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Acute Pain Management

A Practical Guide

Fourth Edition

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Fourth Edition

A Practical Guide

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Contents

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Preface

Since the first three editions of this book were published, knowledge relating to the treatment of acute pain has continued to grow at an ever-increasing rate, as has the quantity and quality of evidence available. There have also been greater changes in the complexity of acute pain therapies and in the type of patient seen with acute pain.

Increasingly it has been recognized that comprehensive acute pain management does not mean just care of patients with pain from mainly postoperative and trauma-related causes, but includes the management of many patients with acute pain arising from a wide variety of conditions. There has been a growing shift in emphasis from the management of the symptom of acute pain to the practice of acute pain medicine, using a more biopsychosocial and multidisciplinary approach to the treatment of individual patients with a variety of medical, surgical, and psychological comorbidities.

This fourth edition remains a practical book on adult nonobstetric acute pain management only and detailed information about the anatomy, neurochemistry, and pathophysiology of acute pain has been omitted. It aims to provide nurses and nursing students, medical students, doctors in training (interns, house officers, residents, and registrars), and allied health staff with simple and practical information that will help them manage their patient with acute pain safely and effectively. Each of the chapters has been revised and updated, often extensively, to reflect current knowledge and practice. As more patients are leaving the hospital at a much earlier stage after surgery, or major injury, or medical illness than in the past and may require analgesia including opioids for short-term ongoing management of their acute pain at home, a new chapter looking at the prescription of opioid medications at the time a patient leaves the hospital has also been added. In this setting consideration must be given to possible risks that might be associated with this prescription, and what information the patient and their treating doctors and other healthcare professionals might need to have.

Suggested drugs, doses, and treatment regimens are guidelines only and may have to be adapted according to different patients and clinical situations.

Key references have been added to the text, but a comprehensive summary of available evidence is not possible in a book of this size. Both authors have been involved as editors in the second and third editions of *Acute Pain Management: Scientific Evidence* published by the Australian and New Zealand College of Anaesthetists and the Faculty of Pain Medicine, and endorsed by many national and international professional bodies including the International Association for the Study of Pain. PEM was the lead editor for the second and third editions and SAS is the lead editor for the fourth edition to be published in 2015. Readers are referred to this document (http://www.fpm.anzca.edu.au/resources/books-and-publications) for a more detailed overview of the evidence available for each of the chapters in this book.

Provision of safe and effective acute pain management as well as advances in acute pain medicine result from the work of many. We would like to acknowledge the help and advice of just some of the many colleagues with whom we have worked—nurses, anesthesiologists, and pharmacists, as well as those in drug and alcohol, chronic pain, surgical and medical services.

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Disclosures

Pamela Macintyre has no conflicts of interest to disclose.

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Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our knowledge, changes in practice, treatment, and drug therapy may become necessary or appropriate. Readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of the practitioners, relying on their own experience and knowledge of the patient, to make diagnoses, to determine dosages and the best treatment of each individual patient, and to take all safety precautions.

The content includes discussion of "off label" use of some medications.

Authors

Pamela E. Macintyre, after starting her anesthetic training in England and completing it in Adelaide, Australia, spent two years working in Seattle, Washington, leaving just as Dr. Brian Ready was starting his pioneering anesthesiology-based postoperative pain management service. After returning to Adelaide she was given the chance to set up the first formal Acute Pain Service (APS) in Australasia. Dr. Ready and his team kindly shared copies of their guidelines, protocols, and educational materials to serve as a basis for the start of the APS in Adelaide. Dr. Ready was also a coauthor for the first two editions of this book.

Pam Macintyre has been the director of the APS at the Royal Adelaide Hospital in Adelaide, South Australia, since it was established at the beginning of 1989. Her areas of interest range from general hospital-wide non-APS acute pain treatments to the management of acute pain in more complex patients (especially the older patient, the opioid-tolerant patient and the patient with an addiction disorder) and the safety of and education about acute pain medicine.

Stephan A. Schug is a German trained specialist anaesthetist with an MD in pharmacology. He worked for the University of Cologne, Germany, before becoming chair of anaesthesiology at the University of Auckland in New Zealand. He is currently chair of anaesthesiology in the Pharmacology and Anaesthesiology Unit of the University of Western Australia and director of pain medicine at Royal Perth Hospital.

His main research interests are the pharmacology of analgesics and local anesthetics, the management of acute, chronic and cancer pain, regional anesthesia and analgesia, organizational structures for pain management and reduction of adverse events in hospitals.

Overall he has written over 250 publications, book chapters, and books, mainly in the areas of regional anesthesia and acute and chronic pain management and is often invited to present at national and international conferences.

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CHAPTER 1

Introduction

Over the past years, advances in the management of acute pain have continued, although reports of inadequate pain relief in hospital patients persist. While inadequate staff education and cost restraints may still play a role in this, there has been better recognition of some of the factors that are linked to interindividual variation in reports of pain and response to analgesic medications, as well as a change to looking at outcomes related to pain relief in broader terms—that is, more than just pain scores immediately after surgery or injury. There has also been an increasing shift in emphasis from the management of the symptom of acute pain to the practice of acute pain medicine, using a more biopsychosocial and multidisciplinary approach to the treatment of patients with a variety of medical, surgical, and psychological comorbidities.

Evidence-based medicine is said to be "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al., 1996) and acute pain management practices should also be based on the best possible evidence available. However, if a patient is to get good pain relief and good outcomes from their acute pain treatment, individual variability needs to be considered. Appropriate alterations may need to be made to treatment guidelines, even if they are evidence based, and also to some of the outcomes being sought.

Individualization of treatment does not just apply to the drugs and techniques used for pain relief (see Chapters 4 through 10). There are also some clinical situations or patient groups where pain management may be more problematic and additional knowledge is required (see Chapters 12 through 15).

1.1 Effectiveness of acute pain management

1.1.1 Assessment of effectiveness

Since the 1960s, studies of adult hospital patients have consistently highlighted inadequacies in the treatment of acute pain. Changes made to treatment over the last 20 years or more have included the introduction of new techniques for the delivery of analgesic drugs (e.g., patient-controlled and epidural analgesia), the development of the concept of multimodal analgesia, the use of new drugs and new ways of using old drugs and the establishment of acute pain services. Despite this, around 40% of hospital patients in general still report moderate and severe pain, with the highest percentage—around 50%—reported in surgical patients (Wadensten et al., 2011; Carr et al., 2014). Nearly 10% may also have moderate or severe pain at the time of discharge from hospital (Carr et al., 2014), some requiring ongoing opioid analgesia at home—see Chapter 15.

One cause of inadequate analgesia is the ongoing prescription of opioids via one of the more traditional routes of administration (e.g., intermittent intramuscular [IM] or subcutaneous [SC] opioid analgesia). However, even IM, SC,

and oral opioid analgesia can be improved if treatment is individualized and timely—see Chapter 7. And while patient-controlled analgesia (PCA) and epidural analgesia are considered to provide better pain relief, they will only be safe and effective if appropriately managed and monitored. If a patient is just given a PCA machine, with inadequately trained nursing and medical staff and without adequate explanation of the technique, results may be at best disappointing and at worst, unsafe. Similarly, the practice of epidural analgesia without adequate staff education, regular anesthesiology review, and 24-hour backup may also lead to problems ranging from inadequate pain relief to delayed recognition of complications such as an epidural hematoma or abscess, and therefore an increased risk to the patient of permanent neurological damage.

While the aim of acute pain management should be to deliver effective pain relief for all patients, assessing its "effectiveness" must take into account not only a patient's pain scores, but also other aspects that might impact on patient outcome. In the short term, the most important aspect is patient function (e.g., ability to undertake physiotherapy, ambulate, cough), the key factor in effective early rehabilitation. An analgesic regimen should not be presumed to have "failed" solely on the basis of reported high pain scores, as there may be many reasons for this. However, functional limitation as a result of pain means that reevaluation of therapy is required. In the long-term, other factors such as the risk of the patient developing persistent postsurgical pain may also be of importance—see below.

1.1.2 Variability in effectiveness

Apart from the drug or technique used to provide pain relief, various other factors can affect the degree of pain or pain relief experienced. In most but not all cases, the differences are of interest only and cannot yet be used as a basis for individualizing patient treatment.

For example, morphine appears to have greater efficacy in women in both experimental opioid and clinical PCA opioid (but not opioid analgesia in general) studies (Niesters et al., 2010). Pain reports are also higher in females than in males with similar disease processes or in response to experimental pain stimuli (ANZCA and FPM, 2010) and after surgery (Gerbershagen et al., 2014).

Cultural and ethnic differences in response to pain in both the experimental and clinical settings have also been reported, as have disparities in the treatment of pain, including the likelihood of being given an opioid for pain relief (ANZCA and FPM, 2010; Meghani et al., 2012).

Genetic differences can affect both the individual's sensitivity to pain as well as their response (both effect and adverse effects) to opioids (Smith and Muralidharan, 2012). Of particular importance in the acute pain setting is the genetic variability in the enzyme CYP2D6 which is responsible for the metabolism of codeine to morphine, and can result in very different plasma levels of morphine for a given codeine dose—see Chapter 4.

Other factors that have been shown to be predictors of higher postoperative pain reports are younger age (pain decreases as age increases) and the presence of preoperative pain (Sommer et al., 2010; Gerbershagen et al., 2014). Preoperative anxiety and depression or negative affect and pain catastrophizing may also correlate with higher postoperative opioid requirements and/or pain intensity (ANZCA and FPM, 2010; Sommer et al., 2010). The fact that

the surgery is major may not predict higher reports of pain, as pain can be severe even after minor surgery, if patients do not get the analgesia they require (Gerbershagen et al., 2013).

1.2 Adverse effects of undertreated severe acute pain

In the past, many believed that pain was a natural, inevitable, acceptable, and harmless consequence of surgery and trauma. However, undertreatment of severe acute pain, coupled with the physiological response to surgery known as the injury or stress response, can have a number of adverse consequences including an increased risk of persistent (chronic) pain (see Table 1.1) (ANZCA and FPM, 2010).

Unfortunately, while the risks of undertreated acute pain are well known, there is limited evidence that better pain relief will attenuate even some of these risks. A lower risk of cardiovascular and respiratory complications after surgery, for example, has really only been shown to follow the use of epidural analgesia (Popping et al., 2014) (see Chapter 9).

1.3 Acute pain management and patient outcomes

However, effective analgesia may at least partially reverse some of the harmful effects outlined in Table 1.1 and will assist in early mobilization and rehabilitation of the patient. Thus, treatment of acute pain is important not only for the humanitarian reasons of patient comfort and satisfaction, but also because it may lead to better patient outcomes—both in the short- and long term.

