid consumption following Caesarean section performed under general or regional anaesthesia, but the impact on opioid-related side-effects was not evaluated (Bamigboye & Hofmeyr, 2009 **Level I**).

Prior caesarean section is a risk factor for chronic pelvic pain (Latthe et al, 2006 **Level I**). Persistent post-surgical pain has been reported in 6% to 12% of women following Caesarean section (Nikolajsen et al, 2004 **Level IV**), is likely to be neuropathic in nature and may be under-recognised (Gillett & Jones, 2009).

Key messages

1. Epidural and combined spinal-epidural analgesia provide superior pain relief for labour and delivery compared with systemic analgesics (**S**) (**Level I** [Cochrane Review]).
2. Combined spinal-epidural in comparison with epidural analgesia reduces time to effective analgesia and increases the incidence of pruritus (**U**), does not increase maternal satisfaction (**R**), but increases the risk of urinary retention (**N**) (**Level I** [Cochrane Review]).
3. Epidural analgesia does not increase the incidence of Caesarean section or long-term backache (**S**) (**Level I** [Cochrane Review]).
4. Epidural analgesia is associated with increased duration of labour and increased rate of instrumental vaginal delivery (**S**) (**Level I** [Cochrane Review]).
5. Hypnosis used in labour reduces analgesic requirements (**S**) and improves satisfaction (**N**) (**Level I** [Cochrane Review]).
6. Acupuncture reduces analgesic requirements in labour (**U**) (**Level I** [Cochrane Review]).
7. TENS may reduce severe pain in labour but does not reliably reduce pain scores (**U**) or analgesic requirements (**N**) (**Level I** [Cochrane Review]).
8. Local anaesthetic wound infiltration and abdominal nerve blocks reduce opioid consumption following Caesarean section (**N**) (**Level I** [Cochrane Review]).
9. Continuous or one-to-one support by a midwife or trained layperson during labour reduces analgesic use, operative delivery and dissatisfaction (**U**) (**Level I**).
10. There is no significant difference in any outcome between use of bupivacaine and ropivacaine for epidural labour analgesia (**U**) (**Level I**).

11. Patient-controlled epidural analgesia provides effective analgesia but optimal settings are not clear (**N**) (**Level I**).
12. Single-injection intrathecal opioids provide comparable early labour analgesia to epidural local anaesthetics with increased pruritus (**U**) (**Level I**).
13. Systemic opioids in labour increase the need for neonatal resuscitation and worsen acid-base status compared with regional analgesia (**U**) (**Level I**).
14. Nitrous oxide has some analgesic efficacy and is safe during labour (**U**) (**Level I**).

11.1.3 Pain management during lactation

A number of general principles apply when administering analgesic and antiemetic drugs for pain management during lactation:

- the choice of drugs 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 drug concentration in milk, and the infant should be observed for effects of medication transferred in breast milk.

The effects of many analgesic and antiemetic drugs during lactation have not been adequately investigated, leaving clinical decisions to be made on evidence derived from pharmacokinetic or observational studies, case reports and anecdote. For most drugs, 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 drugs in human milk (Ito, 2000; Berlin & Briggs, 2005; Ilett & Kristensen, 2005) including drugs relevant to pain management (Rathmell et al, 1997; Spigset & Hagg, 2000; Bar-Oz et al, 2003) have been reviewed. The maternal plasma concentration, which is influenced by the dose and the ability of the mother to metabolise the drug, is an important determinant of drug levels in milk. High lipid solubility, low molecular weight, low protein binding and the unionised state favour secretion into breast milk. Most drugs have a milk-to-plasma ratio of 1 or less (Ito, 2000). The neonatal exposure is often 0.5% to 4% of the maternal dose, but infant drug metabolism may be impaired, and much of the data is from single maternal dose studies rather than chronic therapy (Berlin & Briggs, 2005). A safe level of infant exposure to a drug 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). Until about the third to fourth postpartum day only very small amounts of colostrum are secreted, so early breastfeeding is unlikely to pose a hazard, even from drugs administered in the peripartum period.

Lactating women having surgical procedures with general anaesthetic have been advised to discard their milk for 24 hours following the operation. Following single intraoperative doses of midazolam (2 mg), propofol (2.5 mg/kg), and fentanyl (100 mcg), less than 0.1% of the drugs were excreted into milk within 24 hours, suggesting that interruption of breastfeeding may not be required (Nitsun et al, 2006 **Level III-3**).

Drugs that might be prescribed during lactation have been categorised according to their risk for the baby. Some of the drugs that might be used in pain management are listed with comments in Table 11.3.

Paracetamol and non-steroidal anti-inflammatory drugs

The weight-adjusted maternal dose of paracetamol transferred to the neonate was 1.85% (Notarianni et al, 1987). Although neonatal glucuronide conjugation may be deficient, the drug 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.

If an anti-inflammatory is required, nsNSAIDs are preferable to aspirin (Berlin & Briggs, 2005 **Level IV**). Despite similar proportional transfer as paracetamol, salicylates are eliminated slowly by the neonate, cause platelet dysfunction and have been associated with Reye's syndrome; aspirin in analgesic doses cannot be recommended as safe (Bar-Oz et al, 2003).

NsNSAIDs must be considered individually, but in general milk levels 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). Diclofenac and ketorolac are minimally transported into breast milk and short-term or occasional use is compatible with breastfeeding. The safety of naproxen is less clear but it is also considered compatible (Rathmell et al, 1997). Indomethacin (indometacin) has been associated with central maternal side effects, such as agitation and psychosis, in previously healthy postnatal women (Clunie et al, 2003 **Level IV**). Following a single 200 mg dose of celecoxib, less than 0.5% of the weight-adjusted maternal dose was present in breast milk, suggesting that breastfeeding during routine dosing poses minimal risk (Gardiner et al, 2006 **Level III-3**; Hale et al, 2004 **Level III-3**).

Opioids and tramadol

With some provisos, the short-term use of opioids is generally considered safe during lactation (Ravin, 1995) as most opioids are secreted into breast milk in low doses.

An association between opioid exposure in breast milk and episodes of apnoea and cyanosis in infants has been described (Naumburg & Meny, 1988 **Level IV**), leading some to suggest that opioids should be avoided if the neonate experiences such events during the first week of life. Morphine has been recommended as the opioid of choice if potent analgesia is required in breastfeeding mothers (Ito, 2000 **Level IV**). About 6% of the weight-adjusted maternal dose of morphine is transferred in breast milk (Feilberg et al, 1989), but the oral bioavailability in the infant is low (about 25%), so only small amounts reach the infant. In mothers treated with IV PCA morphine for 48 hours following Caesarean section, levels of morphine and M6G were low in breast milk, suggesting minimal drug would be transferred to the neonate (Baka et al, 2002).

Pharmacokinetic studies also 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 neonate was 3%, levels in colostrum became undetectable within several hours and the nursing infant appeared unaffected (Steer et al, 1992 **Level IV**).

Breastfed infants whose mothers received pethidine (meperidine) were less alert and oriented to auditory cues after Caesarean section than those of mothers receiving morphine (Wittels et al, 1997 **Level II**). As norpethidine (normeperidine) accumulates in breast milk with repeated use and has very slow neonatal elimination, pethidine use during breastfeeding is not recommended (Ito, 2000).

Codeine has a milk-to-plasma ratio of slightly more than 1 suggesting it is generally safe (Meny et al, 1993), but morphine toxicity and death has been reported in a breastfed neonate whose mother was an ultra-rapid metaboliser of codeine (Madadi et al, 2008 **Level IV**). A relationship between infant central nervous system (CNS) symptoms (decreased alertness, lethargy, poor

feeding) and maternal symptoms, codeine dose, and in some cases CYP2D6 phenotype, has been identified (Madadi et al, 2009 **Level III-3**).

As oxycodone is concentrated in human breast milk, and breastfed infants may receive >10% of a therapeutic dose, safety with repeated maternal dosing has been questioned (Ito, 2000). As a component of multimodal analgesia in the first 72 hours after Caesarean section, there may be minimal risk to breastfeeding infants as only a low volume of milk is ingested during this period (Seaton et al, 2007 **Level III-3**).

Use of tramadol (100 mg 6 hrly) on days 2 to 4 after Caesarean section 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 et al, 2008 **Level III-2**). However, as with other drugs, these data cannot be directly extrapolated to long-term use at later postpartum stages when the volume of ingested milk is higher.

Methadone is considered compatible with breastfeeding. 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 days 3, 14 and 30 following birth (Jansson et al, 2008 **Level III-3**).

Other medications related to pain relief

After epidural administration, local anaesthetics showed acceptable milk-to-plasma ratios of 1.1 for lignocaine (lidocaine) and 0.34 for bupivacaine (Ortega et al, 1999) and 0.25 for ropivacaine (Matsota et al, 2009), which are considered safe (Rathmell et al, 1997). Use of epidural analgesia (local anaesthetic ± fentanyl) during labour (Chang & Heaman, 2005 **Level III-3**) or as PCEA after Caesarean section (Matsota et al, 2009 **Level IV**) did not influence neurobehavioural scores in healthy term infants.

There is very little information about antiemetic use, and in almost all cases the manufacturers do not recommend their use during lactation (for recommendations see Table 11.3). Animal studies suggest possible CNS effects in the newborn, but human anecdotal experience is favourable.

In a single case report, the milk-to-plasma concentration of gabapentin was 0.86, the relative infant dose was 2.4%, and no adverse effects were noted in the infant. While suggestive of safety during lactation, a careful individual risk-benefit analysis was suggested (Kristensen et al, 2006 **Level IV**).

Table 11.3 The breastfeeding patient and drugs used in pain management

Drug	Comments
Opioids	
buprenorphine, codeine, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, pentazocine, tramadol	Safe to use occasional doses. Use repeated doses with caution, especially if infant is premature or <4 weeks old; monitor infant for sedation and other adverse effects
Paracetamol	Safe to use
Aspirin	Avoid due to theoretical risk of Reye's syndrome; ibuprofen is preferred
Other NSAIDs	
NsNSAIDs, Coxibs	Safe to use Limited data; appear safe
Ketamine	Limited data, avoid use

Drug	Comments
Local anaesthetics	
bupivacaine, cinchocaine, levobupivacaine lignocaine (lidocaine), mepivacaine, prilocaine, ropivacaine	Unlikely to cause problems
Antidepressants	
SSRIs: citalopram, fluvoxamine, paroxetine, sertraline	SSRIs are used in postnatal depression (some consider sertraline one of the preferred antidepressants in breastfeeding).
fluoxetine	Use an alternative SSRI because of fluoxetine's long half-life
Tricyclic antidepressants (TCAs): amitriptyline, clomipramine, dothiepin (dosulepin), doxepin, imipramine, nortriptyline, trimipramin	TCAs have been used to treat postnatal depression. Avoid doxepin if possible; a single case of neonatal respiratory depression has been reported
Other antidepressants: moclobemide	Appears to be safe; contact specialised information service
mirtazapine, venlafaxine	Contact specialised information service
Anticonvulsants	
carbamazepine	Safe to use; monitor infant for drowsiness and poor suckling
phenytoin sodium	May be used
sodium valproate	Should be safe to use
clonazepam	Risk of sedation in infant; contact specialised information service
gabapentin, tiagabine	Contact specialised information service
pregabalin	No data available
lamotrigine, topiramate	Excreted in breast milk; contact specialised information service
Antiemetics, antinauseants	
Phenothiazines: prochlorperazine	Safe to use
promethazine	Safe to use; however, may cause drowsiness or tiredness in mother
Others: dimenhydrinate	Safe to use
metoclopramide	Safe to use (used to stimulate lactation)
dolasetron, granisetron, ondansetron, tropisetron	Contact specialised information service; no data available, although 1 or 2 doses after delivery should not be a concern
domperidone	Used during first months of breastfeeding to stimulate lactation; mother may be less drowsy than with metoclopramide
hyoscine hydrobromide	Safe to use occasional doses

Drug	Comments
droperidol, haloperidol	Avoid if possible, or contact one of the pregnancy drug information centres; if used monitor infant for sedation

Source: Information taken with permission from *Australian Medicines Handbook 2009*.

Key messages

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

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

☑ Local anaesthetics, paracetamol and several non-selective NSAIDs, in particular ibuprofen, are considered to be safe in the lactating patient (**U**).

☑ Morphine and fentanyl are considered safe in the lactating patient and are preferred over pethidine (**U**).

11.1.4 Pain management 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 fourth postpartum day. Women are often inadequately warned and remain ill informed of the best available treatments for postnatal pain. In the first 6 months postpartum, backache was reported by 44% of women and perineal pain by 21%, and many indicated they would have liked more help or advice (Brown & Lumley, 1998). 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 et al, 2007 **Level IV**). Breast, especially nipple, pain may result in abandonment of breastfeeding (Morland-Schultz & Hill, 2005).

Perineal pain

A number of obstetric and surgical factors contribute to perineal pain following delivery. After adjusting for parity, perineal trauma, and length of labour, women with instrumented versus unassisted vaginal deliveries reported more perineal pain (Thompson et al, 2002 **Level IV**). Restrictive use versus routine mediolateral episiotomy reduced the rate of episiotomy from 75% to 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 & Mignini, 2009 **Level I**). In comparison with interrupted suturing methods, continuous suturing (particularly of all layers rather than skin only) was associated with reductions in pain and analgesic use (Kettle et al, 2007 **Level I**).

Non-pharmacological treatments

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, and pulsed electromagnetic energy was more effective than ice packs (East et al, 2007 **Level I**). Although improvement in perineal pain has been reported with ultrasound, there is insufficient evidence to fully evaluate efficacy (Hay-Smith, 2000 **Level I**).

For women without prior vaginal delivery, antenatal perineal massage (from 35 weeks gestation) reduced the incidence of perineal trauma requiring suturing (NNT 14; CI 9 to 35) and the requirement for episiotomy (NNT 23; CI 13 to 111), but values for NNT were high.

Effects on acute postpartum pain have not been reported, but a reduction in the incidence of pain at 3 months postpartum was reported in women who used antenatal massage and had previously given birth vaginally (Beckmann & Garrett, 2006 **Level I**).

Pharmacological treatments

Paracetamol is moderately effective for perineal pain during the first 24 hours after birth. nsNSAID suppositories reduced perineal pain in the first 24 hours postpartum (Hedayati et al, 2003 **Level I**). Both oral celecoxib and diclofenac reduced perineal pain, with slight advantages of celecoxib for pain scores at rest and incidence of gastrointestinal symptoms (Lim et al, 2008 **Level II**).

Topical local anaesthetics (lignocaine, cinchocaine, pramoxine plus hydrocortisone preparations) and placebo did not improve pain relief in the 24 hours postpartum. One trial reported a reduction in supplemental analgesic requirements with epifoam (1% hydrocortisone and 1% pramoxine in mucoadhesive base). The use of systemic analgesics was not standardised across studies and may be a confounding factor (Hedayati et al, 2005 **Level I**). 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 et al, 2008 **Level II**).