Table 1.1 Adverse effects of undertreated severe acute pain

Cardiovascular	Tachycardia, hypertension, increased peripheral vascular resistance, increased myocardial oxygen consumption, myocardial ischemia, altered regional blood flow, deep-vein thrombosis, pulmonary embolism
Respiratory	Decreased lung volumes, atelectasis, decreased cough, sputum retention, infection, hypoxemia
Gastrointestinal	Decreased gastric and bowel motility
Genitourinary	Urinary retention
Neuroendocrine/metabolic	Increased catabolic hormones: glucagon, growth hormone, vasopressin, aldosterone, renin, and angiotensin Reduced anabolic hormones: insulin, testosterone Catabolism leads to hyperglycemia, increased protein breakdown and negative nitrogen balance; these factors impair wound healing and promote muscle wasting
Musculoskeletal	Muscle spasm, immobility (increasing risk of deep-vein thrombosis), muscle wasting leading to prolonged recovery of function
Central nervous system	Chronic (persistent) pain due to central sensitization
Psychological	Anxiety, fear, helplessness, sleep deprivation—leading to increased pain and potential long-term psychological effects

1.3.1 Short-term outcomes

Compared with conventional opioid analgesia (oral, IM), PCA results in better pain relief and greater patient satisfaction, without increasing the incidence of opioid-related side effects. Epidural analgesia has been shown to provide better pain relief compared with parenteral opioid analgesia and decrease the risk of postoperative pulmonary and cardiac complications along with enabling earlier return of bowel function.

Acute pain management may also assist in the achievement of other improved patient outcomes. For example, appropriate analgesic strategies are important components of many "early recovery after surgery" (ERAS) protocols—see Chapter 9—which allow patients to go home at a much earlier stage after their operation than in the past, without an increase in the rate of postoperative complications (Lv et al., 2012).

1.3.2 Long-term outcomes

Outcomes in the longer term are also important. The pain relief chosen may impact on the risk of the patient developing persistent postsurgical pain—see Chapter 12. It is also possible that ongoing treatment of acute pain with opioids after discharge from hospital may lead, in some patients, to inadvertent long-term opioid use and the risk of diversion and abuse (Macintyre et al., 2014)—see Chapter 15.

The ability of analgesic drugs to reduce the risk of cancer recurrence and spread after surgery has also been under discussion. Chemical mediators released as part of the perioperative physiological surgical stress response are thought to be one of the factors implicated in the promotion of cancer growth and metastases after cancer surgery (Gottschalk et al., 2010). Animal studies have shown conflicting results about the effects of morphine on cancer growth, however, studies of nonsteroidal anti-inflammatory drugs have shown some promise that COX-2 inhibition may reduce the risk of cancer recurrence and spread—both in prevention of morphine-induced cancer growth as well as in the absence of an opioid; animal models of spinal anesthesia have also suggested an anticancer effect (Ash and Buggy, 2013).

Evidence from human studies is lacking and while some benefit from regional anesthesia has been suggested in some cancer patient groups, better randomized and prospective studies are needed.

Key points

1. Acute pain relief continues to be suboptimal for many patients.
2. The "effectiveness" of any analgesic strategy must take into account more than a patient's pain scores, and assess other aspects of pain relief (e.g., function) that impact on patient outcome both in the short- and long term.
3. A number of factors can affect the degree of pain reported or pain relief experienced—for example, age and sex of the patient, and psychological and genetic makeup. In most cases, the differences are of interest only and cannot yet be used as a basis for individualizing patient treatment.

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CHAPTER 2

Delivery of effective acute pain management

As noted in the previous chapter, acute pain relief for many patients remains suboptimal, despite the advances of the past 20–30 years. One of the reasons for continued inadequate treatment could be that it is not so much a case of "what is used" but "how it is used."

To a large extent, effective management of acute pain depends on the different components of the systems involved in its delivery. These include factors related to staff and patient education and the systems (including guidelines and protocols) that institutions have in place. These factors may be as, if not more, important than the analgesic techniques and drugs themselves.

In many institutions, acute pain services (APSs) will play a key role in the delivery of acute pain management, especially when more complex analgesic techniques are involved and when management involves more complex patients.

Some thought also needs to be given to how ongoing management of acute pain will be managed, if needed, once the patient is discharged from hospital—see Chapter 15.

2.1 Education

A continued reason for deficiencies in the management of acute pain is inadequate education of medical, nursing, and allied health staff and students, patients, and their families and friends. Unfortunately, adequate education is still not always provided in schools of medicine and nursing, with some studies showing that more time is allocated to teaching about pain in veterinary and dental schools (Macintyre et al., 2014).

2.1.1 Medical staff

Education of junior medical staff should include all aspects of the management of acute pain. Responsibility for more conventional methods of analgesia is often delegated to these junior staff and while they will not be directly responsible for the more advanced methods of pain relief, they must have a sound working knowledge of them. As well as having an awareness of possible complications and drug interactions, they should be able to explain the techniques to both patients and their relatives.

2.1.2 Nursing staff

Ward nurses are directly involved in the management of all forms of pain relief and play a key role in ensuring that analgesia, whether simple or sophisticated, is safely and effectively managed. Education and accreditation programs are therefore essential.

General education will lead to a better practical understanding of the relevance of appropriate pain relief for patient wellbeing and outcome, as well as the drugs and techniques used and how to adjust analgesic regimens according to effect and side effects. The importance of patient education as well as issues related to the treatment of pain in cognitively impaired patients and in patients from different cultures as well as in other more complex patient groups (e.g., those with an addiction disorder) also needs to be recognized.

Specialized education will then lead to a better understanding of more sophisticated methods of pain relief such as patient-controlled analgesia (PCA), and epidural or other regional analgesia.

The time available for education within a hospital is often limited and priorities must therefore be set regarding the importance of various pain topics. It is much more important, for example, for nurses to understand the principles of safe opioid titration than for them to be taught excessive detail about the physiology of pain.

Many institutions require some form of certification or accreditation before nurses can assume responsibility for a patient whose pain is being managed using one of the more advanced methods of pain relief listed above.

Accreditation programs often consist of

- Verbal and written information (e.g., lectures—face-to-face or online, workshops, and booklets).
- Written assessment (e.g., multiple choice questionnaires).
- Practical assessment (e.g., demonstration of ability to program machines, administer epidural bolus doses).

Reaccreditation every 1–2 years will help ensure that knowledge and practices are regularly updated. Formal education programs need to be supplemented with informal "one-on-one" teaching in the ward.

2.1.3 Patients

Evidence for the benefit of patient education in terms of better pain relief is inconsistent, although patient satisfaction is likely to be increased and anxiety decreased (Royal College of Anaesthetists, 2012). However, patients who learn to assess their pain, know a little about the side effects of treatment, and are made aware that they should ask for more pain relief when needed, will have more control over the dose and delivery of analgesic drugs, regardless of the analgesic technique used.

Information should be given to each patient and tailored to the needs of that patient. It can be presented in a number of ways—verbally, in a booklet, or on a video/CD/DVD. Increasingly, good-quality patient information is also available on the websites of professional colleges and organizations. In general, a mix of verbal and written/visual probably gives the best results (ANZCA and FPM, 2010). As most patients remember only a small part of any information presented at one time, it may need to be repeated.

Examples of written patient information available on the Internet and in printed form are given in the Appendices at the end of this chapter. Written and verbal information should also be given at the time of discharge from hospital if ongoing acute pain management will be needed—see Chapter 15.

The education requirements for patients are twofold—general and specialized.

2.1.3.1 General

Patients should know why effective analgesia is important for their recovery as well as their comfort. The benefits of physiotherapy and early mobilization should be explained and that pain relief with movement is a key aim. They should be assured that every attempt will be made to make them as comfortable as possible, but that pain scores of zero at all times are usually not achievable.

Methods used in the measurement of pain should also be outlined. In some patients an explanation that high pain scores do not always mean that higher opioid doses must be given, and that in some circumstances other analgesic regimens (drug and nondrug) may be of more benefit, may be required. It is also worth explaining that excessive sedation means they need a little less opioid.

Patients should be encouraged to tell their doctors and nurses if analgesia is inadequate or if they are experiencing side effects. If intermittent opioid regimens are being used, the importance of asking for the next dose as soon as they begin to feel uncomfortable should be explained. They should not feel they are "bothering" busy nursing or medical staff.

Many patients (or their relatives) are still concerned about the risks of addiction, dependence, or tolerance to opioids. Repeated explanations, where appropriate, may be required to allay these fears.

2.1.3.2 Specialized

Explanations of individual analgesic techniques such as PCA and epidural analgesia should be given, including expected duration of therapy and subsequent analgesic management. The description of PCA does not have to be technically detailed. However, patients must know that they can press the button whenever they are uncomfortable and that they are the only ones allowed to do so (i.e., family and staff are not permitted to do so).

The possible side effects and complications of epidural analgesia should also be explained, including the need to immediately report any increasing back pain or neurological symptoms which may occur at any time before or after discharge from hospital.

2.2 Guidelines and protocols

The aim of guidelines is to try and improve the quality of clinical decision making, improve quality of care, and minimize potential harm. Concerns that guidelines may restrict clinical practice are not new and it is said that even Plato, in the fourth century BC, worried that they could limit treatment flexibility as they are usually based on what works for the average patient only (Hurwitz, 1999). Guidelines should aim to assist and not dictate clinical practice and clinical judgment is still required to individualize patient treatment. However, while it is recognized that they may not be suitable for all patients on all occasions, guidelines can still form a good foundation for treatment choices. They also enable some consistency in understanding and practice between all staff in the hospital.

Even where good guidelines exist, it is their dissemination and implementation that often remains the greatest obstacle to their use. This may be especially the case when guideline developers are remote from the site of practice and there is no sense of local "ownership." Resource availability, the availability of staff with pain management expertise who can act as guidelines "champions," and the

existence of formal quality assurance programs to monitor pain management, can all improve the use and effectiveness of guidelines. It is also important that guidelines are kept up to date and based on the best evidence, where available.

Regardless of drug or technique used for pain relief, or whether analgesia is considered "simple" or "advanced" (e.g., PCA and epidural analgesia), guidelines and "standard" orders can help make pain relief safer and more effective (ANZCA and FPM, 2010). As well as information about the drugs to be used (e.g., indications, contraindications, doses, dose intervals, and available drug concentrations), consideration should also be given to "standardizing" other aspects of the delivery of analgesia. These include education of nursing and medical staff, and patients; monitoring requirements, including regular assessments of adequacy of analgesia and adverse effects; the response to inadequate analgesia; the response to and treatment of side effects; nursing procedures and protocols; equipment used; and labeling of infusion pumps and lines.

Examples of "standard orders" and treatment guidelines are given in Chapters 7 through 10 of this book.

Guidelines relating to the management of acute pain have also been issued by professional bodies in a number of countries (ANZCA and FPM 2010; American Society of Anesthesiologists Task Force on Acute Pain, 2012). Procedure-specific guidelines for pain after a number of operations are also available (PROSPECT).