Breast pain

Painful breasts are a common reason for ceasing breastfeeding (Morland-Schultz & Hill, 2005). 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 (Amir, 2003).

Nipple pain is experienced by 30% to 90% of women and tends to peak around the third day postpartum (Morland-Schultz & Hill, 2005). Topical agents (such as lanolin, wet compresses, hydrogel dressings, collagenase or dexpanthenol ointment) produce mild improvements in nipple pain, but no one agent was shown to be superior. Education in relation to proper breastfeeding technique is important for decreasing the incidence of nipple pain (Morland-Schultz & Hill, 2005 **Level I**).

Mastitis defined by at least two breast symptoms (pain, redness or lump) and at least one of fever or flu-like symptoms occurs in 17% to 33% of breastfeeding women, with most episodes occurring in the first 4 weeks (Amir et al, 2007 **Level IV**; Jahanfar et al, 2009 **Level I**). Infective mastitis is most commonly from *Staphylococcus aureus*, and non-infective mastitis is equally common. Currently, there is insufficient evidence to confirm efficacy for antibiotics in relieving symptoms, but only two trials met the inclusion criteria for analysis (Jahanfar et al, 2009 **Level I**).

Symptomatic therapies for breast engorgement have been inadequately investigated, but cabbage leaves and cabbage extract cream were no more effective than placebo (Snowden et al, 2001 **Level I**). Similarly, ultrasound was not effective and observed benefits may be due to the effect of radiant heat or massage (Snowden et al, 2001 **Level I**).

Uterine pain

Uterine pain or 'after pains' often worsen with increasing parity, are experienced by most multiparous women, and result 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 increased the requirement for analgesia for pain after birth due to persistent uterine contraction (RR 2.53; CI 1.34 to 4.78), but also decreased mean blood

loss and the incidence of postpartum haemorrhage compared with no uterotonic drugs (Liabsuetrakul et al, 2007 **Level I**).

Paracetamol and nsNSAIDs had similar efficacy for reducing uterine cramping pain and were modestly effective compared with placebo (Skovlund et al, 1991a **Level II**; Skovlund et al, 1991b **Level II**; Huang et al, 2002 **Level II**; Hsu et al, 2003 **Level II**).

High-intensity TENS was more effective than low-intensity TENS for postpartum uterine pain, but also produced more local discomfort (Olsen et al, 2007 **Level III-2**).

Key messages

1. Routine episiotomy does not reduce perineal pain (**U**) (**Level I**).
2. Paracetamol and non-selective NSAIDs are effective in treating perineal pain after childbirth (**U**) (**Level I**).
3. Paracetamol and non-selective NSAIDs are equally but only modestly effective in treating uterine pain (**U**) (**Level II**).
4. Topical agents may improve nipple pain, but no one treatment is superior (**N**) (**Level I**).
5. There is only limited evidence to support the effectiveness of local cooling treatments in treatment of perineal pain after childbirth (**Q**) (**Level I**).
6. Topical local anaesthetic preparations are not effective for perineal pain after childbirth (**N**) (**Level I**).

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**).

11.2 The older patient

The need to manage acute pain in the older patient is becoming more common as the population ages. Advances in anaesthetic and surgical techniques mean that increasingly older patients, including patients over 100 years old (Konttinen & Rosenberg, 2006), are undergoing more major surgery (Kojima & Narita, 2006). Medical conditions that are more common in older people may also lead to acute pain; these include acute exacerbations of arthritis, osteoporotic fractures of the spine, cancer and pain from other acute medical conditions including ischaemic heart disease, herpes zoster and peripheral vascular disease.

Factors that can combine to make effective control of acute pain in the older person more difficult than in younger patients include: a higher incidence 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.

11.2.1 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 11.4. The information in this table centres on opioids in view of their widespread use. The changes, the onset of which can be highly variable between individuals, are generally attributable to ageing alone but may be compounded by the higher incidence of degenerative and other concurrent diseases in older people.

Table 11.4 Direction and approximate magnitude of physiological changes apparent in an older population (> 70 years) and the effects of individual changes on pharmacokinetic variables

Physiological process	Magnitude	Likely kinetic / dynamic consequence	Dose strategy
Whole body			
Cardiac output	↓ 0–20%	↓ central compartment volume ↑ peak concentration after bolus	▪ smaller initial bolus dose ▪ slower injection rate
Fat	↑ 10–50% then ↓	Drug specific changes in distribution volume	▪ drug specific – dose based on total body weight or lean body weight
Muscle mass/ blood flow	↓ 20%		
Plasma volume	Little change		
Total body water	↓ 10%	↓ distribution volume (water-soluble drugs)	
Plasma albumin Alpha 1 glycoprotein Drug binding	↓ 20% ↑ 30–50% Drug specific	↑ free fraction of drug ↔ hepatic clearance of high extraction drugs ↑ hepatic clearance of low extraction drugs ↑ cerebral uptake of drug	▪ potential for changes in clearance and oral bioavailability ▪ potential for changes in cerebral effects
Liver and gut			
Liver size Hepatic blood flow	↓ 25–40% ↓ 25–40%	↓ hepatic clearance of high extraction drugs ↔ hepatic clearance of low extraction drugs	▪ minimal effect on IV bolus dose ▪ ↓ maintenance dose ▪ potential for changes in oral bioavailability
Phase 1 (eg oxidation) Phase II	↓ 25% Little change	↓ hepatic clearance (some low extraction drugs)	

Physiological process	Magnitude	Likely kinetic / dynamic consequence	Dose strategy
Kidney			
Nephron mass Renal blood flow Plasma flow at 80 years Glomerular filtration rate Creatinine clearance	↓ 30% ↓ 10% / decade ↓ 50% ↓ 30–50% ↓ 50–70%	↓ clearance (polar) drugs Little effect on opioids (parent compound) ↓ clearance of some active metabolites (eg M6G)	▪ ↓ maintenance dose (renally cleared drugs) ▪ assume, and monitor for, accelerated accumulation of polar active (M6G) or toxic (M3G, norpethidine) metabolites
CNS			
Cerebral blood flow and metabolism Cerebral volume	↓ 20% ↓ 20%	↓ distribution to the CNS ↓ apparent volume in the CNS	▪ little net effect on dose
Active BBB transport (efflux)	↓ (drug specific)	↑ apparent volume in the CNS ↑ apparent increase in CNS sensitivity	▪ ↓ bolus dose during titration ▪ ↓ maintenance dose
Pain threshold sensitivity	Little change		▪ need for titration unchanged
Concentration response (opioids)	↑ 50% for some opioids	↑ response to opioids	▪ ↓ bolus dose during titration ▪ ↓ maintenance dose

Note that the net effect of these changes in drug disposition may be minimal

M6G: morphine-6-glucuronide; M3G: morphine-3-glucuronide.

Source: Reproduced with kind permission from Macintyre & Upton, Acute Pain Management in the Elderly Patient Table 28.1, p 506 *Clinical Pain Management: Acute Pain*, Hodder Arnold.

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, by studying the effects of fentanyl and alfentanil on the electroencephalogram (EEG) it was concluded that the pharmacokinetics were unaffected by age, but that the sensitivity of the brain to these opioids was increased by 50% in the older person (Scott & Stanski, 1987). Whether this can be attributed to changes in the number or function of opioid receptors in the CNS (in older rats there are fewer μ- and κ-opioid receptors (Vuyk, 2003) or whether it is due to an increased penetration of opioids in the CNS is unclear. Some of the changes that may lead to increased drug sensitivity in the older patient are discussed below (see Section 11.2.2).

11.2.2 Physiology and perception of pain

Reviews by Gibson (Gibson, 2003), Gibson and Farrell (Gibson & Farrell, 2004) and Gagliese and Farrell (Gagliese & Farrell, 2005) summarise the age-related changes that occur in pain perception and the neurophysiology of nociception.

In general, in the nervous system of the older person, there are extensive alterations in 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 the pain inhibitory system.

The peripheral nerves show a decrease in the density of both myelinated and, particularly, unmyelinated peripheral nerve fibres, an increase in the number of fibres with signs of damage or degeneration and a slowing of the conduction velocity; in rats, reductions in substance P, calcitonin gene-related peptide (CGRP) and somatostatin levels have been reported.

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. Decreases in noradrenergic and serotonergic neurons may contribute to the impairment of descending inhibitory mechanisms and may underlie the decrease in pain tolerance seen in the older person (see below). 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; 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 remains a subject of debate and recent functional MRI (fMRI) studies show more similarities than differences in the magnitude of activation in the brain response to acute noxious stimulation (Cole et al, 2008).

Variations in pain perception are best determined in controlled situations where severity of the noxious stimulus is standardised and mood is not an active variable. This can be done with experimental pain stimuli, or to a lesser extent, with standard medical procedures such as venipuncture and wound dressings.

The results of studies looking at the effects of experimental pain stimuli (brief noxious stimuli that do not result in tissue injury) on pain thresholds are conflicting and seem to depend on the type of stimulus used. In general, older people tend to have higher thresholds for thermal stimuli while results from mechanical stimulation are equivocal and there may be no change over the age groups with electrical stimuli (Gibson, 2003 **Level I**). The significance of these observations in the clinical setting, where pain is associated with tissue injury, remains uncertain although they could indicate some deficit in the early warning function of pain and narrow the gap between identification of the pain stimulus and recognition of a stimulus that might cause tissue injury (Gibson, 2006). For example, in patients with an acute myocardial infarction, greater intensity of chest pain was inversely correlated with lower pain threshold (Granot et al, 2007 **Level IV**); 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 and using a variety of experimental pain stimuli, there is a reduced ability in older people to endure or tolerate strong pain (Gibson, 2003 **Level I**). This could mean that severe pain may have a greater impact on the more vulnerable older person.

Also noted have been significantly smaller increases in pain threshold following prolonged noxious stimulation and prolonged recovery from hyperalgesia (Zheng et al, 2000 **Level III-2**; Gibson, 2006). Using experimental pain stimuli it can be shown that the threshold for temporal summation is lower in the elderly (Gibson & Farrell, 2004). In subjects given trains of brief electrical stimuli of varying frequency, older subjects showed temporal summation at all frequencies of stimulation whereas summation was not seen at the lower frequencies in younger subjects (Farrell & Gibson, 2007 **Level III-2**). Temporal summation of thermal stimuli was increased in the older compared with younger subjects (Edwards & Fillingim, 2001 **Level III-2**; Lautenbacher et al, 2005 **Level III-2**) and more prolonged (Edwards & Fillingim, 2001 **Level III-2**), but temporal summation of pressure pain showed no age-related effects (Lautenbacher et al, 2005

Level III-2). 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 (Zheng et al, 2000 **Level III-2**). The underlying reason for these findings is again that the older person may have impaired descending inhibitory mechanisms and a reduced capacity to down-regulate after sensitisation leading to prolonged recovery (Gagliese & Farrell, 2005).

Clinical implications

There are a number of clinical reports, summarised by Gibson (Gibson, 2003 **Level IV**; Gibson, 2006 **Level IV**) and Pickering (Pickering, 2005 **Level IV**), suggesting that pain symptoms and presentation may change in the older patient; pain becomes a less frequent or 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; 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. For example, in older patients, right upper quadrant or epigastric pain associated with cholecystitis may be absent in 85%; 30% of those with peptic ulcer disease and up to 90% with pancreatitis may have no abdominal pain; in those with advanced peritonitis pain may be a symptom in only 55%; and reports of atypical pain or absence of pain occur in up to 33% of older patients with an acute myocardial infarction and 50% with unstable angina (Pickering, 2005 **Level IV**).

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% to 20% each decade after 60 years of age (Thomas et al, 1998 **Level III-2**). Older men undergoing prostatectomy reported less pain on a present pain intensity scale and McGill Pain Questionnaire (but not a visual analogue scale [VAS]) in the immediate postoperative period and used less PCA opioid than younger men undergoing the same procedure (Gagliese & Katz, 2003 **Level III-2**). In a study of pain following placement of an IV cannula (a relatively standardised pain stimulus), older patients reported significantly less pain than younger patients (Li et al, 2001 **Level IV**).

11.2.3 Assessment of pain

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 reported pain intensity decrease with increasing cognitive impairment (Farrell et al, 1996; Herr et al, 2006). Reasons for this could include a diminished memory, impairment of capacity to report, or it could be that less pain is experienced (Farrell et al, 1996; Herr et al, 2006).

However, studies in patients with dementia suggest that they may not experience less pain. 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 et al, 2006 **Level III-2**).

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; those 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 et al, 2006 **Level III-2**).

Undertreatment of acute pain is more likely to occur in cognitively impaired patients (Feldt et al, 1998 **Level III-2**; Forster et al, 2000 **Level III-2**; Morrison & Siu, 2000 **Level III-2**).

A common form of acute cognitive impairment in the older patient is delirium or confusion, which is associated with increased postoperative morbidity, impaired postoperative rehabilitation and prolonged hospital stays (Bekker & Weeks, 2003; Bitsch et al, 2006; Fong et al, 2006; Greene et al, 2009 **Level III-3**). Delirium is more common 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 confirmed that postoperative cognitive dysfunction (POCD) is relatively common after non-cardiac surgery and that the older patient is particularly at risk (Newman et al, 2007 **Level I**).

Risk factors associated with the development of delirium include old age, infection, pre-existing dementia, pre-existing depression, hypoxaemia and reduced cerebral oxygen saturation, anaemia, drug withdrawal (eg alcohol, benzodiazepines), fluid and electrolyte imbalance, unrelieved pain and some drugs — for example, those with central anticholinergic activity (eg atropine, tricyclic antidepressants, major tranquilizers, some antiemetics), benzodiazepines, opioids, ketamine, oral hypoglycaemics, NSAIDs and anticonvulsants (Aakerlund & Rosenberg, 1994; Moore & O'Keeffe, 1999; Morrison et al, 2003 **Level III-2**; Alagiakrishnan & Wiens, 2004; Bitsch et al, 2006; Fong et al, 2006; Vaurio et al, 2006; Casati et al, 2007; Greene et al, 2009; Morimoto et al, 2009). While delirium is associated with early postoperative cognitive dysfunction, it may not have a long-term effect (Rudolph et al, 2008 **Level IV**).

Measurement of pain

Patient self-report measures of pain

Unidimensional measures of pain intensity (see Section 2) are more commonly used to quantify pain in the acute pain setting than multidimensional measures. Unidimensional measures used in younger adult populations, and which have been shown to be appropriate for use in the older patient, include the verbal numerical rating scale (VNRS), Faces Pain Scales, verbal descriptor scale (VDS) and the numerical rating scale (NRS; a calibrated VAS), with more equivocal support for use of the VAS.

In a comparison of five pain scales — VAS, VNRS, NRS, VDS and FPS — in an experimental setting, all the scales could effectively discriminate different levels of pain sensation in older people. However the VDS was the most sensitive and reliable and considered to be the best choice in the older adult, including those with mild-to-moderate cognitive impairment, although it ranked second to the NRS for patient preference (Herr et al, 2004 **Level III-2**).