2.3 Acute pain services

The first anesthesiologist-based APS in the United States was started by Ready in 1986 (Ready et al., 1988). Since that time many hospitals worldwide have followed suit and the number continues to grow.

There is a very wide diversity of APS structures, with no consensus as to the best model, and no agreed definition of what might constitute such a service. Currently, APS structures vary from nurse-based, usually anesthesiologist-led but without daily participation by an anesthesiologist (Rawal, 1997), to anesthesiologist-based and providing 24 hour cover, with or without involvement of pharmacists or other staff (Ready et al., 1988; Macintyre et al., 1990; Schug and Haridas, 1993). From the early days when an anesthesiologist-based APS was primarily a postoperative pain service, APSs in some centers have evolved into comprehensive inpatient pain services, extending their work beyond the surgical setting and throughout the hospital as a whole. There has also been a shift in emphasis in these services from protocol-driven management of the symptom of acute pain to the practice of acute pain medicine, using a more biopsychosocial and multidisciplinary approach to the treatment of patients with a variety of medical, surgical, and psychological comorbidities (Upp et al., 2013).

All rely on APS nurses and regardless of the model chosen, an organized team approach is important. Whether simple or "high-tech" analgesic options are used, patients whose pain relief is managed by an APS may have less pain, suffer fewer side effects, and express greater satisfaction, than patients whose pain management is supervised by less experienced staff (ANZCA and FPM, 2010).

Unfortunately, many APSs have tended to concentrate on the "high-tech" approaches to pain relief and placed much less emphasis on improving the simple methods of analgesia throughout their hospital. This approach benefits only a small proportion of patients. This need not be the case, as the organization of an APS can be such that pain management for all patients in the institution will improve.

All APSs should also assist in the development of undergraduate and postgraduate education programs and evidence-based acute pain medicine guidelines and protocols to be used throughout the hospital, and collaboration and communication with other medical and nursing services at both local and, sometimes, national levels (Table 2.1).

Table 2.1 Role of an acute pain service

- Education (initial, updates)
  - Anesthesiologists
  - Nurses (accreditation/reaccreditation programs)
  - Patients and carers/families
  - Medical and nursing students
  - Junior medical staff
  - Surgeons and physicians
  - Pharmacists
  - Physiotherapists
  - Hospital administrators
  - Health insurance carriers
- Introduction and supervision of more advanced analgesic techniques including:
  - Patient-controlled analgesia
  - Epidural and intrathecal analgesia
  - Other continuous regional analgesia techniques
- Assistance in improving traditional analgesic treatment regimens including:
  - Intermittent opioid regimens (IM, SC, IV, and oral)
  - Non-opioid analgesia
- Standardization of
  - Equipment
  - "Standard orders" for simple and advanced analgesic techniques
    - Drugs, doses, and drug dilutions
    - Diagnosis and treatment of side effects
    - Specific monitoring requirements for each analgesic technique
  - Nursing procedure protocols
  - Guidelines for the monitoring of all patients receiving opioids
  - Guidelines for the use of other analgesic drugs and adjuvant agents
  - Nondrug treatment orders, for example, the use of oxygen, antireflux, and antisyphon valves
- 24-hour availability of pain service personnel for
  - Scheduled daily rounds of all patients under care of the APS
  - Additional reviews as needed of patients with ongoing pain problems
  - Treatment of complications of pain treatment
  - Initiation of new pain management modalities on request
  - Provision of advice about any pain management problems in any other patient
- Collaboration and communication with other medical and nursing services including:
  - Chronic pain clinics

(*continued*)

Table 2.1 (continued) Role of an acute pain service

- Drug and alcohol services
- Psychiatry services
- Palliative care services
- Surgical and medical services
- Collaboration and communication with hospital pharmacy services
- Regular audit of activity and continuous quality improvement
- Clinical research

Key points

1. Safe and effective acute pain management, including "simple" techniques of pain relief, may result more from appropriate education and better organizational structures for the delivery of pain relief than the analgesic drugs and techniques themselves.
2. Guidelines can improve the quality of clinical decision making and care and minimize potential harm. However, they may not be suitable for use in all patients and clinical judgment in their application is always required.
3. In many APSs, emphasis has shifted from protocol-driven management of acute pain to the practice of acute pain medicine using a more biopsychosocial and multidisciplinary approach to patient treatment.

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Appendix 2.1: Examples of patient information available on the Internet

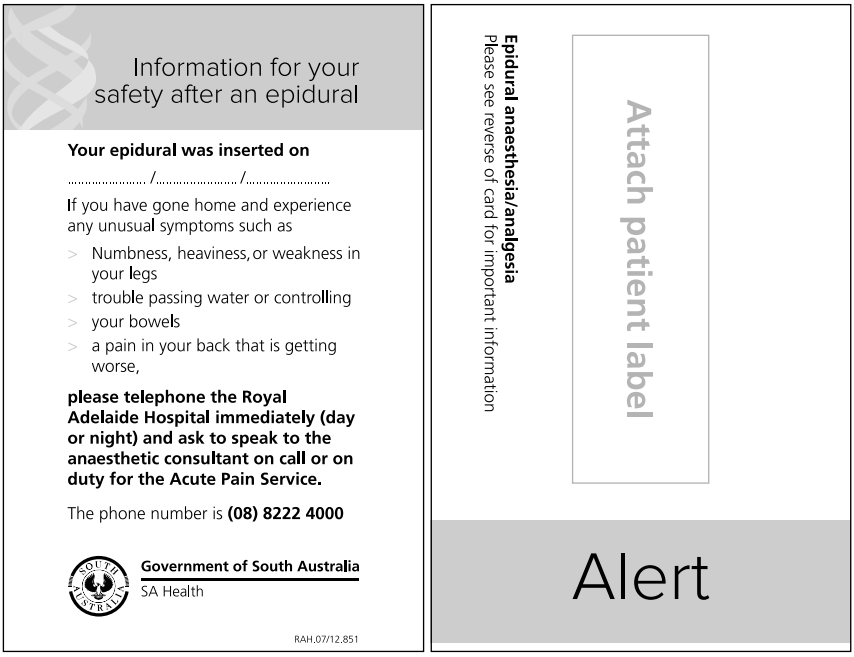
Australian and New Zealand College of Anaesthetists, Faculty of Pain Medicine

1. *Managing Acute Pain: A Guide for Patients.* http://www.fpm.anzca.edu.au/resources/books-and-publications. Accessed October 2013.

Royal College of Anaesthetists

1. *Epidurals for Pain Relief after Surgery* (2008). http://www.rcoa.ac.uk/system/files/PI-EPRS-2008.pdf. Accessed October 2013.
2. Nerve damage associated with a spinal or epidural injection (2013). http://www.rcoa.ac.uk/system/files/PI-Risk11_1.pdf. Accessed March 2014.

Appendix 2.2: Example of an epidural analgesia information card given to patients on discharge from hospital



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CHAPTER 3

Assessment and monitoring

The International Association for the Study of Pain defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Merskey, 1979: 250).

Pain is therefore a very individual and subjective experience. There are many behavioral, psychological, and social factors that may increase or decrease the patient's response to, and report of, pain. These factors may include previous pain experiences, cultural background, social supports, meaning, and consequences of the pain (e.g., disease or surgical prognosis, loss of employment) and psychological factors such as fear, anxiety, or depression. These will interact to produce what the patient then describes as pain. The experience of pain is therefore different from nociception (see below).

Effective and safe management of acute pain is best achieved by tailoring pain therapies to the individual patient. This means selection of an appropriate treatment regimen which is then modified as needed, based on assessments of adequacy of pain relief and onset of any side effects or complications. Over the years, emphasis has been placed on the need to assess pain on a regular basis and as the "fifth vital sign," a term first promoted by the American Pain Society (Veterans Health Administration, 2000). However, in many instances, the need to also monitor for the early onset of adverse effects related to treatment has not received the same attention. Without this, individualized, effective yet safe management of acute pain is not possible.

In the chapters that follow, suggested strategies for the optimal use of many of the drugs and techniques used in acute pain management are outlined, as are some of the various side effects and complications that may result from their use. The basic tools that will allow pain and the response to therapy to be assessed and for treatment regimens to be adjusted to suit individual patients are described below.

3.1 Types of pain

Pain can be broadly classified into two types—nociceptive and neuropathic, although both may be present in the same patient at the same time. It is useful to differentiate between the two as the type of pain may affect treatment choice. The response to analgesic strategies and the duration of pain may also vary. Common clinical features of the different pain types are summarized in Table 3.1 (Victorian Quality Council, 2007; Scott and McDonald, 2008; ANZCA and FPM, 2010).

Nociceptive pain (somatic or visceral) is the most common type of pain seen in acute clinical settings. It results from stimulation of specialized sensory nerve endings called nociceptors, as a consequence of tissue damage and subsequent inflammation. Inflammatory mediators such as prostaglandin enhance the sensitivity of nociceptors, a process described as peripheral sensitization. Ongoing peripheral nociceptive stimuli will increase the excitability of neurons

Table 3.1 Features of nociceptive and neuropathic pain

Pain type	Clinical features may include:
Nociceptive pain	
Somatic	Sharp, hot, or stinging pain which is usually well localized to the area of injury
Visceral	Dull, cramping, or colicky pain which is often poorly localized
	Pain may be referred over a wide area
	There may be associated symptoms such as nausea and sweating
Neuropathic pain	History of injury or disease leading to damage of peripheral or central nervous system (see examples in Chapter 12)
	Usually some evidence of damage to peripheral or central nervous system (e.g., sensory or motor loss), but if resulting from very minor nerve injury neurological signs or symptoms may be absent
	Pain confined to the innervation area correlating with this damage, but often poorly localized
	Pain that is different in nature to nociceptive pain, for example, burning, shooting, or stabbing pain
	Pain may be spontaneous or paroxysmal, with no clear triggers
	Pain that appears to be responding poorly to opioids
	Pain that appears to respond well to antineuropathic agents
	Phantom phenomenon
	Increased sympathetic activity (alterations in skin color, temperature and texture, sweating)
	Allodynia: the sensation of pain in response to a stimulus that does not normally cause pain (e.g., light touch)
	Hyperalgesia: an increased (i.e., exaggerated) response to a stimulus that is normally painful
	Dysesthesias: unpleasant abnormal sensations

in the spinal cord, leading to central sensitization. Peripheral and central sensitization result in amplification of subsequent pain stimuli and a lowered pain threshold.

Neuropathic pain has been defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system"—the lesion or disease may involve the peripheral or central nervous systems (Haanpaa et al., 2011). Following such injury, a number of changes occur and these are summarized in Chapter 12. As a result of these changes, the patient may exhibit signs and symptoms that are typical of neuropathic pain (Table 3.1). Neuropathic pain is a common cause of chronic pain, but it is also an often unrecognized component of acute pain—see Chapter 12.

3.2 Assessment of pain and pain relief

The key components of assessment are the pain history, measures of pain severity, the functional impact of pain, and response to treatment. There also needs to

be an understanding of some of the psychological factors that may contribute to the reported pain experience.

3.2.1 Pain history

A pain history, in addition to a general medical history and examination, provides important information that will help in both the diagnosis of the cause and type of pain and response to treatment. The basic elements of a pain history are summarized in Table 3.2. A pain history should not only be done when the patient is first seen, but repeated whenever there is a change in the nature or intensity of the pain, or when pain is not responding well to treatment.

3.2.2 Measurement

A number of simple clinical techniques are available for assessment and measurement of pain and its response to treatment (Scott and McDonald, 2008; ANZCA

Table 3.2 Basic elements of a pain history

Site of Pain	Primary location and any radiation
Conditions associated with pain onset	E.g., time of onset, precipitating events
Character of the pain	Sensory descriptors, e.g., sharp, throbbing, aching
	Neuropathic pain characteristics, e.g., burning, shooting
Intensity of the pain	At rest and on movement
	Duration
	Whether it is continuous or intermittent
	Any aggravating or relieving factors
Associated symptoms	E.g., nausea, sweating
Evaluation of function	Effect of pain on mobility, activities and sleep
Current and prior treatments for pain	Doses of current and previous medications including analgesic drugs, frequency of use, efficacy, side effects
	Other nondrug treatment
	Health professionals consulted
Relevant medical history	Prior or coexisting pain and medical conditions and treatment outcomes
Other patient factors	Beliefs concerning the cause of the pain
	Knowledge, expectations, and preferences for pain management
	Expectations of outcome of pain treatment
	Typical coping response for stress or pain, including presence of anxiety or psychiatric disorders (e.g., depression or psychosis)
	Family expectations and beliefs about pain, stress, and postoperative course

Source: Adapted with permission from *Acute Pain Management: Scientific Evidence*, Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010).

and FPM, 2010). Given the multidimensional nature of the pain experience, it is not surprising that there is often a poor correlation between the patient's assessment of pain and the estimate by others of the pain that the patient is experiencing. The best pain measures involve self-reporting by the patient rather than observer estimation.

Assessment of function is also important, particularly if a patient is unable to give a self-report of pain (e.g., because of cognitive impairment or language difficulty).

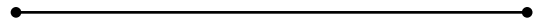
3.2.2.1 Unidimensional measures

In adults, three common self-report measures of pain intensity (a single dimension of pain) are the visual analog scale (VAS), the verbal numerical rating scale (VNRS) and the verbal descriptor scale (VDS). Each of these methods is reasonably reliable as long as endpoints and adjectives are carefully selected and standardized. While often used to compare levels of pain between patients, these methods of scoring pain are probably of most use when measuring changes within each patient.

There is a good correlation between the VAS, VNRS, and VDS (ANZCA and FPM, 2010).

3.2.2.1.1 Visual analog scale

The VAS uses a 10 cm line with endpoint descriptors such as "no pain" marked at the left end of the line and "worst pain imaginable" marked at the right end. There are no other cues marked on the line. The patient is asked to mark a point on the line that best represents their pain. The distance from "no pain" to the patient's mark is then measured in millimeters—this is the VAS score (0–100).



No pain *Worst pain imaginable*

The disadvantages of the VAS system are that it can be more time consuming than other simple scoring methods, specific equipment is needed (albeit very simple equipment such as pen and paper or a ruler), and some patients may have difficulty understanding or performing this score. One advantage is that the wording can be written in many different languages.

The VAS scale can also be adapted to measure other variables such as patient satisfaction, side effects such as nausea and vomiting, and degree of pain relief. The endpoints of a VAS for the latter would be "no relief" and "complete relief."

The numerical rating scale (NRS), a calibrated VAS with the numbers 0 to 10 marked on a horizontal line, is also sometimes used.

3.2.2.1.2 Verbal numerical rating scale

The VNRS is similar to the VAS. Patients are asked to imagine that "0 equals no pain" and "10 equals the worst pain imaginable" and then to give a number that would best represent their pain. Similarly, they could be asked to imagine that "0 equals no pain relief" and "10 equals complete relief of pain." The advantage of this type of system is that it does not require any equipment. However, problems may occur if there is a language barrier.

3.2.2.1.3 Verbal descriptor scale

Verbal descriptor or verbal rating scales use different words to rate the severity of pain, such as none, mild, moderate, severe, and excruciating. These scales are quick and easy to use and may be more reliable in some patients (e.g., the older patient). A VDS can also be used to measure pain relief with words such as none, slight, moderate, good, and complete.

3.2.2.1.4 What pain score is "comfortable"?

It is usually not possible, practical, or safe to aim for complete pain relief at all times with most of the drugs and drug administration techniques used in the treatment of acute pain. The aim of treatment should be patient comfort, both at rest and with physical activity.

Just as pain is a very individual experience, the correlation of "comfort" and a specific pain score may show marked interpatient variability. Therefore, alterations in analgesic regimens need to take into account a number of factors, including the patients' pain score, the level that they would regard as comfortable, and their functional ability as well as any preexisting pain and analgesic (particularly opioid) medications. The presence or absence of side effects from analgesic drugs will also affect what alterations are made to treatment orders. Changes based solely on a particular pain score may lead to excessive treatment in some patients and undertreatment in others.

Discrepancies between pain behavior and a patient's self-report of pain may result from different coping skills. Staff should not necessarily assume, for example, that a patient who is reading or sleeping is comfortable.

Similarly, high pain scores may not always require the dose of analgesic to be increased. This does not mean that the patient's report of pain is to be disbelieved, but that the appropriate therapeutic response to the reported pain may vary. For example, patients who are very anxious may report high pain levels (see below), yet treatment (not necessarily drug treatment) of that anxiety, rather than an automatic increase in opioid dose, may be preferable. Other patients may have pain which is less responsive to opioid drugs (e.g., neuropathic pain) and which may require treatment using other analgesic medications.

A reduction in pain intensity of 30%–35% has been rated as clinically meaningful by patients with acute pain from a variety of sources (e.g., after surgery, trauma, and acute cancer pain) (ANZCA and FPM, 2010).

3.2.2.1.5 When should pain be assessed?

Patients are often asked to rate their pain only when resting. However, a better indicator of the effectiveness of analgesia is an assessment of pain caused by physical activity such as coughing, deep breathing, or other movement. Therefore, pain scores at rest and with activity should be recorded.

Pain should be reassessed regularly during the treatment period. The frequency of this assessment will vary according to the analgesic regimen chosen and the patient's response to therapy. The frequency should be increased if pain is poorly controlled or if the pain stimulus or treatment interventions are changing. A repeat pain history will help determine if the nature of the pain has changed, if there a new cause for the pain (e.g., postoperative complication) or whether a change should be made to the analgesic regimen.

3.2.2.2 Assessment of neuropathic pain

The unidimensional tools described above are not adequate when it comes to identifying or quantifying neuropathic pain. In the acute pain setting, diagnosis often relies on a clinical assessment of the patient and recognition of signs and symptoms that are typical of neuropathic pain—see Table 3.1. In this setting specifically, response to medications (e.g., poor response to opioids, good response to antineuropathic agents) can be a useful indicator of the presence of neuropathic pain, as well as listening to the patient's description of pain: common descriptors include spontaneous, shooting ("electric-shock like") or burning pain, dysesthesia ("pins and needles," "ants crawling"), allodynia, and hyperalgesia (Searle et al., 2012).

A variety of screening tools assessing such verbal descriptions of neuropathic pain, with or without examination of the patient, have been developed to assist with its diagnosis. Most can identify patients with neuropathic pain with relatively high specificity and sensitivity, but cannot replace clinical assessment and judgment. Tools that have been validated for the diagnosis of neuropathic pain in general include *Douleur Neuropathique en 4 questions* (DN4), the *Leeds Assessment of Neuropathic Symptoms and Signs* (LANSS), the *Neuropathic Pain Questionnaire* (NPQ), *ID-Pain*, and the *PainDetect* questionnaire (Haanpaa et al., 2011). Many of them have been validated in a wide range of languages.

3.2.2.3 Other measures of pain

In some patients it may not be possible to obtain reliable self-reports of pain (e.g., where there are problems with communication due to language difficulties or cognitive impairment). In such patients, alternative measures of pain will be needed, such as assessment of patient behaviors (e.g., grimacing, groaning, guarding, or rubbing) or observing physiological responses to pain (e.g., increases in heart rate or blood pressure, sweating).

In older patients (see Chapter 14), a good correlation has been shown between unidimensional and behavioral measures in those who are cognitively intact, but it is not known if the same correlation exists in those with cognitive impairment.

Unfortunately, these changes in behavior are not unique to acute pain and assessment of pain by observation of patient behavior and/or vital signs should be reserved only for situations when self-report measures cannot be used.

Examples of some of the many observational pain assessment measures that have been developed to assist in the assessment of pain in patients who are unable to self-report include *Assessment of Discomfort in Dementia* (ADD), *Pain Assessment in Advanced Dementia* (PAINAD), *Non-communicative Patients' Pain Assessment Instrument* (NOPPAIN), *Pain Assessment Checklist for Seniors with Limited Ability to Communicate* (PASLAC), and the *Abbey Pain Scale* (Herr, 2011; Lints-Martindale et al., 2012). The *Algoplus* has been specifically developed for the assessment of acute pain in nonverbal adults (Rat et al., 2011).

3.2.2.4 Assessment of function

Measurement of pain is only one part of the evaluation of analgesic adequacy. Assessment of function, for example, the ability to take deep breaths, cough and ambulate after surgery, gives an important indication of the effectiveness of pain relief. An analgesic regimen should not be presumed to have "failed" solely on the basis of reported high pain scores, as there may be many reasons for this. However, functional limitation as a result of pain means that reevaluation of therapy is required.

Table 3.3 Functional activity scores

Score	Comments
A	No limitation of relevant activity
B	Mild limitation of relevant activity
C	Severe limitation of relevant activity

Source: Victorian Quality Council. *Acute Pain Management Measurement Toolkit.* http://www.health.vic.gov.au/qualitycouncil/downloads/apmm_toolkit.pdf Accessed February 2011.

Note: The score is assessed relative to the patient's baseline functional ability and based on activity that is relevant to the cause of the acute pain.

A number of assessment tools have been used to measure functional impact of pain in the chronic setting. However, a simple way to document functional ability in a patient with acute pain is to use the functional activity score (FAS) (Victorian Quality Council, 2007). It is designed to assess, using a "score" of A, B, or C (see Table 3.3), whether a patient's current level of pain relief enables them to undertake a relevant activity (e.g., deep breathing and coughing after a laparotomy, knee flexion after knee surgery), and act as a trigger for intervention should this not be the case. The score is assessed on the basis of limitation due to the "new" acute pain and not any preexisting baseline restrictions.