In a comparison of VAS, VDS and NRS, in younger and older patients using PCA after surgery, the NRS was also the preferred pain scale in both patient groups, with high reliability and validity, although the VDS also had a favourable and similar profile; use of the VAS in the older patients resulted in high rates of unscorable data and low validity (Gagliese et al, 2005 **Level III-2**).

Similarly, after a comparison of the Faces Pain Scale and Red Wedge Scale (RWS) in older patients (65 years or older) after cardiac surgery, when VAS and VDS were also measured in each patient, the VDS was shown to be the most reliable, followed by the RWS; the VAS was the least suitable (Pesonen et al, 2008 **Level III-1**). Using the same comparisons in patients aged 76 to 96 years with non-surgical pain that included an acute component, it was shown that those with normal cognitive function were able to use all fours scales well, while only the VDS

(using familiar words such as none, slight, moderate, severe and unbearable) could be used with reasonable success in patients with mild, moderate and severe cognitive impairment (Pesonen et al, 2009 **Level III-2**). That the VDS may be of most use has been confirmed by other studies (Closs et al, 2004 **Level III-2**; Herr et al, 2004 **Level III-2**).

Self-assessment pain scales can be used reliably in most older patients with mild-to-moderate cognitive impairment, and in a significant number of patients with severe impairment, although a trial of different scales may be warranted (Pautex et al, 2005) and the patients may need more time to understand and respond to questions regarding pain (Gagliese & Melzack, 1997). 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 (Herr et al, 2006).

Other measures of pain

Assessment of pain in non-communicative 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 severity. In cognitively intact adults some of these behaviours have been shown to correlate reasonably well with patient self-report of pain (Bell, 1997). However, they may not always be valid indicators of pain in the non-verbal adult (Farrell et al, 1996) and can be difficult to interpret (Herr et al, 2006).

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 et al, 2006). More than 20 different observational pain assessment scales have been developed and used in patients with varying degrees of dementia. Examples include: Faces Pain Scales (Herr et al, 2004); Abbey Pain Scale (Abbey et al, 2004), Pain Assessment in Advanced Dementia (PAINAD, a simple, reliable and validated five-item observational tool) (Warden et al, 2003; Leong et al, 2006), Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) (Fuchs-Lacelle & Hadjistavropoulos, 2004) and Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID) (Husebo et al, 2007). For a more detailed and critical review of 10 pain-assessment tools for use with non-verbal adults see Herr et al (Herr et al, 2006).

11.2.4 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; these patients, because of their age, comorbidities, or concurrent medications, 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 Sections 11.2.4 and 11.2.5 concentrate on the use of analgesic drugs and techniques in the older patient, as with other patients, physical and psychological strategies should also be employed.

Non-selective non-steroidal anti-inflammatory drugs, coxibs and paracetamol

Older patients are more likely to suffer adverse gastric and renal side effects following administration of nsNSAIDs and may also be more likely to develop cognitive dysfunction (Pilotto et al, 2003; Peura, 2004; Juhlin et al, 2005). In elderly (age over 65 years) medical inpatients, use of nsNSAIDs was a significant risk factor for renal function deterioration; other risk factors were loop diuretics, hypernatraemia and low serum albumin levels (Burkhardt et al, 2005).

Coxibs have a significantly lower incidence of upper gastrointestinal complications and have no antiplatelet effects, which might be of some advantage in the older patient; the risk of other adverse effects, including effects on renal function and exacerbation of cardiac failure,

are similar to nsNSAIDs (Argoff, 2005; Savage, 2005). Compared with paracetamol and placebo, administration of parexocib after orthopaedic surgery resulted in a significant but transient reduction in creatinine clearance at 2 hours; there was no difference at 4 and 6 hours (Koppert et al, 2006 **Level II**).

Longer-term use of high doses of both coxibs and nsNSAIDs (possibly apart from naproxen) appear to increase the risk of cardiovascular (CV) and cerebrovascular events and regular use of nsNSAIDs may interfere with the clinical benefits of low-dose aspirin (see Section 4.2). Extra precautions are therefore required in older patients.

There is no consistent evidence on the effect of ageing on clearance of paracetamol but there is probably no need to reduce the dose given in older people (Divoll et al, 1982; Miners et al, 1988; Bannwarth et al, 2001).

Opioids and tramadol

Despite the age-related changes listed in Table 11.4, there may be few differences in fentanyl pharmacokinetics (Scott & Stanski, 1987) or the pharmacokinetics of morphine and oxycodone (Villesen et al, 2007) and buprenorphine (Kress, 2009) in the older patient.

After oral administration, the bioavailability of some drugs may be increased, leading to relatively higher blood concentrations (Mangoni & Jackson, 2004).

Opioid dose

Older patients require less opioid than younger patients to achieve the same degree of pain relief (Macintyre & Jarvis, 1996 **Level IV**; Woodhouse & Mather, 1997 **Level IV**; Gagliese et al, 2000 **Level IV**; Upton et al, 2006), 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 & Upton, 2008).

In the clinical setting there is evidence of an age-related 2- to 4-fold decrease in morphine and fentanyl requirements (Macintyre & Jarvis, 1996 **Level IV**; Woodhouse & Mather, 1997 **Level IV**; Gagliese et al, 2000 **Level IV**). This is in agreement with the findings by Scott and Stanski (Scott & Stanski, 1987) that the sensitivity of the brain to fentanyl and alfentanil was increased by 50% in older people. It has been suggested that doses of fentanyl, sufentanil and alfentanil should all be reduced by up to 50% in older patients (Shafer, 1997); reductions in the doses of other opioids is also advised (Macintyre & Upton, 2008).

In patients over 75 years the elimination half-life of tramadol was slightly prolonged (Scott & Perry, 2000). Lower daily doses have been suggested (Barkin et al, 2005).

Opioid metabolites

Reduced renal function in the older patient could lead to a more rapid accumulation of active opioid metabolites (eg M6G, M3G, hydromorphone-3-glucuronide, nordextropropoxyphene, norpethidine, desmethyl-tramadol) (see Section 4.1).

Side effects of opioids

The fear of 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 (ie 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 et al 1994). In older people, fentanyl may cause less postoperative cognitive dysfunction than morphine (Herrick et al, 1996 **Level II**) and less confusion (Narayanaswamy et al, 2006), although administration of an appropriate opioid medication is

often associated with higher levels of cognitive function compared with cognitive function if postoperative pain is undertreated (Lynch et al, 1998; Morrison & Siu, 2000). Herrick at al (Herrick et al, 1996 **Level II**) reported no statistically significant difference in the incidence of confusion, but the rates were 4.3% for patients given fentanyl and 14.3% for those receiving morphine. Pethidine was associated with a higher incidence of confusion compared with morphine (Adunsky et al, 2002 **Level III-3**) and a variety of other opioids (Morrison et al, 2003 **Level III-2**).

Local anaesthetics

Age-related decreases in clearance of bupivacaine (Veering et al, 1987; Veering et al, 1991) and ropivacaine (Simon et al, 2006) have been shown. Older patients are 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 & Glass, 2003).

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 et al, 2002; Magnusson et al, 2002; Vuyk, 2003). 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 et al, 2008). 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.

Tricyclic antidepressants

Clearance of tricyclic antidepressant (TCA) drugs may decrease with increasing patient age and lower initial doses are recommended in older people (Ahmad & Goucke, 2002). Older people may be particularly prone to the side effects of TCAs (Ahmad & Goucke, 2002; Fine, 2004) including sedation, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention and gait disturbances which may increase the risk of falls. Adverse effects appear to be most common with amitriptyline and nortriptyline may be preferred in this patient group (Ahmad & Goucke, 2002; Argoff, 2005; McGeeney, 2009). In addition, clinical conditions that may require TCAs to be administered with caution are more common in older people and include prostatic hypertrophy, narrow angle glaucoma, CV disease and impaired liver function; ECG abnormalities may be a contraindication to the use of TCAs in older people (Ahmad & Goucke, 2002).

Anticonvulsants

As with TCAs, initial doses of anticonvulsant agents should be lower than for younger patients and any increases in dose should be titrated slowly (Ahmad & Goucke, 2002). As renal function declines with increasing age, elimination of gabapentin and pregabalin may be reduced and lower doses will be required (McGeeney, 2009).

The 'second generation' drugs such as gabapentin and topiramate may be less likely to result in adverse effects in the older patient (Argoff, 2005). The relatively high frequency of side effects such as somnolence and dizziness with pregabalin may be a problem in this group of patients (Guay, 2005). However, other features of gabapentin and pregabalin, such as a lower risk of drug-drug interactions, lower (less than 3%) protein binding, no hepatic metabolism and the lack of any need to monitor liver function and blood count on a regular basis, means that these drugs may be well-suited to the older patient population (McGeeney, 2009).

11.2.5 Patient-controlled analgesia

Many pharmacological and non-pharmacological treatments may be used in the management of acute pain in older people, either alone or in combination. However, differences between older and younger patients are more likely to be seen in treatments using analgesic drugs.

PCA is an effective method of pain relief in older people (Gagliese et al, 2000; Mann et al, 2000; Mann et al, 2003). Compared with younger patients (mean age 39 years), older patients (mean age 67 years) self-administered less opioid than the younger group, but there were no differences in pain relief, satisfaction with pain relief and level of control, or concerns about pain relief, adverse drug effects, risks of addiction or use of the equipment (Gagliese et al, 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 et al, 1990 **Level II**). In older patients PCA also resulted in significantly lower pain scores compared with intermittent SC morphine injections (Keita et al, 2003 **Level II**).

11.2.6 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 7.2). Older patients given PCEA (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 et al, 2000 **Level II**). 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 et al, 2005 **Level II**).

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. High thoracic epidural analgesia (TEA) also improved left ventricular function (Schmidt et al, 2005 **Level III-3**; Jakobsen et al, 2009 **Level III-3**) and myocardial oxygen availability (Lagunilla et al, 2006 **Level II**) in patients with ischaemic heart disease prior to coronary artery bypass surgery (CABG) surgery, and partly normalised myocardial blood flow in response to sympathetic stimulation (Nygard et al, 2005 **Level III-3**). However, epidural analgesia in patients undergoing CABG surgery has not been shown to improve ischaemic outcome (Barrington et al, 2005 **Level II**).

After a small study during and after surgery for hip fracture, older patients who had received epidural bupivacaine/fentanyl analgesia had significantly better pain relief than those who were given IM oxycodone; there was no difference in the number of patients who developed postoperative ischaemia or hypoxia, however the number of episodes and total duration of ischaemia in each patient was markedly greater in the oxycodone group (Scheinin et al, 2000 **Level II**).

Epidural morphine requirements decrease as patient age increases (Ready et al, 1987). However, a comparison of fentanyl PCEA in patients aged over 65 years with those aged 20 to 64 years showed no difference in fentanyl requirements although pain relief on coughing (at 24 hours) was better in the older patient group; there was no difference in the incidence of pruritus (Ishiyama et al, 2007 **Level III-3**).

Age is also a determinant of the spread of local anaesthetic in the epidural space and the degree of motor blockade (Simon et al, 2002; Simon et al, 2004), thus smaller volumes will 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 blockade decreased as patient age increased (Li et al, 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 & Upton, 2008).

Older patients may be more susceptible to some of the adverse effects of epidural analgesia, including hypotension (Crawford et al, 1996; Simon et al, 2002; Veering, 2006).

11.2.7 Intrathecal opioid analgesia

Intrathecal 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 et al, 2009 **Level I**). Advanced patient age is considered by some to be a risk factor for respiratory depression and it has been suggested that patients over the age of 70 years be monitored in an intensive care setting (Gwirtz et al, 1999 **Level IV**). However, others report that older patients (average age 69 years) given up to 200 mcg intrathecal 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 acute pain service (APS) according to strict guidelines (Lim & Macintyre, 2006 **Level IV**).

The 'optimal' dose of intrathecal morphine that should be given to older patients remains unknown and any evidence for the 'best' dose remains inconsistent. Intrathecal morphine doses of 200 mcg given in addition to general anaesthesia in older patients (average age 70 years) undergoing abdominal aortic surgery led to better postoperative analgesia and reduced postoperative analgesia requirements compared with those given general anaesthesia only; no conclusion could be made about adverse effects as total patients numbers were small (Blay et al, 2006 **Level II**).

A comparison of three doses of intrathecal 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; there was no difference seen in the incidences of nausea and vomiting or respiratory depression (Murphy et al, 2003 **Level II**).

Use of intrathecal morphine in addition to IV PCA morphine after colorectal surgery led to better pain relief and lower PCA morphine requirements compared with PCA morphine alone, but sedation was increased and there were no differences in time to ambulation, duration of hospital stay or incidence of confusion (Beaussier et al, 2006 **Level II**).

11.2.8 Other regional analgesia

Possible advantages of regional blockade in older patients include a reduction in the incidence of side effects compared with central neuraxial blockade (Zaric et al, 2006 **Level II**). Patient outcome may also be improved when older patients receive regional rather than opioid analgesia after surgery. After fixation of a fractured hip, 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 just paracetamol and metamizol, 28% of whom required additional morphine analgesia (Rosario et al, 2008 **Level IV**).

The duration of action of sciatic nerve (Hanks et al, 2006 **Level III-2**) and brachial plexus blocks (Paqueron et al, 2002 **Level III-2**) is prolonged in the older patient.

In older (greater than 65 years of age) patients undergoing urological surgery via a flank incision, paravertebral blockade 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 et al, 2005 **Level II**).

Unlike epidural analgesia, age did not influence the spread of bupivacaine in the thoracic paravertebral space (Cheema et al, 2003 **Level III-2**).

Key messages

1. Experimental pain thresholds to a variety of noxious stimuli are altered in older people; there is also a reduction in tolerance to pain (**Q**) (**Level I**).
2. PCA and epidural analgesia are more effective in older people than conventional opioid regimens (**U**) (**Level II**).
3. Reported frequency and intensity of acute pain in clinical situations may be reduced in the older person (**U**) (**Level III-2**).
4. 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 may be preferred (**S**) (**Level III-2**).
5. Undertreatment of acute pain is more likely to occur in cognitively impaired patients (**N**) (**Level III-2**).
6. There is an age-related decrease in opioid requirements; significant interpatient variability persists (**U**) (**Level IV**).
7. The use of nsNSAIDs and coxibs in older people requires extreme caution; paracetamol is the preferred non-opioid analgesic (**U**) (**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, 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**).

☑ The age-related decrease in opioid requirements is related more to the changes in pharmacodynamics that accompany aging than to the changes in pharmacokinetics (**N**).

11.3 Aboriginal and Torres Strait Islander peoples

Aboriginal and Torres Strait Islander peoples are a heterogeneous group both in terms of their links to traditional cultural beliefs and links to the land, as well as in their degree of urbanisation and understanding of Western biomedical concepts. The appropriate assessment and treatment of pain in Aboriginal and Torres Strait Islander patients needs to take into account a number of factors including cultural and language differences between the patient and health care worker.

A study looking at issues associated with pain management in the palliative care setting in rural and remote Aboriginal peoples interviewed patients, carers, Aboriginal health care workers and other healthcare staff (McGrath, 2006 **Level IV**). While the focus was on palliative care, many of the conclusions and comments made can be extrapolated to pain management in general in this group of patients. The authors reported that Aboriginal patients may have a higher pain threshold and be less likely to complain of pain (particularly men, who may not want to appear weak by expressing their pain); there was also a fear of Western medicine. Pain may also be seen as a punishment for some misdeed (Honeyman & Jacobs, 1996 **Level IV**).

The prevalence of musculoskeletal pain in general (Vindigni et al, 2004 **Level IV**) and back pain specifically (Honeyman & Jacobs, 1996 **Level IV**) was reported to be high in non-urban Australian Aboriginal communities. However, it was uncommon for Aboriginal people to present with pain as a complaint and public expression of pain and illness behaviours were uncommon, including after painful injections in children and after acute injuries in adults (Vindigni et al, 2004 **Level IV**).

Aboriginal people may be reserved and unobtrusive when experiencing pain and health professionals may mistakenly label them as stoic (National Palliative Care Program, 2006). Such behaviour may lead to undertreatment of pain, and cultural issues, including marked shyness with strangers (especially where there is a gender difference), gratuitous concurrence (saying 'yes' to be polite), different health belief systems and language differences, may further complicate management (Howe et al, 1998 **Level IV**). Aboriginal people place a lot of importance on non-verbal communication so that words may be used only infrequently, they may avert their eyes or turn their head away when questions are asked, hide under a blanket or feign sleep (National Palliative Care Program, 2006).

Past unfortunate experiences with healthcare services can result in some not wishing to be cared for in an acute care hospital, even though their treatment requires admission. There may also be concerns about the use of morphine for the treatment of pain as some may believe that morphine hastens death and will therefore refuse to take pain relief medication; discussions with the patient as well as family may be required and a specific person (as well as the patient) may need to give consent before morphine is administered (National Palliative Care Program, 2006). Therefore, despite having significant pain, some Aboriginal patients may present late depending on access to health care facilities and attitudes to Western biomedical models of health care. Provision of quality analgesia requires sensitivity to cultural practices and beliefs, and behavioural expression of pain. Use of Aboriginal interpreters, health workers and liaison officers to assess pain is beneficial as in some cases English skills, although present, are limited and interpreters can help with non-verbal communication issues.

A study of Aboriginal women after surgery found that they had culturally appropriate ways of expressing and managing pain that were not well-understood by non-Aboriginal nurses (Fenwick & Stevens, 2004 **Level IV**). It was reported that the Aboriginal women were generally

silent about their pain even when asked, and that, in part at least, this arose from fear of pain (including its origin and significance in relation to themselves and the external world) and a belief that the nurses would know about the pain they were experiencing so that there was no need to tell them. In addition, access to appropriate pain relief may be more limited. In one Central Australian hospital, fewer Aboriginal patients were referred to the APS than non-Aboriginal patients, despite being the predominant patient group in that institution (Fenwick & Stevens, 2004).

Pain assessment by some conventional methods may not be appropriate. A verbal descriptor scale but not a numerical rating scale was a useful measure of pain (Sartain & Barry, 1999 **Level III-3**). This is consistent with the fact that specific numbers and numerical scales are not part of many Aboriginal language systems and more descriptive terms are used for quantification.

Aboriginal and Torres Strait Islander peoples can use PCA effectively if given adequate information about the technique. However, communication is often difficult and so techniques such as continuous opioid infusion techniques tend to be used more commonly in Aboriginal and Torres Strait Islander peoples than in other patient groups (Howe et al, 1998 **Level IV**). In addition, consent for invasive procedures such as epidural analgesia may be difficult to obtain; there may be communication difficulties or the patient may need to discuss the proposed consent with other members of the family.

Medical comorbidities such as renal impairment and diabetes are more common in Aboriginal and Torres Strait Islander peoples as well as New Zealand Maoris (Howe et al, 1998 **Level IV**; Bramley et al, 2004 **Level IV**; McDonald & Russ, 2003 **Level IV**). This may affect the choice of analgesics (see Section 11.6).

Key messages

1. The verbal descriptor scale may be a better choice of pain measurement tool than verbal numerical rating scales (**U**) (**Level III-3**).
2. Medical comorbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander peoples and New Zealand Maoris, and may influence the choice of analgesic agent (**U**) (**Level IV**).
3. Clinicians should be aware that pain may be under-reported by this group of patients (**U**) (**Level IV**).

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

☑ Communication may be hindered by social, language and cultural factors (**U**).

☑ Provision of quality analgesia requires sensitivity to cultural practices and beliefs, and behavioural expressions of pain (**N**).

11.4 Different ethnic and cultural groups

Australia is a culturally diverse nation with a relatively large immigrant population. In the 2006 Census, 71% of people were born in Australia and English was the only language spoken at home by 79% of these. The four most common languages used at home other than English were Chinese languages (2.3%), Italian (1.6%), Greek (1.3%) and Arabic (1.2%) (Australian Bureau of Statistics, 2006). In many other countries in the world there is also significant cultural and ethnic diversity.

There is a need to understand different cultures when considering pain assessment and management. This extends beyond the language spoken, because an individual's culture also influences their beliefs, expectations, methods of communication and norms of behaviour, as do the culture and attitudes of the health care provider (Green et al, 2003; Davidhizar & Giger, 2004). It is important for clinicians to be aware of both verbal and non-verbal indicators of pain and be sensitive to both emotive and stoic behaviours in an individual's response. Some cultural attitudes may limit pain-relief seeking behaviour. 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 (Green et al, 2003).

Communication problems may make it difficult to adequately help non-English speaking 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 et al, 1998 **Level IV**). When language is an obstacle, care should be used when enlisting non-professional interpreters to translate, because family members and friends of the patient may 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 the experimental and clinical settings have been reported. A review of studies investigating differences in responses to experimentally induced pain found that cultural differences influenced pain tolerance but not pain threshold, and concluded that intrinsic difficulties in the translation of pain descriptors between different cultures makes pain tolerance the more relevant pain measure (Zatzick & Dimsdale, 1990). 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 et al, 2007 **Level III-2**). Similarly, African American women were more sensitive to ischaemic pain than non-Hispanic white women (Klatzkin et al, 2007 **Level III-2**). However, the implications of these results for the clinical setting are unclear.

A systemic review looked at the effect of patient race and ethnicity on pain assessment and management across a variety of clinical pain settings (Cintron & Morrison, 2006 **Level III-3**). 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 white patients.

Differences have been reported in patients of different ethnic groups attending emergency departments and requiring analgesia. A review of the treatment of pain in United States emergency departments showed that opioid prescribing for pain-related visits increased over the period 1993 to 2005, but that white patients with pain were more likely than black, Hispanic or Asian patients to receive an opioid, and that these differences did not diminish over time (Pletcher et al, 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 et al, 1996 **Level III-3**; Salamonson & Everett, 2005 **Level III-3**), although the actual self-administered doses of opioid were similar (Ng et al, 1996 **Level IV**). After Caesarean section, 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, body mass index, and duration of operation (Tan et al, 2008 **Level III-2**).

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 Section 2); the NRS, for example has been translated and validated in many languages (Davidhizar & Giger, 2004). 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 (British Pain Society, 2009).

While there is some evidence of differences in pain reports and analgesic use in different cultures or ethnic groups, it should not be used to stereotype patients or promote assumptions about differences in assessment and management of pain or response to pain therapies. Provision of effective analgesia requires sensitivity to a patient's cultural practices and beliefs, and their behavioural expression of pain. However, the large inter-individual 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 or ethnic background.

Key messages

1. Disparities in assessment 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.

☑ Ethnic and cultural background 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**).

☑ Differences between different ethnic and cultural groups should not be used to stereotype patients and lead to assumptions about responses to pain or pain therapies; pain assessment and management should be done on an individual patient basis (**N**).

11.5 THE PATIENT WITH OBSTRUCTIVE SLEEP APNOEA

Acute pain management in a patient with obstructive sleep apnoea (OSA) presents two main problems: choice of the most appropriate form of analgesia and the most suitable location in which to provide it. These difficulties arise primarily from the risk of exacerbating OSA by the administration of opioid analgesics.

Approximately one in five adults have at least mild OSA, one in fifteen have moderate or worse OSA and 75% to 80% of those who could benefit from treatment remain undiagnosed (Young et al, 2004). Therefore, many patients with undiagnosed OSA will have had treatment for acute pain without significant morbidity. This implies that the overall risk is quite low.

Despite the low risk, it has been reported that patients with OSA may be at increased risk of postoperative complications compared with other patients. However, it is possible that the risk lies more with the body size and build of the patient, especially those who are morbidly obese, rather than the fact they have a diagnosis of OSA (Loadsman 2009).

A significantly higher incidence of serious postoperative complications (including unplanned ICU admissions, reintubations, and cardiac events) and longer hospital stay after joint replacement surgery was reported in patients with OSA compared with matched controls

(Gupta et al, 2001 **Level III-3**). However, after outpatient surgery, a preoperative diagnosis of OSA was not associated with an increase in adverse events or unplanned hospital admission (Sabers et al, 2003 **Level III-3**).

Differences in the incidence of oxygen desaturation have also been reported. A study of 2467 patients used three different screening tools to determine if patients were at risk of OSA and reported an incidence of patients at high risk of OSA of between 28% and 33%, depending on the tool used; of the 416 patients consenting to the study, those identified as high risk were also more likely to develop postoperative complications (Chung, Yegneswaran et al, 2008 **Level III-2**). Similarly, screening of 2206 patients reported that 11% were at high risk of having OSA; data from 115 of these OSA-risk patients showed that they had a higher incidence of episodes of oxygen desaturation (Gali et al, 2007 **Level III-2**).

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.

Opioid administration in the postoperative period is known to lead to episodes of pronounced oxygen desaturation while the patient is asleep, which are much more commonly a result of obstructive and central apnoea than a decrease in respiratory rate (Catley et al, 1985 **Level III-2**; Clyburn et al, 1990 **Level III-3**).

However, 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 (Blake et al, 2008; Gross et al, 2006; Chung, Yuan et al, 2008).

A comparison of patients assessed (by history, body mass index and physical examination) to be at risk of having OSA (n = 33) with control patients (n = 30) has shown that patients classified as OSA risk have more obstructive events in the postoperative period (Blake et al, 2008 **Level III-2**). All patients were continuously monitored for 12 hours during the first postoperative night. Those classified as OSA risk had significantly more episodes of obstructive apnoea than control patients (39±22 vs 14±10 events/ hour) and spent more time with oxygen saturation levels lower than 90% (Blake et al, 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 apnoeas (Blake et al, 2008 **Level III-2**). The correlation between a classification of high risk for OSA and a high number of oxygen desaturation each hour was also reported in patients monitored for 48 hours after surgery (Gali et al, 2009) **Level III-3**).

Evidence of the risks associated with analgesia and OSA is very limited. In a number of case reports, the use of opioid medications in patients with OSA appeared to be a common factor in most of the cases where complications, including death, have been reported following intermittent IM, patient-controlled IV and epidural analgesia (Reeder et al, 1991; VanDercar et al, 1991; Etches, 1994; Ostermeier et al, 1997; Cullen, 2001; Lofsky, 2002; Parikh et al, 2002). However, caution is required when interpreting these reports. Most of the cases involved what appear to be excessive opioid doses (eg excessive bolus dose or a background infusion with PCA) and/or inadequate monitoring for respiratory depression (eg it appeared here was an over-reliance on respiratory rate; sedation levels were not checked and/or increasing sedation was not recognised as an early indicator of respiratory depression) and/or protocol failures and/or concurrent administration of sedatives (Macintyre, 2005).

A report by an American Society of Anesthesiologists task force looking at the perioperative management of patients with OSA concluded that there was no good evidence that can be used to evaluate the effects of various postoperative analgesia techniques in patients with OSA (Gross et al, 2006) and no good comparisons between pure agonist opioids such as

morphine and tramadol or non-opioid analgesics. 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 hour after surgery (Hullett et al, 2006 **Level II**). In patients with a body mass index of 28 or more 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 more than 15 respiratory events/ hour and total morphine dose (Blake et al, 2009 **Level II**).

Expert opinion, however, consistently suggests that non-opioid analgesics and regional techniques should be considered, either as an alternative to opioids or to help limit the amount of opioid required (Benumof, 2001; Loadsman & Hillman, 2001; Gross et al, 2006; Chung, Yuan et al, 2008).

Morbid obesity is strongly associated with OSA (Young et al, 2004) and, using polysomnography, OSA was identified in 71% of patients presenting for bariatric surgery (Frey & Pilcher, 2003 **Level IV**). The use of PCA with appropriate bolus doses and monitoring in morbidly obese patients has been reported to be no less safe than regional or other systemic opioid analgesic techniques, although the studies lacked power (Kyzer et al, 1995 **Level II**; Choi et al, 2000 **Level IV**; Charghi et al, 2003 **Level IV**). In a comparison of morbidly obese patients, each of whom had a preoperative sleep study, with (n = 31) and without (n = 9) OSA undergoing laparoscopic bariatric surgery, episodes of postoperative hypoxaemia were frequent despite supplemental oxygen; there was no significant difference between OSA and non-OSA patients (Ahmad et al, 2008 **Level III-2**).

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 et al, 1990; Landsberg et al, 2001). As patients with OSA are more at risk of hypoxaemia after surgery or if given opioids, the use of supplemental oxygen would seem appropriate (Gross et al, 2006) despite concerns about reducing respiratory drive during the apnoeic periods (Lofsky, 2002).

The use of continuous positive airway pressure (CPAP) may help to reduce the postoperative risks and is recommended in patients with OSA (Benumof, 2001; Loadsman & Hillman, 2001). The effectiveness of CPAP (used appropriately) in the prevention of OSA in the postoperative setting is supported by case reports (Reeder et al, 1991; Rennotte et al, 1995; Mehta et al, 2000). Concerns about the risk of CPAP causing gastric distension and anastomotic leaks after upper GI surgery appear to be unfounded (Huerta et al, 2002 **Level III-2**).

The effective use of CPAP in the setting of acute pain management may require 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 (Reeder et al, 1991; Rennotte et al, 1995; Mehta et al, 2000).

Advice on the most appropriate environment for the care of OSA patients requiring analgesia is based on expert opinion only and suggests that the severity of OSA, efficacy of any current therapy, relevant comorbidities (eg cardiac) and the analgesia required be taken into consideration (Benumof, 2001; Loadsman & Hillman, 2001; Gross et al, 2006).