3.2.2.5 Pupil size

Pupil diameter cannot be used to assess whether a patient has satisfactory pain relief. However, it has been used in some studies as one measure of the pharmacodynamic effect of opioids and is known to vary in proportion to blood concentrations of the drug (Fedder et al., 1984; Knaggs et al., 2004). Therefore, it may be a simple way of monitoring the central nervous system (CNS) effects of opioids. If a patient reports inadequate analgesia but has very small pupils (assessed without direct light), it is reasonable to explain to the patient that this means the drug may already be exerting its near-to-maximal effect in the CNS and that different analgesic strategies may be indicated, as further increases in opioid dose may not be safe and/or at least some of their pain may not be responsive to opioids.

3.2.2.6 Patient satisfaction

Assessments of patient satisfaction are often used as an indicator of "good" or "bad" pain relief. However, they are really more a measure of the patient's overall satisfaction with their treatment. They can be influenced by factors other than pain intensity, such as expectations of pain, interference with functioning, analgesia-related adverse effects, and relationship with medical and nursing staff for example, ability to communicate well, kindness, and care shown, and information given (Bennett et al., 2007; ANZCA and FPM, 2010). Patients may report high levels of satisfaction even though they have moderate-to-severe pain.

3.2.3 Effect of psychological factors on acute pain

As outlined earlier, pain is an individual and subjective experience to which psychological and social factors contribute. That is, a number of psychological,

behavioral, environmental, and social factors may influence the patient's response to pain and pain therapy. These factors are important in acute as well as chronic pain settings, and in the transition from acute to chronic pain (see Chapter 12).

Much of the work looking at the effects of various psychological factors on acute pain intensity and opioid use has focused on patients after surgery. In the early postoperative period, preoperative anxiety, depression, and catastrophizing have all been shown to correlate with higher pain intensity and/or opioid requirements (ANZCA and FPM, 2010). The same factors have been cited as predictors of the risk of developing persistent pain after surgery (Hinrichs-Rocker et al., 2009; Theunissen et al., 2012) and have been associated with more widespread reports of pain and persistence of pain after acute musculoskeletal trauma (Macintyre et al., 2014).

Anxiety and depression also seem to be important variables affecting patient-controlled analgesia (PCA) use. Patients with preoperative anxiety or depression may have higher postoperative pain intensities and make more PCA demands, including more "unsuccessful" demands made during the lockout interval (ANZCA and FPM, 2010).

Of course, under-treated pain can also lead to, or increase, patient anxiety, fear, sleeplessness, and fatigue. Aggressive and belligerent behavior may be a sign of that anxiety and distress.

3.3 Assessment of adverse effects

To individualize treatment and maximize patient safety, there needs to be an ongoing assessment of any adverse effects that might be related to pain management therapies. The adverse effects and complications that can result from the treatment of acute pain will vary according to the drug and technique used, and are discussed in more detail in the chapters that follow. However, there are a number of parameters that should be monitored routinely in the acute pain setting if risk to patients is to be minimized. These include signs of excessive opioid doses, regardless of route of administration, and early signs of complications related to regional analgesia, particularly epidural analgesia.

3.3.1 Opioid-induced ventilatory impairment

Although opioids have been used for the treatment of acute pain for hundreds of years, reports of significant morbidity and mortality resulting from their adverse effect on ventilation continue. The true incidence of the problem is difficult to determine because of the many ways in which the effect of opioids on ventilation are evaluated in published studies. Commonly reported methods include assessment of respiratory rate, degree of sedation, and oxygen saturation, with carbon dioxide levels (the best indicator of inadequate ventilation) measured much less frequently.

Opioids cause a dose-dependent depression of ventilation that is usually referred to as respiratory depression. However, as outlined in Chapter 4, the term opioid-induced ventilatory impairment (OIVI) may be a more appropriate term to use as there are three aspects of ventilatory depression that must be considered (Macintyre et al., 2011). These are a central depression of the respiratory center, which can lead to a decreased respiratory rate and/or tidal volume; depression of the CNS in general, leading to reduced consciousness (sedation); and depression of supraglottic airway muscle tone, leading to upper airway obstruction—if obstruction is not complete the patient may snore.

Excessive doses of opioid may affect any or all of these aspects of ventilation, leading to both a rise in carbon dioxide (which can further increase sedation) and a fall in oxygen blood levels. However, any impairment that results is usually progressive and the risk of OIVI should be small if opioid doses are carefully titrated according to the pain the patient is experiencing while the patient is observed on a regular basis for signs of early OIVI.

The best way to monitor all patients on a routine basis for the onset of OIVI is still debated. In general, the options fall into two groups—measures that do not require electronic equipment (respiratory rate, level of sedation) and those that do (pulse oximetry, measurements of carbon dioxide). Of these, measurement of the patient's carbon dioxide level is the most sensitive and accurate way to detect OIVI in the clinical setting—the other options are only surrogate measures and not direct indications of adequacy of ventilation (Macintyre et al., 2011).

The Anesthesia Patient Safety Foundation in the United States has been at the forefront of discussions related to monitoring for OIVI. They recommend that continuous electronic monitoring should be used for all inpatients given an opioid in addition to nursing assessment including the patient's level of sedation (Stoelting and Overdyk, 2011). They recommend that pulse oximetry be used if supplemental oxygen is not given, and that measures of ventilation (carbon dioxide levels) be employed if it is.

Even if it was possible to use electronic monitoring equipment for every patient in hospital, it needs to be remembered that some patients will be taking opioids at home (see Chapter 15), so some simple clinical observation is still required.

3.3.1.1 Measurement of sedation score and respiratory rate

Although still commonly used, a decrease in respiratory rate is known to be a late and unreliable sign of OIVI and a normal rate may coexist with significant OIVI. This has been noted to the detriment of patients in multiple publications, when reliance on respiratory rate as an indicator of OIVI appears to have delayed its identification (Macintyre et al., 2011).

As significant OIVI is almost always accompanied by sedation, the best early clinical indicator is increasing sedation—a general measure of increasing CNS depression. This can be monitored using a simple sedation score that reflects a sensible progression of this depression (Table 3.4). It does mean that the patient must be woken so that their level of sedation can be assessed.

In general, a respiratory rate of ≤8 breaths/min is often considered to indicate OIVI. However, some patients may have rates as low as this, particularly when asleep, in the absence of OIVI. In some centers, these rates would be tolerated as long as the patient's sedation score was <2. As mentioned before, OIVI can coexist with a normal respiratory rate.

Therefore, regular assessment of level of sedation in any patient receiving opioid medications should be the "6th vital sign" (Macintyre et al., 2011).

3.3.1.2 Measurement of oxygen and carbon dioxide levels

Pulse oximetry is commonly used as an easy and noninvasive measure of blood oxygen saturation (SpO_2). The term SaO_2 refers to the oxygen saturation of arterial blood. Similarly, PaO_2 is the partial pressure (level) of oxygen in arterial blood, whereas $ETCO_2$ or $PetCO_2$ refers to end-tidal carbon dioxide levels—that is, at the end of expiration. Transcutaneous measurement of carbon dioxide is also possible ($PtcCO_2$).

Table 3.4 Assessment of opioid-induced ventilatory impairment

Sedation scores	0 = wide awake
	1 = easy to rouse
	2 = easy to rouse but unable to stay awake; early OIVI
	3 = somnolent, difficult to rouse; severe OIVI
	Note: these are reasonably similar to the definitions used in the sedation side of the Richmond Agitation and Sedation Scale often used in intensive care settings (Sessler et al., 2002).
Respiratory rate	Less than 8 breaths/min is often considered to be a sign of OIVI, but this is generally an unreliable indicator
	OIVI can coexist with a normal respiratory rate
Oxygen saturation	May also be unreliable, especially if the patient is receiving supplemental oxygen
	Oxygen saturation may be low for many reasons other than OIVI
	Unless pulse oximetry monitoring is continuous, intermittent episodes of low oxygen saturation may be missed
End-tidal or transcutaneous carbon dioxide levels	The most sensitive and accurate way to detect OIVI in the clinical setting but not yet in common use
	As with pulse oximetry, unlikely to be available on a continuous basis for all patients given an opioid

3.3.1.2.1 Oxygen saturation

Care must be taken in the interpretation of SpO_2 readings as OIVI is only one of the many possible causes of hypoxemia, particularly in the postoperative setting. In addition, if the patient is receiving supplemental oxygen, the added oxygen may mask the onset of OIVI (i.e., "normal" oxygen saturation levels may still be seen).

Reduced lung volumes, particularly vital capacity and functional residual capacity, are commonly seen after major surgery and contribute to a hypoxemia that may last for a few days even with good pain relief. Risk factors for postoperative hypoxemia include advanced age, upper abdominal and to a lesser extent other abdominal surgery, thoracic operations, major joint replacement surgery, obesity, preexisting lung disease, smoking, and severe pain.

In some institutions it is common practice to routinely administer oxygen to patients given patient-controlled or epidural/intrathecal analgesia at least. This practice has been criticized as risking a delay in the diagnosis of hypoxemia (Stoelting and Overdyk, 2011). However, significant hypoxemia can occur very rapidly, whereas the rate of rise of carbon dioxide levels and increase in sedation from CNS depression is relatively slow. Additional oxygen, which will not mask increasing sedation, may allow time for OIVI to be detected and appropriate interventions made (Macintyre et al., 2011).

While a low PaO_2 or SpO_2 in a patient receiving oxygen would indicate major abnormalities in respiratory function, a normal level in a patient receiving oxygen does not exclude abnormalities. When relying on SpO_2 as a measure of the patient's oxygenation, it is important to remember that the relationship between PaO_2 and oxygen saturation is not linear, due to the oxygen–hemoglobin

Table 3.5 Approximate relationship between PaO_2 and oxygen saturation

PaO_2 (mmHg)	PaO_2 (kPa)	Oxygen saturation (%)
100	13.3	98
90	12.0	97
80	10.7	95
70	9.3	93
60	8.0	90
40	5.3	75 (venous blood)
26	3.5	50

dissociation curve. Therefore, an SpO_2 of 93%, for example, which may seem reasonable to some, it is about the same as a PaO_2 of only 70 mmHg (9.3 kPa). Some approximate values worth remembering are listed in Table 3.5.

Unless continuous pulse oximetry is used, episodic hypoxemia (e.g., due to intermittent upper airway obstruction), which may be worse if the patient is asleep, may be missed.

3.3.1.2.2 Carbon dioxide levels

Measurement of a patient's carbon dioxide level is the most accurate way to detect OIVI. Monitors that can measure a patient's $PetCO_2$ or $PtcCO_2$ in general wards are becoming more common. However, it is unlikely that every patient given an opioid in every hospital will be able to have continuous $PetCO_2$ or $PtcCO_2$ and SpO_2 monitoring for some while yet.