Key messages

1. Patients with obstructive sleep apnoea may at higher risk of complications after some types of surgery (**Q**).
2. Patients with obstructive sleep apnoea have an including an increased risk of obstructive episodes and desaturations (**N**) (**Level III-2**).
3. Morbidly obese patients undergoing bariatric surgery may be at increased risk of postoperative hypoxaemia independent of a diagnosis of obstructive sleep apnoea (**N**) (**Level III-2**).
4. Continuous positive airway pressure does not increase the risk of anastomotic leak after upper gastrointestinal surgery (**U**) (**Level III-2**).

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

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

11.6 The patient with concurrent hepatic or renal disease

The clinical efficacy of most analgesic drugs is altered by impaired renal or hepatic function, not simply because of altered clearance of the parent drug, but also through accumulation of toxic or therapeutically active 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 drugs used in pain management, as well as alterations that might be required in analgesic drug regimens, is given in Tables 11.5 and 11.6.

11.6.1 Patients with renal disease

The degree to which analgesic drug regimens require alteration in patients with renal impairment depends largely on whether the drug has active metabolites that are dependent on the kidney for excretion or if the drug may further impair renal function.

There is some limited information about the ability of dialysis to clear the drugs 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; a higher degree of protein binding and use of lower-efficiency dialysis techniques will reduce removal (Dean, 2004).

The available data indicates the following (see Table 11.5 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 drugs delivers 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, codeine, hydromorphone, methadone, morphine and tramadol have been used in patients with renal disease but depending on the degree of impairment and, in the case of local anaesthetics, whether or not administration is prolonged, may require a reduction in dose. Levobupivacaine, with similar clearance mechanisms, and ropivacaine may be safer than bupivacaine because of a higher therapeutic ratio.
- NSAIDs (both nsNSAIDs and coxibs), dextropropoxyphene and pethidine should not be used in the presence of significant renal impairment.

11.6.2 Patients with hepatic disease

Not all patients with hepatic disease have impaired liver function. In patients with hepatic impairment, most analgesic drugs have reduced clearance and increased oral bioavailability, but the significance of these changes in the clinical setting has not been studied in depth. The available data indicates the following (see Table 11.6 for references).

- While there are limited data, dose adjustments are usually not required for alfentanil, buprenorphine, fentanyl, morphine, oxycodone and sufentanil.
- 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 greatly prolonged clearance.
- 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.

Key messages

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**).

Table 11.5 Analgesic drugs in patients with renal impairment

Drug	Comments	Recommendations NB doses must still be titrated to effect for each patient	References
Opioids			
Alfentanil	No active metabolites 92% protein bound; increases in free fraction may result from alterations in protein binding	No dose adjustment required unless renal failure is severe	Craig & Hunter, 2008 Davies et al, 1996 Mercadante & Arcuri, 2004 Murtagh et al, 2007

Drug	Comments	Recommendations NB doses must still be titrated to effect for each patient	References
Buprenorphine	Pharmacokinetics unchanged; predominantly biliary excretion of metabolites Pharmacokinetics also unchanged with dialysis	No dose adjustment required	Boger, 2006 Davies et al, 1996 Filitz et al, 2006 Hand et al, 1990 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004
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	Dose adjustment recommended or use an alternative opioid	AMH, 2008 Craig & Hunter, 2008 Davies et al, 1996 Dean, 2004 Mercadante & Arcuri, 2004
Dextro-propoxyphene	Accumulation of active metabolite (nordextropropoxyphene) can lead to CNS and cardiovascular system toxicity Blood concentrations not significantly changed during dialysis	Use of alternative agent recommended	AMH, 2008 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 Murtagh et al, 2007
Dihydrocodeine	Metabolic pathway probably similar to codeine	Insufficient evidence: use not recommended	Craig & Hunter, 2008 Davies et al, 1996 Murtagh et al, 2007
Fentanyl	No active metabolites Not removed to any significant degree by dialysis	No dose adjustment required; may be used in patients with severe renal impairment	AMH, 2008 Craig & Hunter, 2008 Dean, 2004 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 Murtagh et al, 2007
Hydromorphone	Neurotoxicity from accumulation of H3G possible H3G is effectively removed during dialysis	Dose adjustment recommended or use alternative opioid	AMH, 2008 Davison & Mayo, 2008 Dean, 2004 Mercadante & Arcuri, 2004

Drug	Comments	Recommendations NB doses must still be titrated to effect for each patient	References
Methadone	Methadone and its metabolites are excreted in urine and faeces; in anuric patients it may be mostly in faeces High protein binding, high volume of distribution and moderate water solubility would suggest that it is likely to be poorly removed by dialysis	Dose adjustment may be required in severe renal impairment	AMH, 2008 Davies et al, 1996 Dean, 2004 Launay-Vacher et al, 2005 Lugo et al, 2005 Mercadante & Arcuri, 2004 Murtagh et al, 2007
Morphine	Major metabolites M3G and M6G excreted via kidney and accumulate in renal impairment 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	Dose adjustment recommended or use alternative opioid	AMH, 2008 Angst et al, 2000 Craig & Hunter, 2008 Davies et al, 1996 Dean, 2004 D'Honneur et al, 1994 Hanna et al, 1993 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 Pauli-Magnus et al, 1999 Richtsmeier et al, 1997
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 Higher blood concentrations of oxycodone and metabolites with moderate to severe renal impairment; half life significantly increased in endstage renal disease Oxycodone and its metabolites are dialyzable	No dose adjustment required in most patients	AMH, 2008 Dean, 2004 Kalso, 2005 Lee et al, 2005 Riley et al, 2008

Drug	Comments	Recommendations NB doses must still be titrated to effect for each patient	References
Pethidine	Norpethidine is the only active metabolite and is renally excreted; it is dialyzable Accumulation of norpethidine can lead to neuroexcitation including seizures	Use of alternative agent recommended	AMH, 2008 Craig & Hunter, 2008 Davies et al, 1996 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 Simopoulos et al, 2002
Sufentanil	Minimally active metabolite	No dose adjustment required	AMH, 2008 Davis et al, 1988 Murphy, 2005
Tramadol	Increased tramadol-like effects from active metabolite O-desmethyltramadol (M1) Tramadol is removed by dialysis	Dose adjustment recommended Use of alternative agent recommended with significant renal impairment	AMH, 2008 Launay-Vacher et al, 2005 Mercadante & Arcuri, 2004 MIMS, 2008
Other drugs			
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	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)	AMH, 2008 Crews et al, 2002 De Martin et al, 2006 Jokinen, 2005 Rice et al, 1991
Paracetamol	Terminal elimination half-life may be prolonged Is dialysable	May need to increase dose interval if renal impairment is severe Weak evidence that it may increase the rate of progression to chronic renal failure	AMH, 2008 Craig & Hunter, 2008 Launay-Vacher et al, 2005

Drug	Comments	Recommendations NB doses must still be titrated to effect for each patient	References
NsNSAIDs and coxibs	Can affect renal function Behaviour during dialysis not clearly elucidated for most	Use with caution in patients with mild renal impairment and avoid in patients with severe renal impairment	Launay-Vacher et al, 2005
Clonidine	Half-life is increased in severe renal failure 50% metabolised by the liver; remained excreted unchanged by the kidney	Limited data; dose adjustment has been recommended	Khan et al, 1999 Lowenthal et al, 1993
Tricyclic antidepressants	Amitriptyline is metabolised in the liver to nortriptyline, the active agent Not significantly removed by dialysis	Limited data; metabolite accumulation may occur and increase the risk of side effects but little evidence to indicate need for dose reduction	Lieberman et al, 1985 Murphy, 2005 Dargan et al, 2005
Ketamine	Dehydronorketamine levels are increased but it has only 1% of potency of ketamine Ketamine is not removed well by dialysis	Limited data; probable that no dose adjustment is required	Koppel et al, 1990
Gabapentinoids	Gabapentin: impaired renal function results in reduced clearance in direct proportion to creatinine clearance; about 35% cleared by dialysis	Dose adjustment recommended on basis of creatinine clearance	AMH, 2008 Blum et al, 1994 Wong et al, 1995
	Pregabalin: Impaired renal function results in reduced clearance in direct proportion to creatinine clearance; highly cleared by dialysis	Dose adjustment recommended on basis of creatinine clearance	AMH, 2008 Randinitis et al, 2003

Table 11.6 Analgesic drugs in patients with hepatic impairment

Drug	Comments	Recommendations NB doses must still be titrated to effect for each patient	References
Opioids			
Alfentanil	No significant difference in half-life found in children undergoing liver transplant	Limited data: no dose adjustment required	Davis et al, 1989
Buprenorphine	Lower blood concentrations of buprenorphine and norbuprenorphine	Limited data: no dose adjustment required	Johnson et al, 2005

Drug	Comments	Recommendations NB doses must still be titrated to effect for each patient	References
Dextro-propoxyphene	Reduced oxidation leading to reduced clearance	Limited data: dose adjustment may be required	Tegeder et al, 1999
Fentanyl	Disposition appears to be unaffected	Limited data: no dose adjustment required	Tegeder et al, 1999
Methadone	Increased half-life but limited significance	Limited data: no dose adjustment required in chronic stable liver disease	Lugo et al, 2005 Novick et al, 1985
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	In most patients no dose adjustment required	Kotb et al, 2005 Rudin et al, 2007
Oxycodone	Decreased oxycodone clearance with mild to moderate hepatic impairment	Limited data: no dose adjustment required in most patients	Kalso, 2005 Riley et al, 2008
Pethidine	Reduced clearance	Limited data: dose adjustment may be required; use not recommended	Tegeder et al, 1999
Sufentanil	No difference in clearance or elimination	No dose adjustment required	Chauvin et al, 1989 Tegeder et al, 1999
Tramadol	Reduced clearance	Limited data: dose adjustment may be required if impairment is severe	AMH, 2008 Tegeder et al, 1999 Kotb et al, 2008

Drug	Comments	Recommendations NB doses must still be titrated to effect for each patient	References
Other drugs			
Local anaesthetics	Amide-type local anaesthetics undergo hepatic metabolism and clearance may be reduced in hepatic disease Increased plasma concentrations of ropivacaine after continuous infusion but not single dose	Limited data: dose adjustment may be required with prolonged or repeated use	AMH, 2008 Bodenham & Park, 1990 Jokinen, 2005 Jokinen et al, 2007
Paracetamol	Metabolised in the liver; small proportion metabolised to the potentially hepatotoxic metabolite N-acetyl-p-benzoquinonemine. This is normally inactivated by hepatic glutathione. Clearance is reduced	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 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	AMH, 2008 Benson et al, 2005 Graham et al, 2005 Zapater et al, 2004
Tricyclic antidepressants	Amitriptyline is metabolised in the liver to nortriptyline, the active agent	Reduce dose if hepatic impairment is severe	AMH, 2008
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	Dose adjustment may be required; use not recommended in severe hepatic impairment	Ahmed & Siddiqi, 2006 AMH, 2008
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	Dose adjustment may be required; use not recommended in severe hepatic impairment	Ahmed & Siddiqi, 2006 AMH, 2008

11.7 THE OPIOID-TOLERANT PATIENT

11.7.1 Definitions and clinical implications

Misunderstandings in the terminology related to addiction (see Section 11.8), tolerance, and physical dependence may confuse health care providers and lead to inappropriate and/or suboptimal acute pain management. 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 et al, 2001).

Table 11.7 Definitions for tolerance, physical dependence and addiction

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.
Pseudoaddiction	Behaviours that may seem inappropriately drug seeking but are a result of undertreatment of pain and resolve when pain relief is adequate.

Source: Adapted from Weissman & Haddox (1989), the Consensus statement from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine (2001), Alford et al (2006) and Ballantyne and LaForge (2007).

To the above list should be added opioid-induced hyperalgesia (OIH). Both acute and chronic administration of opioids given to treat pain may paradoxically lead to OIH, with reduced opioid efficacy and increased pain. For a more detailed discussion of opioid tolerance and OIH see Section 4.1.3.

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 (Angst & Clark, 2006; Chang et al, 2007). It is also possible that different opioids vary in their ability to induce OIH and tolerance (see Section 4.1.3 and below under Opioid Rotation).

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 quantitative

sensory testing (QST) may show changes in pain thresholds and tolerability (Chang et al, 2007). In the experimental setting, patients with opioid-managed (morphine or methadone) chronic non-cancer pain (Hay et al, 2009) and those in methadone maintenance programs (Compton et al, 2000 **Level III-2**; Doverty et al, 2001 **Level III-2**; Athanasos et al, 2006 **Level III-2**; Hay et al, 2009 **Level III-2**) have been shown, to be hyperalgesic when assessed with cold pressor testing but not with electrical pain stimuli. However, such testing is uncommon in the clinical setting.

The challenge faced by the clinician 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). There are case reports of patients with cancer and chronic non-cancer pain, taking high doses of opioid and who had developed OIH, whose pain relief improved following reduction of their opioid dose (Angst & Clark, 2006; Chang et al, 2007); there have been no such trials performed 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 et al, 2007). 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 et al, 2007). 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 11.8) (Macintyre & Schug, 2007).

11.7.2 Patient groups

Three main groups of opioid-tolerant patients/patients with OIH are encountered in surgical and other acute pain settings:

- patients with chronic cancer or non-cancer pain being treated with opioids, some of whom may exhibit features opioid addiction (see Section 11.8);
- patients with a substance abuse disorder either using illicit opioids or on an opioid maintenance treatment program (see Section 11.8); and
- patients who have developed acute opioid tolerance or OIH due to perioperative opioid administration, particularly opioids of high potency.

Recognition of the presence of opioid tolerance or OIH may not be possible if the patient's history is not available or accurate. 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.

11.7.3 Management of acute pain

While the discussion below will focus on management of the opioid-tolerant patient, it is recognised that these patients may also have OIH.

Since 2004, a number of articles and chapters have been published outlining suggested strategies for the management of acute pain in the patient taking long-term opioids for both chronic non-cancer pain or because they have an addiction disorder and are in a drug treatment program (Carroll et al, 2004; Mitra & Sinatra, 2004; Kopf et al, 2005; Peng et al, 2005; Roberts & Meyer-Witting, 2005; Alford et al, 2006; Hadi et al, 2006; Mehta & Langford, 2006; Rozen &

DeGaetano, 2006; Basu et al, 2007; Ludlow et al, 2007; Macintyre & Schug, 2007; Roberts, 2008). However, evidence for the most appropriate 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.

In general, management of these patients should focus on:

- effective analgesia;
- use of strategies that may help to attenuate tolerance or OIH;
- prevention of withdrawal; and
- close liaison with other treating clinicians and specialist teams as required and appropriate discharge planning.

Effective analgesia

It is known that opioid requirements are usually significantly higher in opioid-tolerant compared with opioid-naive 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 et al, 1995 **Level III-2**) or epidural analgesia (de Leon-Casasola et al, 1993 **Level III-2**) required approximately three times the dose than their opioid-naive counterparts. Opioid-tolerant patients with chronic pain also reported higher pain scores after surgery and their pain resolved more slowly compared with opioid-naive patients (Chapman et al, 2009 **Level III-2**).

Opioid-tolerant patients reported higher pain scores (both resting and dynamic) and remained under the care of APSs longer than other patients (Rapp et al, 1995 **Level III-2**). Compared with opioid-tolerant patients with cancer pain, opioid-tolerant patients with non-cancer pain had higher rest and dynamic pain scores and required longer APS input, but there was no difference in opioid requirements (Rapp et al, 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 et al, 1994 **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 et al, 1995 **Level III-2**). An explanation to the patient of why good pain relief with opioids may be more difficult to obtain and why the dose that can safely be given will be limited by any onset of excessive sedation may be appropriate.

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 & Sinatra, 2004; Macintyre & Schug, 2007). 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 lower than 5/minute; 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 et al, 2005 **Level IV**). It may also be based on the dose of opioid the patient is already taking (Hadi et al, 2006; Macintyre & Schug, 2007). 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 et al, 1993 **Level III-2**). Effective analgesia using intrathecal or epidural opioids will not necessarily prevent symptoms of opioid withdrawal (Carroll et al, 2004).

Attenuation of tolerance and opioid-induced hyperalgesia

There are a number of strategies that may help attenuate opioid tolerance and OIH, at least to a certain degree. These include:

- use of NMDA- or opioid-receptor antagonists;
- opioid rotation; and
- other adjuvant drugs.

NMDA and opioid-receptor antagonists

As noted in Section 4.1.3, the NMDA receptor is thought to be involved in the development of tolerance and OIH (Chang et al, 2007). In rodents, use of the NMDA-receptor antagonist ketamine has been shown to attenuate both the development of tolerance (Shimoyama et al, 1996; Laulin et al, 2002) and OIH (Laulin et al, 2002; Haugan et al, 2008).

Angst and Clark (Angst & Clark, 2006) summarised a number of RCTs that investigated the effects of a short remifentanil infusion in volunteer subjects with pre-existing experimentally induced mechanical hyperalgesia; the use of remifentanil was shown to aggravate hyperalgesia, the magnitude of the effect was directly related to the dose given, and coadministration of ketamine abolished the effect of remifentanil. However, the evidence for the ability of ketamine to attenuate the acute tolerance and/or OIH seen after intraoperative use of remifentanil infusions is conflicting, with both no benefit (Engelhardt et al, 2008 **Level II**) and prevention of OIH (Joly et al, 2005 **Level II**) shown. 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 et al, 2001; Sator-Katzenschlager et al, 2001; Mitra, 2008). 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 et al, 2008 **Level II**).

Similarly, in rodents, ultra low doses of naloxone have been shown to attenuate opioid tolerance (Crain & Shen, 1995; Crain & Shen, 2000; Wang et al, 2005). Clinical studies have concentrated on the effects of both naloxone and an opioid given acutely, with conflicting results; both improved postoperative pain and reduced opioid requirements and no differences in either have been reported (Angst & Clark, 2006; Sloan & Hamann, 2006). There was no analgesic benefit of adding naloxone to the PCA morphine solution (Sartain & Barry, 1999 **Level II**; Cepeda et al, 2002 **Level II**; Cepeda et al, 2004 **Level II**); in 'ultra low doses' but not in the higher dose studies, the incidence of nausea and pruritus was decreased (Cepeda et al, 2004 **Level II**). In the experimental pain setting in volunteers, the coadministration of ultra-low doses of naloxone to patients given buprenorphine significantly increased tolerance to cold pressor pain (La Vincente et al, 2008 **Level II**). There is no information about the effect of naloxone in patients taking opioids in the longer term.

Use over 3 months of a formulation combining oxycodone and ultra-low-dose naltrexone in the same tablet in patients with chronic pain, in comparison with oxycodone alone, showed that those given the combination had similar pain relief but with significantly smaller doses as well as less constipation, sedation, itching and physical dependence as assessed by a withdrawal scale (Webster et al, 2006 **Level II**).

Opioid rotation

Opioid rotation is commonly used in the treatment of chronic non-cancer and cancer pain when a change to another opioid can improve analgesia and reduce side effects (Quigley, 2004; Mercadante & Arcuri, 2005; Angst & Clark, 2006). Opioid rotation (eg using an opioid that is different from the preadmission opioid) may also be of use in the acute pain setting (Hadi et al, 2006). The concept is based on the rationale that the different opioids do not act to the same degree on different opioid receptor subtypes and are metabolised differently, and also takes

advantage of the fact that cross-tolerance is likely to be incomplete (Jage, 2005; Mitra, 2008) and that the degree of OIH and tolerance appears to vary between opioids (see Section 4.1.3).

Other adjuvants

In an experimental pain setting using intradermal electrical pain stimuli, parecoxib given before a remifentanil infusion, but not if given during, was shown to modulate the hyperalgesia seen after withdrawal of the remifentanil (Troster et al, 2006 **Level II**).

Intrathecal gabapentin has also been shown to attenuate opioid tolerance in rats (Lin et al, 2005), but there are no data from human studies.

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, rhinorrhea and sneezing, trembling, yawning, runny eyes and piloerection or 'gooseflesh' (Tetrault & O'Connor, 2008). The time of onset of withdrawal symptoms after cessation of the drug will depend on the duration of action of the opioid (Tetrault & O'Connor, 2008).

It should be prevented by maintenance of normal preadmission opioid regimens where possible (including, for patients undergoing surgery, on the day of their procedure), or appropriate substitutions with another opioid or the same opioid via another route (Carroll et al, 2004; Mitra & Sinatra, 2004; Macintyre & Schug, 2007). It is important to verify preadmission opioid doses, which may require contact with the patient's doctor, pharmacist or, where available, local regulatory authority. The use of additional 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 nsNSAIDs, paracetamol, ketamine, tramadol, regional analgesia) are of analgesic benefit, opioid-tolerant patients are at risk of opioid withdrawal if a purely non-opioid analgesic regimen or tramadol is used (Carroll et al, 2004; Mitra & Sinatra, 2004; Macintyre & Schug, 2007). For this reason opioid antagonists (naloxone, naltrexone) or mixed agonist-antagonists (eg buprenorphine, pentazocine) should be also avoided (unless the former are needed to treat respiratory depression) as their use may precipitate acute withdrawal reactions (Alford et al, 2006).

Use of intrathecal or epidural opioids will not necessarily prevent symptoms of opioid withdrawal and additional systemic opioids may be required (Carroll et al, 2004).

Clonidine, administered orally or parenterally, will aid in the symptomatic management of opioid withdrawal symptoms (Tetrault & O'Connor, 2008).

Management on discharge

Discharge planning must take into account any regulatory requirements (eg the authority to prescribe an opioid may have 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 of minority patients, the potential for prescribed opioids to be abused or misused. Appropriate use of non-opioid analgesics where possible, communication with the primary physician and health care professionals, and patient education and support must all be considered.

Key messages

1. Opioid-tolerant patients report higher pain scores and have a lower incidence of opioid-induced nausea and vomiting (**U**) (**Level III-2**).
2. Ketamine improves pain relief after surgery in opioid-tolerant patients (**N**) (**Level II**).
3. Opioid-tolerant patients may have significantly higher opioid requirements than opioid-naive patients and interpatient variation in the doses needed may be even greater (**N**) (**Level III-2**).
4. Ketamine may reduce opioid requirements in opioid-tolerant patients (**U**) (**Level IV**).

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**).

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

☑ 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 (**U**).

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

☑ In patients with escalating opioid requirements the possibility of the development of both tolerance and opioid-induced hyperalgesia should be considered (**N**).

11.8 The patient with an addiction disorder

An addiction disorder exists when the extent and pattern of substance use interferes with the psychological and sociocultural integrity of the person (see Table 11.7 above). 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, or these patients may put themselves or others at risk of harm.

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 et al, 2001), even though the alternative term substance dependence is used by other health organisations (Ballantyne & LaForge, 2007). 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 disorder; it also reduces the risk of stigmatisation of patients who have a physical dependence because of long-term opioid therapy (Ballantyne & LaForge, 2007).

Effective management of acute pain in patients with an addiction disorder may be complex due to:

- psychological and behavioural characteristics associated with that disorder;
- presence of the drug (or drugs) of abuse;
- medications used to assist with drug withdrawal and/or rehabilitation;

- complications related to drug abuse including organ impairment and infectious diseases; and
- the presence of tolerance, physical dependence and the risk of withdrawal.

Evidence for the most appropriate management of acute pain in patients with an addiction disorder is limited and 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 et al, 1995) and often requires significant deviations from 'standard' treatment protocols (Macintyre & Schug, 2007). In addition, ethical dilemmas can arise as a result of the need to balance concerns of undermedication against anxieties about safety and possible abuse or diversion of the drugs (Basu et al, 2007).

Identification of patients in whom there may be a risk of drug abuse is difficult. The ability of clinicians to predict which patients may misuse or abuse opioids is known to be poor (Jung & Reidenberg, 2007) and patient self-reports of drug use may not correlate with evidence from drug screens (Turk et al, 2008). Passik and Kirsh (Passik & Kirsh, 2008) recently reviewed a number of the screening tools that can be used to assess the risk of opioid abuse in patients given opioids for the management of chronic pain.

The first step in managing patients with an addiction disorder is identifying the problem, although obtaining an accurate history can sometimes be difficult. Polysubstance abuse is common and many of these patients will use drugs from different groups, the most common of which include CNS depressant drugs such as alcohol, opioids and benzodiazepines, or CNS-stimulant drugs including cocaine, amphetamines (amfetamines) and amphetamine-like drugs, cannabis and other hallucinogens. The group from which the drugs come determines their withdrawal characteristics (if any) and their interaction with acute pain therapy (Mitra & Sinatra, 2004; Peng et al, 2005). Patients should be asked about the route of administration used, as some may be injecting drugs intended for oral use. Confirmation of opioid doses should be sought where possible (Alford et al, 2006).

A number of centres worldwide monitor the use of illicit drugs on a regular basis, including prescription opioids. These include:

- in Australia, the National Drug and Alcohol Research Centre (NDARC) (see the section on Australian Drug Trends Series for Illicit Drug Reporting System [NDARC, 2009]);
- in New Zealand, the Centre for Social and Health Outcomes Research and Evaluation (SHORE) (see the section on the Illicit Drug Monitoring System [SHORE, 2009]);
- the surveillance systems set up by the National Health Service in the United Kingdom (see the section on Statistics of Drug Misuse [NHS, 2008]); and
- in the United States, the Substance Abuse and Mental Health Services of the US Department of Health and Human Services (SAMHSA, 2007), or other schemes specifically tracking prescription opioid abuse, such as Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) (Cicero et al, 2007).

Management of pain in patients with an addiction disorder should focus on:

- effective analgesia;
- use of strategies that may attenuate tolerance, and prevention of withdrawal (as outlined in Section 11.7);
- symptomatic treatment of affective disorders and behavioural disturbances; and
- the use of secure drug administration procedures.

Pain management in patients with an addiction disorder 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). 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).

In all cases, close liaison with other treating clinicians and drug and alcohol services is required. This is especially important if additional opioids are thought to be needed 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 et al, 2005).

11.8.1 Management of acute pain in pregnant patients with an addiction disorder

The majority of women with an addiction disorder are of child bearing age; 0.76% of all births at one institution were to women using opioids and 0.42% to those using amphetamines (Ludlow et al, 2007) The management of acute pain in pregnant patients with an addiction disorder must take into account treatment of the mother as well as possible effects on the child, both before and after birth. Identification of these patients during pregnancy allows time to plan for appropriate management — but this is not always possible. Poor antenatal care is more common in these patients as are other factors related to their use of drugs such as respiratory infections, endocarditis, untreated cellulitis and abscesses, HIV/AIDS and hepatitis (Ludlow et al, 2007). For a detailed review of the anaesthetic issues in these patients see Ludlow et al (Ludlow et al, 2007).

It has been suggested that pregnant patients taking methadone as part of a drug-dependence treatment program should receive whatever dose is needed to prevent heroin use, and that 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 et al, 2007). Additional opioid will be required for any postoperative pain, as with any opioid-tolerant patient, and the infant will require high-level neonatal care because of the risk of withdrawal (Ludlow et al, 2007; Jones et al, 2008). Opioid requirements during labour may not be significantly increased although methadone-maintained patients in this study did have higher pain scores (Meyer et al, 2007). Those taking buprenorphine will also have higher opioid requirements after surgery, and the newborn is still at risk (albeit maybe a lower risk) of withdrawal (Ludlow et al, 2007); again, opioid requirements during labour may not be increased (Jones et al, 2008). Both methadone and buprenorphine should be continued without interruption or, if the patient cannot take oral medications, then an alternative route (or opioid) should be used (Jones et al, 2008). Opioid requirements and the risk of withdrawal — for the patient and the infant — will also be higher in patients still taking heroin prior to delivery (Ludlow et al, 2007). For further information on maternal and neonatal outcomes see Section 11.1.3.

Opioid requirements in those addicted to substances other than opioids should be similar to other patients.

11.8.2 CNS depressant drugs

Although not inevitable, abuse of CNS-depressant drugs (eg opioids, alcohol) is often associated with physical dependence and the development of tolerance (see Section 11.7). Withdrawal from CNS-depressant drugs produces symptoms of CNS and autonomic hyperexcitability, the opposite of the effects of the CNS-depressant drugs themselves.

Opioids

Opioid abuse not only involves the use of heroin but also legally prescribed opioids or prescription opioids illegally obtained. The number of prescriptions for opioids continues to increase in many countries and along with this the incidence of abuse of these drugs (Cicero et al, 2007; Katz et al, 2007). Illicitly obtained prescription opioids now account for a large proportion of all opioids used by patients with an addiction disorder (NDARC, 2009), in some instances exceeding the use of heroin (Fischer et al, 2006; Katz et al, 2007).

Not all aberrant drug behaviours indicate opioid addiction. Those that may 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 et al, 2008), or other features listed under the definition of addiction in Table 11.7 above. Other aberrant behaviours may indicate problematic opioid use caused by a variety of factors other than addiction (Ballantyne & LaForge, 2007).

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 very small, although there are no accurate data and the exact incidence is unknown (Wasan et al, 2006). This may not be the case when these drugs are used in the management of chronic non-cancer pain, where long-term use of opioids may not provide as effective pain relief and the risk of abuse of the drugs may be higher (Ballantyne & LaForge, 2007; Chou et al, 2009; RACP et al, 2009). Both patients with chronic pain and those with an addiction disorder have a high rate of psychiatric comorbidities (such as anxiety, depression and personality disorders) and patients with chronic pain may therefore be more at risk of developing behavioural problems associated with opioid use (Ballantyne & LaForge, 2007).