3.3.1.3 When and whom to monitor for OIVI

The risk of OIVI is higher if other factors such as obesity, chronic obstructive pulmonary disease, obstructive sleep apnea (OSA), and abdominal distension are present, if other CNS depressant drugs are given (e.g., benzodiazepines, clonidine, some antiemetics, sedating antihistamines, and alcohol), (Lee and Domino, 2013) or when the patient is sleeping (Macintyre et al., 2011).

It is therefore sometimes recommended that patients assessed as being at a higher risk of OIVI should be monitored more closely. While this will be the case for selected patients, any attempts to rely more generally on "identification" of an "at-risk" patient will result some being missed. In addition, OIVI occurs in patients who are not assessed as high risk (Stoelting and Overdyk, 2011). It also appears that there is a "peak risk" period for the development of OIVI.

In an analysis of postoperative claims resulting in significant harm (death or severe brain damage in 80% of cases) from OIVI, there was evidence of excessive sedation in 60% of cases, OSA in 40%, coadministration of nonopioid sedative medications (38%), prescribing of opioids or sedatives by more than one physician (34%) and snoring (16%). Over 60% of the patients were obese and over 50% were aged 18–49 years (Lee and Domino, 2013). However, a key finding was that 87% of patients who came to harm from OIVI did so on the first day or night after surgery. It was concluded that patient outcomes may be improved if there was a focus on better monitoring of *all* patients in the high-risk period rather than only

patients deemed to be at high risk. It would seem that the first 24 hours of the commencement of an opioid is when the majority of (but not all) cases of OIVI occur (Ramachandran et al., 2011; Lee and Domino, 2013).

3.3.2 Motor and sensory function, back pain

Risks of epidural analgesia include the development of an epidural hematoma or abscess. This can result in nerve root and spinal cord compression and permanent neurological damage, including paraplegia (see Chapter 9). If a patient has an epidural catheter *in situ*, motor and sensory function should be monitored on a regular basis. Any reduction in function will usually be due to the local anesthetic in the epidural infusion. However, the presence of an epidural hematoma or abscess should always be excluded. This can be done by stopping the infusion for a time and checking that any deficit resolves. If the block does not resolve within a reasonable time, urgent investigation and surgical review will be required—see Chapter 9. Motor and sensory function should also be checked for a period after removal of an epidural catheter.

Increasing back pain may also be a sign of an epidural abscess or hematoma. It is worth noting that not all patients with an epidural abscess will be febrile.

3.3.3 Other parameters

Other parameters requiring assessment in the acute pain setting include blood pressure, heart rate, and urine output.

If a patient becomes hypotensive after receiving an opioid, regardless of route, they may be hypovolemic. Hypotension following epidural analgesia is often said to be more common but, if appropriate dose regimens are used (see Chapter 9), the incidence can be low. Once again, hypotension often indicates an underlying hypovolemia. Bradycardia associated with epidural analgesia could indicate that the level of the block is at T1–4, that is, at the level of the sympathetic nerves supplying the heart.

Urine output is also an important monitoring parameter. Not only might it be a sign of hypovolemia, it should indicate caution with the administration of NSAIDs and some other medications (see Chapter 6).

Key points

1. Key components of assessment are the pain history, measures of pain severity, the functional impact of pain, and response to treatment.
2. Self-reports of pain, both at rest and on movement, should be used whenever possible.
3. Uncontrolled or unexpected pain requires a reassessment of the patient and consideration of the cause of the pain (e.g., new diagnosis, neuropathic pain).
4. Safe and effective use of opioid medications requires individualization of the opioid regimen according to the onset of adverse effects as well as reported pain intensity.
5. Regular assessment of a patient's level of sedation is a more reliable clinical indicator of early OIVI than a decrease in respiratory rate.

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CHAPTER 4

Pharmacology of opioids

Opium and its many preparations have been used for the treatment of pain for over 2000 years. Many of its pharmacological effects, such as euphoria and sedation, appear to have been known as far back as at least 3000 BC, at the time of the ancient Sumerians and Minoans, and mention is made of its analgesic effect in Egyptian mythology (Benedetti and Premuda, 1990). However, while its use has continued over the years, and while it was prescribed by physicians such as Hippocrates for a variety of ailments, the first accepted written reference to its analgesic properties is said to be found in the third century BC writings of Theophrastus (a pupil of Aristotle), who also described its lethal effects (Benedetti and Premuda, 1990).

In 1806, Sertürner isolated the alkaloid of opium later called morphine (after Morpheus—the Greek god of dreams and son of Hypnos, god of sleep) (Hamilton and Baskett, 2000). The introduction of a glass syringe and hollow needle, and their use for subcutaneous (SC) injections in 1853, facilitated both the administration of morphine (Hamilton and Baskett, 2000) and its abuse. Heroin was synthesized and marketed for medical use in 1898 as it was believed to be nonaddictive (Rosow and Dershwitz, 2011).

Opium contains more than 25 different alkaloids. Only two of these have any analgesic action—morphine and codeine. Thebaine, another alkaloid, is used in the manufacture of other opioids including oxycodone, oxymorphone, and buprenorphine.

Drugs derived from the alkaloids of opium are called *opiates*. All drugs that have morphine-like actions, naturally occurring or synthetic, are called *opioids*. The term *narcotic*, derived from the Greek word for stupor, is also often used. However, it is probably best confined to a legal context, where it refers to a wide variety of drugs of addiction.

Morphine, codeine, and thebaine for commercial pharmaceutical use are still obtained from the opium poppy, *Papaver somniferum*. The amount of each alkaloid in the poppy depends on the variety, with poppy cultivars high in concentrations of thebaine now common. The more modern method of production harvests the dried poppy and extracts these alkaloids from the poppy straw.

Morphine remains the standard against which all new analgesics are compared. Although newer opioids may have different properties, in particular with regard to their pharmacokinetics, none is clinically superior in relieving pain. Therefore, many improvements in acute pain management have resulted from the better use of well-established opioids, rather than the use of newer drugs.

Tramadol and tapentadol are included in this chapter. Although not strictly conventional opioids, part of their analgesic effect is mediated via opioid receptors.

The information given below relates to the systemic use of opioid medications. However, some are also given in combination with drugs used for neuraxial analgesia (see Chapter 9).

4.1 Mechanism of action

Until the mid-1970s very little was known about the mechanism of action of opioid drugs. Since then, not only have receptor sites for these drugs been identified, but it was also discovered that the body is capable of producing its own endogenous ligands for these receptors (i.e., endogenous opioids).

4.1.1 Endogenous opioids

Endogenous opioids identified so far are *endorphins, enkephalins, endomorphins*, and *dynorphins*. They are found in the brain, spinal cord, gastrointestinal tract (GI), and plasma, and are released in response to stimuli such as pain or stress.

4.1.2 Opioid receptors

Opioid drugs produce their effect by acting as agonists at opioid receptors, which are found in the brain, spinal cord, and sites outside the central nervous system (CNS) including urinary and GI tracts, lungs, and peripheral nerve endings.

There are three principal types of opioid receptors for which opioids, both exogenous and endogenous, have an affinity. These are mu (μ), also referred to as MOP, delta (δ) or DOP, and kappa (κ) or KOP (Cox et al., 2009). The corresponding endogenous ligands (agonists) are β-endorphins, enkephalins, and endomorphins 1 and 2 at the μ receptor, β-endorphin and enkephalins at the δ receptor, and dynorphins A and B and α-neoendorphin at the κ receptor, respectively (Cox et al., 2009). A fourth receptor type, NOP, is not involved in opioid analgesia. The effects of activation of the different receptors are summarized in Table 4.1.

The pharmacological effects of a given opioid are the result of its receptor specificity, receptor affinity, and intrinsic activity at the various receptors. While receptor affinity determines the amount of opioid needed to occupy a given percentage of receptors, it is the intrinsic activity of the opioid that determines its analgesic efficacy.

According to their intrinsic activity at the opioid receptors, opioid drugs are classified as (Vallejo et al., 2011):

- *Agonists*: Drugs that bind to and stimulate opioid receptors and are capable of producing a maximal response from the receptor (i.e., have no ceiling effect).

Table 4.1 Opioid receptors and their effects

Receptor	Effects
mu (μ) or MOP	Analgesia, opioid-induced ventilatory impairment (OIVI), sedation, nausea and vomiting, inhibition of gut motility, euphoria, pruritus, tolerance, immune suppression
delta (δ) or DOP	Analgesia, opioid-induced ventilatory impairment
kappa (κ) or KOP	Analgesia, sedation, dysphoria, diuresis, miosis

Source: Modified from Vallejo R, Barkin RL, Wang VC. 2011. *Pain Physician* **14**(4): E343–60.

- *Antagonists*: Drugs that bind to but do not stimulate opioid receptors and may reverse the effect of opioid agonists.
- *Partial agonists*: Drugs that stimulate opioid receptors but have a ceiling effect (i.e., produce a submaximal response compared with an agonist).
- *Agonist–antagonists*: Drugs that are agonists at one opioid receptor type and antagonists at another.

Genetic polymorphisms of the μ-opioid receptor have been described and have been shown in some studies to affect pain relief and opioid requirements in patients given morphine and fentanyl after surgery (ANZCA and FPM, 2010). However, as yet, results are inconsistent and there are no reliable implications for opioid dosing or effect.

4.1.3 Placebo response

It is appropriate to discuss the issue of placebo response under the heading of mechanisms of action of opioids, as a major component of the analgesic placebo response is mediated via the endogenous opioid system. It is well known that some patients will obtain pain relief from nonanalgesic medications or interventions, or a greater than expected degree of relief from an analgesic drug or technique. This is known as the placebo analgesic response and it results, at least in part, from the release of endogenous opioids and nonopioid neuromodulators that can alter the experience of pain (Colloca et al., 2013). This has been confirmed by observations that pain relief obtained from nonanalgesic treatment is, at least to a significant degree, reversible by the administration of an opioid antagonist such as naloxone (Colloca et al., 2013).

4.2 Effects of opioids

As the main effects of most opioids are mediated via their activity at the μ-opioid receptor, both their analgesic effect and the spectrum of possible adverse effects are very similar. The adverse effects reviewed below relate to the use of opioids in the acute pain setting and in the short term. Additional effects that may be associated with long-term use will not be discussed but include increased risk of fractures, immunosuppression, and endocrine dysfunction (Baldini et al., 2012).

4.2.1 Analgesia

The major desirable effect of opioids is analgesia, which is mediated mainly via the μ receptor, although δ and κ receptor effects can also contribute to pain relief.