A large survey, to which over 9000 patients with chronic non-cancer pain responded (a 64% response rate), found that users of prescription opioids had higher rates of opioid and non-opioid illicit drug misuse and alcohol abuse compared with those not using prescription opioids (Edlund et al, 2007 **Level III-2**). However, it is difficult to get accurate information on the rate of opioid addiction in chronic pain patients, especially as a variety of definitions are used that may not differentiate between problematic drug use and true addiction (Ballantyne & LaForge, 2007). The prevalence of addiction in chronic pain patients prescribed opioids is reported to range from 0% to 50% (Hojsted & Sjogren, 2007 **Level IV**). Others have reported that, on the basis of urine toxicology, up to 30% to 40% of patients prescribed opioids for the management of their chronic pain misuse those drugs (Turk et al, 2008 **Level IV**).

More recently, focus has turned to the use of 'abuse deterrent' formulations; 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, and combination of the opioid with an opioid antagonist such as naloxone (Katz et al, 2007). Suboxone® is a trade name for a combination formulation of buprenorphine and naloxone, now commonly used in opioid-addiction treatment programs (see below).

Alcohol and benzodiazepines

There is no cross-tolerance between opioids and alcohol or benzodiazepines and there is therefore no pharmacological reason to use higher than 'standard' initial opioid doses in patients with an alcohol or benzodiazepine addiction.

Alcohol and/or benzodiazepine abuse is relatively common and prevention of withdrawal should be a clinical priority in all patients. If benzodiazepines are administered for the treatment of withdrawal signs and symptoms, patient sedation levels must be monitored, especially if they are receiving concurrent opioids. Excessive sedation will limit the amount of opioid than can safely be given.

Cannabinoids

Evidence supporting the effectiveness of cannabinoids in the management of acute pain is mixed (see Section 4.3.8). Although anecdotal reports suggest higher opioid doses may be required for the management of acute pain in patients who are heavy users of cannabinoids there is no published information to support this.

11.8.3 CNS stimulant drugs

Abuse of CNS-stimulant drugs (eg cocaine, amphetamines, ecstasy) is associated with a psychological rather than physical dependence and only a low degree of tolerance; these drugs do not exhibit any cross-tolerance with opioids, and while behavioural and autonomic effects are seen during acute exposure, withdrawal symptoms are predominantly affective rather than physical.

Although cocaine and ecstasy (N-Methyl-3,4-methylenedioxyamphetamine or MDMA) are known to enhance the analgesic effects of morphine in animals (Kauppila et al, 1992; Gatch et al, 1999; Nencini et al, 1988), 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 & Clow, 2004 **Level III-2**) and those taking cocaine reduced cold-pressor pain thresholds (Compton, 1994 **Level III-2**). There are no data from the clinical setting of any difference in opioid requirements compared from patients who do not use these drugs.

Withdrawal from methamphetamines is characterised by increases in sleepiness 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 et al, 2005).

11.8.4 Drugs used in the treatment of addiction disorders

Methadone

Methadone is a long-acting opioid agonist used in the management of patients with an opioid addiction. It is usually given once a day, which is often enough to suppress symptoms of opioid withdrawal; the duration of any analgesic effect from the dose is likely to be much shorter (Alford et al, 2006; Basu et al, 2007). Dividing the daily dose on a temporary basis (eg giving the methadone in two equal doses twice a day) may allow some of the analgesic effect to be seen. In the acute pain setting methadone should be continued, where possible, as usual at the same dose. If there is any doubt about the dose (for example, there is a suspicion that the patient is diverting part or the entire prescribed amount), it may be prudent to give part of the reported dose and repeat this over the day if needed and if the patient is not sedated (Peng et al, 2005). If the patient is unable to take methadone by mouth, substitution with parenteral methadone or other opioids will be required in the short term (Mitra & Sinatra, 2004). Parenteral methadone doses should be based on half to two-thirds of the oral maintenance

dose and can be given in equal divided doses by SC or IM injection 2 to 4 times daily (Alford et al, 2006) or by continuous infusion.

Buprenorphine

Buprenorphine is a partial opioid agonist used in the treatment of opioid addiction and is commonly prescribed in doses of 8 to 32 mg (Roberts & Meyer-Witting, 2005). Administered sublingually, it has a mean terminal half-life of 28 hours (Johnson et al, 2005). It is usually given once every day or two, which again is often enough to suppress symptoms of opioid withdrawal; like methadone the duration of any analgesic effect from the dose is likely to be much shorter (Alford et al, 2006). Preparations that combine buprenorphine and naloxone (poorly absorbed by the sublingual route) are available (Harris et al, 2004). The addition of naloxone to buprenorphine is said to reduce potential parenteral abuse of the drug (Johnson et al, 2005).

While patients in methadone maintenance programs have been shown to be hyperalgesic when assessed with cold pressor testing (Compton et al, 2000 **Level III-2**; Doverty et al, 2001 **Level III-2**; Athanasos et al, 2006 **Level III-2**), much less information is available for the effects of experimental pain stimuli in patients in buprenorphine maintenance programs. In a very small study comparing methadone-maintained (n = 5) and buprenorphine-maintained (n = 7) subjects with opioid-naive controls, both methadone-maintained and buprenorphine-maintained were more sensitive to cold-pressor pain than the controls although to a lesser degree in those taking buprenorphine (Compton et al, 2001 **Level III-2**). In opioid-naive 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 anthyperalgesic effect (Koppert et al, 2005 **Level III-2**).

There are no good data on which to base the management of patients on buprenorphine maintenance programs requiring pain relief. If shorter-acting opioid agonists will be required, a decision needs be made whether or not to continue buprenorphine. Suggestions for management vary from withholding the buprenorphine and substituting an alternative opioid (eg methadone), to continuing the buprenorphine as usual (Roberts & Meyer-Witting, 2005; Alford et al, 2006). However, in practice, there appears to be little problem if the buprenorphine is continued and acute pain managed with the combination of a short-acting pure opioid agonist as well as other multimodal analgesic strategies (Macintyre & Schug, 2007). As with methadone, dividing the daily doses on a temporary basis may take advantage of the analgesic properties of the buprenorphine (Alford et al, 2006).

Close liaison with all treating clinicians and drug and alcohol services should occur. If buprenorphine has been ceased, its reintroduction should be managed in consultation with the prescribing practitioner.

Naltrexone

Naltrexone is a pure opioid antagonist used in the management of patients with opioid or alcohol addiction. The usual oral maintenance dose is up to 25 to 50 mg daily; long acting implantable pellets are also available in some countries (Roberts & Meyer-Witting, 2005; Vickers & Jolly, 2006). Orally administered, naltrexone has an apparent half-life of about 14 hours and binds to opioid receptors for over 24 hours following a single dose (Vickers & Jolly, 2006), which can create difficulties in the acute pain setting.

It has been recommended that, where possible, naltrexone be stopped for at least 24 hours before surgery (Mitra & Sinatra, 2004; Vickers & Jolly, 2006). In these patients and in patients requiring surgery within this 24-hour period, multimodal analgesic regimens (eg NSAIDs, paracetamol, ketamine, tramadol and regional analgesia) should also be employed.

There is experimental evidence of μ-opioid receptor upregulation following antagonist withdrawal (Millan et al, 1988) and abrupt discontinuation of naltrexone may therefore lead to a period of increased opioid sensitivity (Vickers & Jolly, 2006). 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 signs of excessive opioid dose (in particular, respiratory depression).

Reintroduction of naltrexone should be done in consultation with the prescribing practitioner.

11.8.5 Recovering patients

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. 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 (Alford et al, 2006). Effective communication and planning, the use of multimodal analgesic strategies, reassurance that the risk of reversion to an active addiction disorder is small, and information that ineffective analgesia can paradoxically lead to relapses in recovering patients, are important and help avoid under treatment (Mitra & Sinatra, 2004).

Key messages

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

- ☑ Naltrexone should be stopped at least 24 hours prior to elective surgery (**U**).
- ☑ Patients who have completed naltrexone therapy should be regarded as opioid naive; in the immediate post-treatment phase they may be opioid-sensitive (**U**).
- ☑ Maintenance methadone regimens should be continued where possible (**U**).
- ☑ Buprenorphine maintenance may be continued; if buprenorphine is ceased prior to surgery conversion to an alternative opioid is required (**U**).
- ☑ There is no cross-tolerance between central nervous system stimulants and opioids (**U**).

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APPENDIX A

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APPENDIX B

PROCESS REPORT

This is the third 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 party chaired by Dr 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 – the International Association for the Study of Pain (IASP), the Royal College of Anaesthetists (United Kingdom), the Australasian Faculty of Rehabilitation Medicine, the Royal Australasian College of Physicians, the Royal Australasian College of Surgeons, the Royal Australian and New Zealand College of Psychiatrists and the Australian Pain Society – and recommended to its members by the American Academy of Pain Medicine.

In accord with the NHMRC requirement that guidelines should be revised as further evidence accumulates, and as there has been has been a continuing and large 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 third edition.

Since the second edition was published in 2005, a sizeable amount of new evidence relating to the management of acute pain has been published. The aim of this third edition is, as with the first two 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 2009) 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 more than evidence is needed 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 it must 'integrate research evidence, clinical expertise and patient values' (Sackett et al, 1996). 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 care professionals. 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 help select the treatments that are relevant and appropriate to that patient.

This 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 party was convened to coordinate and oversee the development process. An editorial subgroup of the working party (Assoc Prof Pam Macintyre, Prof Stephan Schug, Assoc Prof David Scott, Dr Eric Visser and Dr Suellen Walker) coordinated the development process and edited and/or wrote the sections. The working party also included Dr Douglas Justins (Dean of the Faculty of Pain Medicine, Royal College of Anaesthetists in the United Kingdom) and Prof Karen Grimmer-Somers 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 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 early drafts of the document and contribute more broadly as required. A list of panel members is attached in Appendix A, together with a list of contributing authors and working party 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* (2000), and directed to the ANZCA website for copies of the second edition of the document as well as an update that was published in 2007.

Members of the editorial subgroup of the working party 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 party compiled and edited an initial draft. Once the draft of the document had been prepared, it was sent to all contributors for comment as well as members of the multidisciplinary panel, before being redrafted for public consultation. For the second and subsequent drafts the working party had the assistance of technical editors experienced in NHMRC requirements and processes. To ensure general applicability, there was a very wide range of experts on the contributor and multidisciplinary committee, including medical, nursing, allied health and complementary medicine clinicians and consumers – see Appendix A.

The third 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).

A companion document for consumers – *Managing Acute Pain: a Guide for Patients* – was prepared after publication of the second edition of *Acute Pain Management: Scientific Evidence* and approved by the NHMRC in December 2005 (ANZCA & FPM 2005).

Consideration is being given to revision of this consumer document.

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 Journal of Medical Editors *Conflict of Interest (ICMJE) Uniform Disclosure Form for Potential Conflicts of Interest*. Copies of these statements were forwarded to the NHMRC. 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 on inclusion or exclusion of material.

Review of the evidence

This document is a revision of the second edition of *Acute Pain Management: Scientific Evidence* published in 2005. Therefore most of the new evidence included in the third edition has been published from January 2005 onwards. Evidence-based guidelines have been published 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) and, as for the second edition of this document, clinical practice points have been added.

Levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised 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, 2 or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test and post-test

Clinical practice points

☑	Recommended best practice based on clinical experience and expert opinion

Key messages

These levels of evidence were also used for the Key Messages. However, it was felt that there should be an indication of how the Key Messages in this third edition related to those in the previous edition. The system used by Johnston et al (Johnston et al, 2003) to reflect the implications of new evidence on clinical recommendations was therefore reviewed and adapted. The letters N, U, S, W, Q and R were used in the Key Messages to indicate New, Unchanged, Strengthened, Weakened, Qualified and Reversed respectively – see table below.

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 original report remains unchanged.
Strengthened	The new evidence is consistent with the data used to formulate the original key message. The key message in the original report remains unchanged or expanded. The level of evidence and/or content of the key message in the original report 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 original report 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 original document.
NB	Clinical and scientific judgment informed the choices made by the Working Party members; there was no mandatory threshold of new evidence (e.g. 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) were used to denote the changes (if any) from the last edition of this document.

An example of the use of this system is taken from the Key Messages in Section 7.1 – Patient-controlled analgesia.

Key Messages

1. Intravenous opioid PCA provides better analgesia than conventional parenteral opioid regimens (**S**) (**Level I** [Cochrane review]).
2. Opioid administration by IV PCA leads to higher opioid consumption (**R**), a higher incidence of pruritus (**R**), and no difference in other opioid-related adverse effects (**S**) or hospital stay (**S**) compared with traditional methods of intermittent parenteral opioid administration (**Level I** [Cochrane review]).
3. 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**).
4. Patient preference for intravenous PCA is higher when compared with conventional regimens (**U**) (**Level I**).

Where the new evidence led to reversal of a conclusion and Key Message, this was noted in the text. For the example above this appeared in the text as:

Note: reversal of conclusion

This partly reverses the Level 1 conclusion in the previous edition of this document; earlier meta-analyses had reported no difference in opioid consumption or opioid-related adverse effects

Key messages were based on the highest levels of evidence available. Key messages referring to information extracted from Cochrane meta-analyses were marked '**Level I** [Cochrane Review]', and these were listed first.

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. Searches were limited to articles concerning humans published mainly in English, and literature published between January 2005 and August 2009 was highlighted. One of the members of the working party, who is fluent in German, translated key texts written in German, which were highlighted during the search. These texts were used for validation purposes only. 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' and 'complications'. Hand searches were also conducted of a large range of relevant journals from 2005 onwards and bibliographies of relevant papers were checked.

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 and to inform best practice, it was important to concentrate on the highest ranked, highest quality evidence available.

Secondary evidence: High quality systematic reviews of randomised-controlled trials (NHMRC **Level I**) were the preferred evidence source. This approach was efficient as many high quality systematic reviews of specific aspects of acute pain management have already been undertaken by the Cochrane Collaboration and other reputable evidence-synthesis groups (such as members of the Oxford Pain Group). Systematic reviews that included non-randomised controlled studies were assigned the level of evidence of their component studies, as outlined in the NHMRC designation of evidence levels (NHMRC 1999) (see below).

Primary evidence: Where **Level I** reviews were not available, the next preferred level of evidence was single randomised controlled trials (NHMRC **Level II**). Where these were not available, other experimental evidence or case series were accepted as the best available evidence by the guideline developers (reflecting NHMRC **Level II** and **Level IV**). According to NHMRC guidelines (NHMRC 1999), **Level IV** evidence is obtained from case series, either post-test or pre-test and post-test; the levels refer to evidence about interventions. Publications describing results of audits or papers that were comprehensive clinical reviews, for example, were also included as **Level IV** evidence.

Expert opinion: In the few instances where no relevant published evidence was available, expert opinion was included as the best available information.

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 record audit, quality processes or single case reports.

Examples of evidence level decision-making: For examples of the decisions that were made about assigning levels to low quality evidence where there was limited evidence available, see the table below.

Examples of decisions made assigning levels to evidence of lower quality	
Systematic reviews of articles including those with the lowest level of evidence designated as **Level III-2** were cited as **Level III-2**	A systematic review looking at the benefits or otherwise of preoperative education for orthopaedic patients highlighted the difficulties of comparing studies of variable methodological quality (Johansson et al 2005)
Evidence from audits or case series that directly affects patient safety cited as **Level IV**	The amount of morphine a patient requires is better predicted by their age rather than weight (adds to safety of prescribing) (Macintyre & Jarvis 1996) The routine use of a continuous infusion with patient-controlled analgesia (PCA) markedly increases the risk of respiratory depression (Schug & Torrie 1993) Delays in the diagnosis and treatment of an epidural abscess in a patient

	with neurological signs greatly increases the risk of an incomplete recovery (Davies et al 2004)
Evidence from a single case report or letter that *directly affects patient safety* cited as **Level IV**	Electrical corruption of PCA pumps resulting in uncontrolled delivery of syringe contents (Notcutt et al 1992) The need for antisyphon valves when using PCA in order to prevent inadvertent delivery of an excessive dose of opioid (Kwan 1995)

Quality scoring

Where Cochrane reviews or reviews from other reputable sources were available, no additional methodological quality evaluation was undertaken, and what was available in the review was accepted as the quality scoring for these guidelines. For the remaining systematic reviews containing controlled trials (**Level I**) and primary RCT evidence (**Level II**), methodological quality was evaluated using a purpose-built system, which identified studies that were subsequently included in the review. The purpose-built criteria included the presence of a CONSORT diagram (Moher et al 2001), explicit inclusion and exclusion criteria, sound description of the intervention and clear outcome measures. No quality evaluation was undertaken for lower ranked evidence (**Level III** and **Level IV**), when this was the highest available level of evidence. 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 level and highest quality references were used. If it 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.

Management of retracted publications

In May 2009, two editorials (Shafer et al 2009; White et al 2009) were published in *Anesthesia and Analgesia* giving details of 21 publications that had been retracted by a number of journals because of allegations of scientific fraud. The editorial by Shafer (Shafer et al 2009) contains a list of the retracted articles. This list can also be found at http://www.aaeditor.org/HWP/Retraction.Notice.pdf.

The position of the journal was that unretracted articles 'remain part of the unimpeached literature, at least for now'. In a companion editorial White et al (White et al 2009) reviewed both the retracted and unimpeached literature, 'distinguishing our understandings that remain fully supported from those that are no longer supported by the unimpeached literature.' Also in May 2009, Eisenach (Eisenach 2009) the editor of *Anesthesiology*, presented a graph of numbers of citations of retracted and unretracted articles affected by this issue and called for research re-examining the conclusions of the retracted articles.

A July 2009 editorial by Neal (Neal 2009) described contact with 'the lead or high ranking authors' of six original articles and one review article in that editor's journal and which had not been retracted. These articles are listed in this editorial. He concluded that 'Based on the attestations of the involved coauthors and the investigations of the Chief Academic Officer of Baystate Medical Center, the Editorial Board of *Regional Anesthesia and Pain Medicine* is comfortable recommending that practitioners continue to make clinical decisions based on the information contained within the seven below cited articles.'

Of the references listed in the May 2009 retraction notice (Shafer 2009), four were included in the second edition of *Acute Pain Management: Scientific Evidence* along with a further two publications that were not included in this list of retractions.

There are no precedents for how best to manage a problem such as this. However, the editors responsible for the development of this third edition of *Acute Pain Management: Scientific Evidence* decided against including any publications by the individuals affected by these retractions when listed as first author on the papers. An assessment was made of each of the meta-analyses that cited affected articles. This was based upon the other papers included in these meta-analyses, other supporting evidence and independent consideration by an expert in biostatistics. In some cases, although cited, the affected references were not actually included in the meta-analysis performed. In other cases, assessment indicated that the strength of the evidence may be reduced because of the inclusion of affected publications.

Following the consensus that appeared to rapidly emerge among editors of the leading peer-reviewed journals in anaesthesiology and pain medicine despite initial concerns about meta-analyses that included this work (White et al 2009), the editors of the third edition of A*cute Pain Management: Scientific Evidence* felt that indiscriminately omitting all meta-analyses purely on the basis of inclusion of one or two of those papers would be to deny inclusion of some important credible information in the document. Indeed, the purpose of meta-analysis is to aggregate results from the literature as a whole, thereby diluting the impact of any one specific study.

Just prior to finalisation of this third edition of *Acute Pain Management: Scientific Evidence*, an article was published in *Anesthesiology* in December 2009 (Marret et al, 2009) which examined in detail the effect that excluding data obtained from the retracted articles would have on the results of 14 systematic reviews (six quantitative and eight qualitative) in which they were cited. Marret et al (Marret et al, 2009) reanalysed the data after excluding results from affected articles and concluded that withdrawal of these articles did not alter the conclusions of five out of the six quantitative reviews (meta-analyses): the sixth meta-analysis has not been included in *Acute Pain Management: Scientific Evidence*. Thus there was agreement with the assessments that had already made about the validity of these meta-analyses which included the retracted articles. Marret et al (Marret E et al, 2009) concluded that meta-analyses were 'vulnerable' if data from retracted studies made up more than 30% of the total.

A footnote has been added to the relevant sections indicating the systematic reviews (quantitative and qualitative) that includes affected articles along with a summary of the effect, if any, on the results obtained. Also, specific note has been made in the text of the third edition of *Acute Pain Management: Scientific Evidence* where retraction of the affected papers involved key messages that were published in the second edition. Should additional information become available it will be added as needed before publication of this document. Information that comes to light after publication will be posted as appropriate on the *Acute Pain Management: Scientific Evidence* website.

Cost analyses

The area of acute pain management remains remarkably deficient in research on costs and cost-benefit. Where this information was available it was reported. One obvious example is the costs associated with the adverse effects of treatment. Information to assist clinicians to better manage both pain and some of the adverse effects of treatment, as well as better individualise treatment for each patient, may assist in minimising such costs. This is again noted as an area warranting further research.

Public consultation

Following acceptance of the draft by the contributors and the multidisciplinary committee, its availability was advertised in a national newspaper. The public consultation period was from August 10th to September 10th 2009. The draft was made available on a website (www.acutepain.org.au) and Colleges of many of the contributors and multidisciplinary consultative committee members were notified of the availability of the draft and asked to disseminate this information to their members.

The public was invited to provide comments on the draft and 15 submissions and comments were received from the following individuals.

Submissions

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Dr Dan Carr	Tufts Medical Center and Tufts University School of Medicine Boston United States
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Comments

Name	Affiliation
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Dr Michael Duncan	Guys' and St Thomas' NHS Foundation Trust London United Kingdom

Topics raised

The main topics raised in these submissions and comments related to:

- use of pethidine in acute pain management;
- effect of lignocaine on postoperative outcome;
- continuous peripheral nerve blockade;
- definition of pain;
- problems of ongoing opioid prescriptions;
- use of coxibs after surgery;
- aspects of pain-related physiology;
- psychological aspects of acute pain; and
- complications after central neuraxial blockade.

Implementation, dissemination and revision

The Australian and New Zealand College of Anaesthetists (ANZCA) and its Faculty of Pain Medicine (FPM) will be responsible for the dissemination, implementation, and updating of this document. The document will be available on the internet (formatted to allow for downloading and printing) as well as in hard copy. ANZCA will distribute hard copies to all its members and trainees and to all contributors and multidisciplinary consultative committee members. ANZCA will also notify the Colleges of all contributors and multidisciplinary consultative committee members of the availability of the document and ask them to disseminate the information to their members. In addition, information will be send to all national and international organisations that endorse this document for distribution to their members. This is further expected to heighten awareness of its availability. The document will also be promoted at relevant professional meetings and conferences and by editorials in professional journals.

The ANZCA working party responsible for this document will continue to monitor the literature relevant to acute pain management. As new evidence becomes available, further revision will be required. Unless earlier revision is indicated, it is anticipated that the document will be revised again in 2014.

Areas identified as requiring further research

As in the second edition of this document, the Working Party identified the same areas that warrant urgent further research using appropriate research approaches. These relate primarily to:

1. The management (including pain assessment and education) of acute pain in specific patient groups including:
   - elderly patients;
   - patients who are cognitively impaired;
   - patients requiring prehospital analgesia;
   - patients from difference cultural and ethnic backgrounds;
   - Aboriginal and Torres Strait Islander peoples;
   - patients with obstructive sleep apnoea;
   - patients who are opioid-tolerant;
   - patients with a opioid addiction disorder; and
   - patients with or at risk of persistent postoperative pain.

   The only area in which research had improved was in children.
2. Issues of cost and cost-effectiveness.

The NHMRC is encouraged to fund primary research projects that will address this current lack of evidence.

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ABBREVIATIONS AND ACRONYMS

5HT	5-hydroxytriptamine (serotonin)
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotrophic hormone
ADEC	Australian Drug Evaluation Committee
ADH	antidiuretic hormone
ADLs	activities of daily living
AERD	aspirin-exacerbated respiratory disease
AIDS	acquired immunodeficiency syndrome
ALA	aminolaevulinic acid
ALCAR	acetyl-L-carnitine
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ANZCA	Australia and New Zealand College of Anaesthetists
APS	acute pain service
ARAC	Australasian Regional Anaesthesia Collaboration
ASA	American Society of Anesthesiologists
ASIC	acid-sensing ion channel
ATP	adenosine triphosphate
BDNF	brain-derived neurotrophic factor
BK	bradykinin
CABG	coronary artery bypass graft
CAMs	complementary or alternative medicines
CCL3	chemokine (C-C motif) ligand 3
CGRP	calcitonin gene-related peptide
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CI	confidence interval
CNS	central nervous system
COMT	catechol-O-methyltransferase
COX-2	cyclo-oxygenase-2
CPAP	continuous positive airway pressure
CPNB	continuous peripheral nerve blockade
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
CV	cardiovascular

CYP	cytochrome P450
DIS	daily interruption of sedation
DNA	deoxyribonucleic acid
DNIC	diffuse noxious inhibitory control
DRASIC	subtype of acid sensing ion channel
DRG	dorsal root ganglia
DSP	distal symmetrical polyneuropathy
DVT	deep vein thrombosis
EBP	epidural blood patch
ECF	extracellular fluid
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyelograph
EREM	extended-release epidural morphine
FAS	Functional Activity Scale
FBT	fentanyl buccal tablets
FDA	Food and Drugs Administration
FFA	free fatty acid
FLACC	Faces, Legs, Activity, Cry and Consolability
fMRI	functional magnetic resonance imaging
FPM	Faculty of Pain Medicine
g	gram
GCH1	guanosine triphosphate cyclohydrolase 1/dopa-responsive dystonia
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
H3G	hydromorphone-3-glucuronide
HIV	human immunodeficiency virus
HPβCD	hydroxypropyl beta-cyclodextrin
HSAN	hereditary sensory and autonomic neuropathy
HSN	hereditary sensory neuropathy
HZ	herpes zoster
IASP	International Association for the Study of Pain
ICF	intracellular fluid
ICU	intensive care unit
ICV	intracerebroventricular
iGluR	ionotropic glutamate receptor
IL	interleukin
IM	intramuscular
IN	intranasal
INN	International Non-proprietary Name

INR	International Normalised Ratio
IR	immediate-release
IV	intravenous
IVRA	intravenous regional anaesthesia
LMWH	low molecular weight heparin
LTP	long-term potentiation
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MAM	monoacetylmorphine
MAOI	monoamine oxidase inhibitor
MC1R	melanocortin-1 receptor
mcg	microgram
MEDD	morphine equivalent daily dose
mg	milligram
mGluR	metabotropic glutamate receptor
mL	millilitre
MLAC	minimum local anaesthetic concentration
mm	millimetre
MOBID	Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale
MOR	mu-opioid receptor
MRI	magnetic resonance imaging
MS	methionine synthetase
N_2O	nitrous oxide
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
NDARC	National Drug and Alcohol Research Centre
NFCS	Neonatal Facial Coding Scale
ng	nanogram
NHMRC	National Health and Medical Research Council
NIPS	Neonatal Infant Pain Scale
NK1	neurokinin-1
NMDA	N-methyl-D-aspartate
NNH	number-needed-to-harm
NNT	number-needed-to-treat
NO	nitric oxide
NRS	numerical rating scale
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug

nsNSAID	non-selective non-steroidal anti-inflammatory drug
OIH	opioid-induced hyperalgesia
OR	odds ratio
OSA	obstructive sleep apnoea
OTC	over-the-counter
OTFC	oral transmucosal fentanyl citrate
P_2X_3	purinergic receptor subtype
PACSLAC	Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PACU	postanaesthesia care unit
PAINAD	Pain Assessment in Advanced Dementia
PAR	proteinase-activated receptor
PCA	patient-controlled analgesia
PCEA	patient-controlled epidural analgesia
PCINA	patient-controlled intranasal analgesia
PCRA	patient-controlled regional analgesia
PCS	Pain Catastrophising Scale
PCTS	patient-controlled transdermal system
PDPH	post-dural puncture headache
PG-BA	polyethylene glycol and benzyl alcohol
PGE_2	prostaglandin E2
PGH	prostaglandin endoperoxide
PGI_2	prostacyclin
PHN	post-herpetic neuralgia
PIPP	premature infant pain profile
PNB	peripheral nerve block
PNS	peripheral nerve stimulator
POCD	postoperative cognitive dysfunction
PONV	postoperative nausea and vomiting
PPI	proton pump inhibitor
PPP	Paediatric Pain Profile
PPPM	Parents Postoperative Pain Measure
PTA	Polymyxin E, tobramycin and amphotericin B
QOL	quality of life
QST	quantitative sensory testing
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
RCT	randomised controlled trial
rESS	revised Edmonton Staging System
RNA	ribonucleic acid
RR	relative risk
RVM	rostroventromedial medulla

RWS	Red Wedge Scale
SACD	subacute combined degeneration
SC	subcutaneous
SCI	spinal cord injury
SF-36	Short Form 36 of Medical Outcomes Study
SHORE	Social and Health Outcomes Research and Evaluation
SIP	Sickness Impact Profile
SL	sublingual
SNP	single nucleotide polymorphism
SPID	summed pain intensity difference
SR	slow-release
SSRI	selective serotonin reuptake inhibitor
SUNCT	Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing
TCA	tricyclic antidepressant
TdP	Torsades de Points
TEA	thoracic epidural analgesia
TENS	transcutaneous electrical nerve stimulation
THC	tetrahydrocannabinol
T_{max}	time to reach maximum serum concentration
TNF	tumour necrosis factor
TNS	Transient Neurological Symptoms
TOTPAR	total pain relief
TRP	transient receptor potential
TTH	tension-type headaches
US	ultrasound
USP	United States Pharmacopeia
VAS	visual analogue scale
VDS	verbal descriptor scale
VNRS	verbal numerical rating scale
VPL	ventral posterolateral nucleus of the thalamus
VPM	ventral posteromedial nucleus of the thalamus
VR	virtual reality
VZV	varicella-zoster virus
WMD	weighted mean difference

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