All full μ agonists are capable of producing the same degree of pain relief. Therefore, they can theoretically be made equianalgesic if adjustments are made for dose and route of administration (Table 4.2). However, it must be noted that standard equianalgesic dose tables often present average data based on older single-dose studies of the drugs in a variety of clinical situations (Knotkova et al., 2009; Vallejo et al., 2011). Inter-individual differences in pharmacodynamics, pharmacokinetics, comorbidities, concurrent medications, age and genetics as well as incomplete cross-tolerance between opioids in patients on long-term opioid therapy, are just some of the variables that can have a significant effect

Table 4.2 Equianalgesic doses and half-lives ($T_{1/2}$) of some commonly used opioids

Opioid	IV/IM/SC (mg)	Oral (mg)	$T_{1/2}$ (h)
Morphine	10	30	2–3
Alfentanil	0.75–1.5	–	1–2
Buprenorphine	0.4	0.8(SL)[a]	2–3 IV/IM
			24 SL
Codeine	130	200	2–4
Diamorphine[b]	5	60	0.5[b]
Fentanyl	0.15–0.2	–	3–5
Hydrocodone	–	20–30	
Hydromorphone	1.5–2	6–7	3–4
Methadone	10	10–20	8–60
Oxycodone	10	20	2–3
Pethidine (meperidine)	75–100	300	3–4
Sufentanil	0.02	–	2–3
Tramadol	100	150	5–7
Tapentadol	–	100	

Notes:

- The table has been compiled from values obtained from multiple references including Gupta et al. (2011), Vallejo et al. (2011), Analgesic Expert Group (2012), and ***Australian Medicines Handbook*** (2013).
- Published reports vary in the suggested doses considered to be equianalgesic to morphine. Therefore, titration to clinical response in each patient is necessary.
- Suggested doses are often based on single dose studies only. Therefore, use of the data to calculate total daily dose requirements may not be appropriate.
- These are doses that are thought to be equianalgesic. They are ***not*** recommended initial doses and are ***not*** suggesting that an IV dose of an opioid is the same as the SC or IM dose. Therefore, titration to clinical response in each patient is necessary.
- There may be incomplete cross-tolerance between these drugs. In patients who have been receiving one opioid for a prolonged period, it is usually necessary to use a dose lower than the expected equianalgesic dose when changing to another opioid, and to titrate to effect.

[a] SL, Sublingual.

[b] Rapidly hydrolyzed to morphine.

on the total daily doses that may be required (Knotkova et al., 2009; Vallejo et al., 2011).

If a change is made from one opioid to another, particularly if high doses or long-term use has been necessary, it is suggested that the alternative opioid be started at a lower than equianalgesic dose in the first instance. Subsequent doses can then be titrated to effect and side effects.

If a change is made from a parenteral route (intramuscular [IM], SC, or intravenous [IV]) to the oral route of administration, the bioavailability of the opioid has to be considered. In general, larger doses will be needed orally because of the "first-pass" effect as a proportion of an orally administered drug is metabolized by the liver and gut wall after absorption from the GI tract. This effect reduces the amount of unchanged drug that reaches the systemic circulation and thus the analgesic effect.

Table 4.3 Adverse effects of opioids

Respiratory system	Opioid-induced ventilatory impairment, cough suppression
Central nervous system	Sedation, euphoria or dysphoria, nausea and vomiting, miosis, cognitive impairment (and delirium), muscle rigidity, myoclonus, seizures
Gastrointestinal and genitourinary systems	Delayed gastric emptying, constipation, spasm of the sphincter of Oddi, urinary retention
Cardiovascular system	Vasodilatation, bradycardia, prolonged QT interval (some opioids)
Pruritus	Possibly more common with morphine
Allergy	A "true" allergy is uncommon
Longer-term effects	Tolerance, opioid-induced hyperalgesia, physical dependence

For all the above reasons, the suggested equianalgesic doses listed in Table 4.2 should be used as guides only. The list is limited to opioids in common use and not all will be available in every country. Furthermore, formulations, generic names, and trade names may vary.

Most opioids have a similar spectrum of adverse effects (see Table 4.3). Clinical trials in acute pain management have shown that opioids administered in equianalgesic doses to large population groups have a similar incidence and degree of side effects. However, there may be individual differences in patient responses and some patients may experience more side effects with one particular drug. In these instances, opioid rotation, that is, a change to another opioid, is appropriate.

4.2.2 Effect on the respiratory system

4.2.2.1 Depression of ventilation

Opioids cause a dose-dependent depression of ventilation that is usually referred to as respiratory depression. However, the term opioid-induced ventilatory impairment (OIVI) may be more appropriate as there are three elements to consider rather than just depression of the respiratory center only (Macintyre et al., 2011). These are

- Central depression of the respiratory center, decreasing respiratory rate and/or tidal volume
- Depression of the CNS in general, leading to reduced consciousness (sedation)
- Depression of supraglottic airway muscle tone, leading to upper airway obstruction (if obstruction is not complete the patient may be heard snoring)

Excessive doses of opioid may cause a progressive impairment of ventilation resulting in hypoxia and hypercapnia. Hypercapnia has a further direct depressant effect on the CNS.

The risk of OIVI is higher if other CNS depressant drugs (e.g., benzodiazepines, clonidine, some antiemetics, sedating antihistamines, and alcohol) are also given (Lee and Domino, 2013) or when the patient is sleeping. Other factors such as obesity, chronic obstructive pulmonary disease, obstructive sleep apnea, and abdominal distension may add to the risk (Macintyre et al., 2011). It does not

necessarily mean that these patients are more sensitive to opioids, but that they will have less ability (or physiological reserve) to cope with even a slightly excessive dose. For detail on the clinical relevance and the appropriate monitoring for OIVI related to opioid administration, see Chapter 3.

Pain appears to act as a physiological antagonist to OIVI. Therefore, in most cases and, and if opioid doses are carefully titrated according to the pain the patient is experiencing, the risk of OIVI is very small. However, OIVI can occur if the pain is either not or incompletely opioid responsive (e.g., neuropathic pain) and yet opioid administration is continued.

4.2.2.2 Cough suppression

Opioids directly inhibit the cough center in the medulla and may be used for the treatment of cough.

4.2.3 Nausea and vomiting

Nausea and vomiting are very common adverse effects of opioids and result from activity in the vomiting center located in the brain stem. This center may be activated by stimuli from the chemoreceptor trigger zone (CTZ), upper GI tract and pharynx, vestibular (motion) apparatus, and higher cortical areas (e.g., by olfactory, visual, or emotional stimuli) (Scholz et al., 2011). Opioids cause nausea and vomiting by stimulation of opioid receptors in the CTZ and the GI tract and these effects are enhanced by vestibular stimulation. Opioids can also increase vestibular sensitivity so that even slight movement, such as turning the head or moving in bed, may be enough to trigger nausea and vomiting in some patients. Most evidence for the use of different antiemetics in the acute pain setting comes from studies looking at postoperative nausea and vomiting (PONV).

Although the side-effect profiles of equianalgesic doses of opioids are similar, individual patients may report more PONV with one particular opioid. In this situation changing to another opioid (e.g., from morphine to fentanyl) is worth considering, especially when other measures, such as appropriate administration of antiemetics, have failed.

It must be remembered that opioids are only one of the many factors that can influence the incidence of PONV. Other reasons include younger patient age, female gender, cigarette smoking (decreases the risk), history of motion sickness or previous PONV, type and duration of surgery, and use of volatile agents and nitrous oxide (Gan et al., 2014).

Coadministration of other analgesic agents that enable good pain relief to be obtained with a lower dose of opioid ("opioid-sparing") may also lead to a reduction in the incidence of PONV and should always be considered. Opioid-sparing with a lower risk of PONV has followed coadministration of nonsteroidal anti-inflammatory drugs, ketamine, pregabalin, and gabapentin (ANZCA and FPM, 2010) (see Chapter 6).

A number of antiemetic drugs are available and they differ with regard to site of action. Therefore, as with analgesic agents, the use of a combination of antiemetic drugs that work at different receptor sites may be more effective than a single drug. If one drug is ineffective, then a drug from another class should be administered. In patients considered to be at moderate-to-high risk of PONV, antiemetic prophylaxis and treatment should include combination therapy.

4.2.3.1 Antiemetics

There are a number of different classes of antiemetic drugs that act at the various receptor sites involved in the emetic response—dopamine, serotonin (5-hydroxytryptamine [5-HT], acting at the 5-HT_3 receptor), acetylcholine (acting at muscarinic receptors), histamine and neurokinin 1 (NK_1). Corticosteroids are also effective antiemetic agents.

4.2.3.1.1 5-HT_3 receptor antagonists

Antagonists at the 5-HT_3 receptor include ondansetron, tropisetron, granisetron, and palonsetron. They are among the most effective in prevention and treatment of PONV and have variable durations of action. They are generally well-tolerated with few significant side effects (Scholz et al., 2011). Those that have been reported include headache and dizziness and some may lead to prolongation of the QT interval in some patients.

4.2.3.1.2 Butyrophenones

The butyrophenones droperidol and haloperidol have both been used for the prevention and treatment of PONV. Both these drugs may cause prolongation of the QT interval, which in rare instances, could lead to *torsades de pointes* and death. It was because of this risk that the Food and Drug Administration in the United States imposed a "black box" warning on droperidol in 2001. However, the effect is dose dependent and it is generally considered that low doses (e.g., 0.625 mg or less) are unlikely to pose a risk (Scholz et al., 2011; Schaub et al., 2012; Gan et al., 2014). Droperidol remains a commonly used, effective, and generally well-tolerated antiemetic agent for parenteral use. Haloperidol is used less often but is also effective.

4.2.3.1.3 Benzamides

Metoclopramide is often used as an antiemetic as well as a prokinetic agent (i.e., it stimulates gastric motility). However, it appears to have little if any antiemetic effect in the commonly used dose of 10 mg (Gan et al., 2014). Extrapyramidal side effects including acute dystonic reactions can occur. Although the incidence is dose dependent, they may also occur after just a single dose in some patients.

4.2.3.1.4 Phenothiazines and antihistamines

Prochloperazine, perphenazine, cyclizine, and promethazine are also used as antiemetics. They have been less well studied than the drugs listed above. Cyclizine and promethazine especially can lead to sedation. It is suggested that promethazine should not be given to a patient also receiving an opioid because of the increased risk of OIVI. Extrapyramidal side effects can also occur.

4.2.3.1.5 Neurokinin-1 (NK-1) receptor antagonists

Aprepitant is an effective antiemetic and may result in less vomiting compared with ondansetron (Gan et al., 2014). It is the first drug of this class to be developed and approved for use.

4.2.3.1.6 Anticholinergic agents

Scopolamine (hyoscine) has also been used to treat nausea and vomiting (Gan et al., 2014). It is available as a transdermal patch and is particularly effective for movement-induced nausea and vomiting. It may be associated with significant

anticholinergic side effects such as sedation, dry mouth, visual disturbances and confusion and is not widely used in the management of PONV.

4.2.3.1.7 Corticosteroids

Dexamethasone is a very effective antiemetic. Most of the evidence to date suggests that administration of a single dose only will not increase the risk of postoperative wound infection (Gan et al., 2014). Also effective but used much less often is methylprednisolone.

4.2.4 Other central nervous system effects

Opioid administration can lead to other CNS effects including sedation (discussed in Section 4.2.1), miosis, and cognitive impairment. Euphoria, commonly sought when opioids are used recreationally, is rarely seen in the acute pain setting where dysphoria is more common. Muscle rigidity, myoclonus, and seizures have also been reported, but are very unlikely if opioids are given in the doses used clinically for pain relief. The only exception is the risk of seizures that may result from norpethidine (normeperidine) toxicity—see Section 4.5.9.

4.2.4.1 Miosis

Opioids cause constriction of the pupils (miosis). Very small pupils ("pin point") are not necessarily an indication of a clinically significant excessive opioid dose in patients with good analgesia, but who are wide awake. Pupil size can be a reasonable clinical indicator of CNS concentrations of an opioid—see Chapter 3.

4.2.4.2 Cognitive impairment

Postoperative confusion (delirium) is often blamed on opioids, but opioids in therapeutic doses are only one of the many risk factors implicated in its development. It is more common in patients of advanced age and those with preexisting frailty, dementia, or depression (Shim and Leung, 2012). Precipitating factors can include infection, fluid or electrolyte disturbances, hypoxemia or sleep deprivation as well as poorly controlled pain (Shim and Leung, 2012), and benzodiazepine or alcohol withdrawal (Chaput and Bryson, 2012). Other medications that have been linked to an increased risk include benzodiazepines (Shim and Leung, 2012) and drugs with anticholinergic side effects (Chaput and Bryson, 2012).

Initial treatment should aim at finding and treating any reversible cause. Suggested pharmacological treatment options include low-dose haloperidol and olanzapine; benzodiazepines should only be used for delirium related to benzodiazepine or alcohol withdrawal because of the risk of sedation (Chaput and Bryson, 2012).

4.2.5 Gastrointestinal and genitourinary systems effects

Opioid receptors are found in the bowel wall (in the myenteric plexus), biliary tract, ureters, and bladder. In the GI tract they alter smooth muscle activity leading to delayed gastric emptying, reduction of bowel motility and constipation. This inhibition is both locally (an effect on opioid receptors in the bowel wall) and centrally mediated. While some decrease in bowel motility is inevitable,

it is usually not necessary or appropriate to withhold opioids to facilitate the return of bowel function after surgery. Adequate fluid intake and mobilization should be encouraged and stool softeners and cathartics may be recommended (in the absence of contraindications), if opioids are to be given for more than a couple of days. Oral naloxone, methylnaltrexone, and alvimopan have been shown to reduce the effect of opioids on the bowel (ANZCA and FPM, 2010)—see Section 4.7.

Opioids may also cause increases in biliary tract pressure and spasm of the sphincter of Oddi. There is little clinical difference between the opioids commonly used in clinical practice. It is reversible by naloxone, but in the clinical setting this would also reverse analgesia.

Urinary retention can occur owing to inhibition of the voiding reflex. This may also be reversed by naloxone, especially if it follows epidural or intrathecal opioid administration. It is not necessary for all patients receiving epidural or intrathecal opioid analgesia to be catheterized or to remain catheterized (ANZCA and FPM, 2010).

4.2.6 Cardiovascular effects

Opioids can reduce sympathetic tone, leading to hypotension and bradycardia. This is particularly likely in patients who have an increase in their sympathetic tone, such as those with pain or poor cardiac function, and patients who are hypovolemic. Opioids may also cause arterial and venous vasodilatation by a direct effect on vascular smooth muscle or through the release of histamine (notably morphine, diamorphine, pethidine [meperidine], and codeine). In clinical practice and particularly in the postoperative period, a significant decrease in blood pressure following administration of an opioid in a supine patient often indicates that the patient is hypovolemic. Postural (orthostatic) hypotension may occur when a supine patient given opioids sits or stands.

Prolongation of the QT interval has been of concern with some opioids such as methadone and propoxyphene—see Sections 4.5.6 and 4.5.10 below—as it may, rarely, lead to *torsades de pointes*, a polymorphic ventricular tachycardia (Spevak et al., 2012).

4.2.7 Pruritus

Pruritus is a reasonably common side effect of opioids. It is not associated with a rash and is not an allergic response to the drug. If pruritus is opioid-related, the patient will typically complain of itching over the face, neck, and trunk. Itching confined mainly to the patient's back is usually due to other causes (e.g., the plastic covering of a mattress may result in sweating and itching). While the exact mechanisms underlying the development of pruritus remain unclear, it is likely that, at least in part, it results from activation of μ-opioid receptors; dopamine and 5-HT_3 receptor activation may also be involved (Ganesh and Maxwell, 2007).

Pruritus does not always require treatment. If the itching disturbs the patient, the safest treatment in the first instance is to change opioids (e.g., from morphine to fentanyl). If treatment is required, a variety of options are available. As pruritus is more common after neuraxial opioid administration, most studies looking at treatment have been carried out in this setting.

A number of drugs, some based on the possible mechanisms that may underlie pruritus, have been investigated. Naloxone has consistently been shown to be

effective, but in order to avoid fluctuations in blood concentrations very low-dose infusions have been recommended (Kumar and Singh, 2013). However, especially in patients receiving parenteral opioids, it may be difficult to attenuate the itch without affecting analgesia. Nalbuphine, an opioid agonist–antagonist, is also effective (Ganesh and Maxwell, 2007). Others medications with some evidence of efficacy include 5-HT_3 antagonists (ondansetron, tropisetron, granisetron), and droperidol (Kumar and Singh, 2013). Antihistamines appear to have little benefit and may add significantly to the risk of sedation, depending on the drug given.

4.2.8 Allergy

Patients and staff alike will often mistakenly report any adverse reaction to a drug as an allergy (e.g., nausea and vomiting following the administration of opioids). True allergic reactions to opioids are rare and mediated by the immune system, and result in signs and symptoms that are similar to other allergic reactions including rash, urticaria, bronchoconstriction, angioneurotic edema, and cardiovascular disturbances.

4.2.9 Tolerance, opioid-induced hyperalgesia, physical dependence

Patients on long-term opioid therapy may develop a tolerance to the drug, although some degree of tolerance may also be seen in patients who have been taking an opioid continuously for a week or more. Tolerance refers to the progressive decrease in analgesic effect seen for the same dose of opioid, or the need for progressively larger doses to maintain the same effect (see Chapter 14). Opioid-induced hyperalgesia (OIH) is also likely to be present. This means that opioids can, paradoxically, lead to increased pain sensitivity (hyperalgesia) rather than analgesia, and reducing rather than increasing the dose of opioid may improve pain relief (ANZCA and FPM, 2010). The mechanisms underlying the development of tolerance and OIH appear to overlap with those thought to produce and maintain persistent pain states (see Chapter 12).

The clinical significance of tolerance to opioids versus OIH is difficult if not impossible to determine in any particular patient. If OIH is suspected in patients taking long-term opioids (presenting as inadequate analgesia despite high doses), a decrease in opioid dose may improve pain relief. However, if opioid analgesia is inadequate in opioid-tolerant patients receiving additional opioids for management of their acute pain, tolerance should be assumed as long as there are no other identifiable reasons for the pain (e.g., postoperative complication, neuropathic pain). In this situation opioid doses should be increased as appropriate and/or antihyperalgesic coanalgesics such as ketamine considered.

It has been suggested that acute tolerance and OIH may develop following intraoperative remifentanil administration, but the evidence for and the clinical relevance of this remains unclear (Treskatsch et al., 2014).

Patients tolerant to one opioid will usually be tolerant to all other opioids. This is called cross-tolerance. However, the degree of cross-tolerance that occurs is unpredictable and appears to be incomplete.

Tolerance also develops to opioid-related side effects, but to varying degrees and at varying rates. Tolerance to nausea and vomiting, cognitive impairment, sedation, and OIVI occurs rapidly; tolerance to constipation and miosis develops very slowly, if at all. However, despite tolerance to the effects of opioids, side effects including OIVI may occur when opioid doses are suddenly and markedly increased

above usual "baseline" levels. This has been noted in opioid-tolerant patients using patient-controlled analgesia (PCA), where a much higher incidence of excessive sedation has been seen compared with opioid-naive patients (Huxtable et al., 2011).

Physical dependence refers to the physiological adaptation of the CNS to opioids and is characterized by the development of a withdrawal (or abstinence) syndrome if the opioid is antagonized (by opioid antagonists or agonist–antagonists), suddenly stopped, or abruptly reduced in dose. Therefore, opioids should not be withdrawn abruptly, but by tapering doses over time.

4.3 Predictors of opioid dose

It is known that there is a very large inter-patient variation in the amount of opioid required for the relief of acute pain. Traditionally, the dose of opioid prescribed for a patient was based on the patient's weight, but there is little clinically significant correlation between patient weight and opioid requirement.

The best clinical predictor of opioid dose in an opioid-naive patient is patient age. Figure 4.1 shows the average IV PCA morphine requirements of 1010 opioid-naive patients in the first 24 hours after major surgery. The total amount of morphine used in 24 hours decreased significantly as patient age increased and was not associated with increased pain (Macintyre and Jarvis, 1996). Although the weight of the patient had some effect on dose, it was clinically insignificant in comparison to the overall inter-patient variation.

From Figure 4.1 it can be seen that after the age of 20 years, where the average requirement was around 80 mg morphine in 24 hours, first 24-hour morphine requirements decreased by about 1 mg for each additional year of age. These results were used to generate the age-based immediate-release (IR) opioid doses for intermittent oral and SC administration in opioid-naive patients listed in Figure 7.1 of Chapter 7.

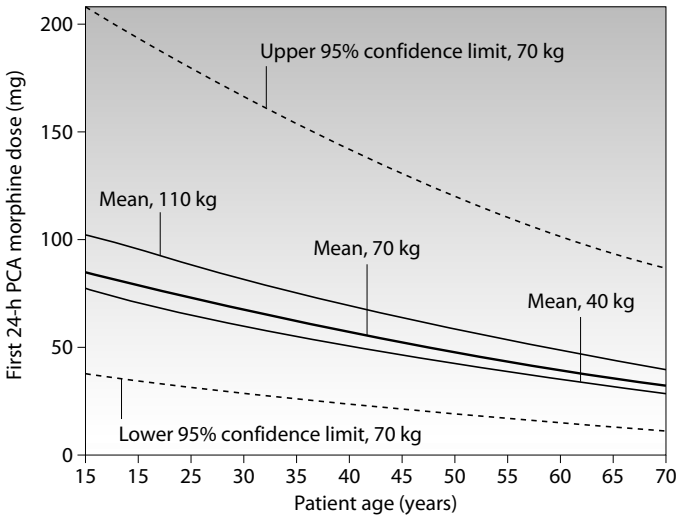

Figure 4.1 First 24-h PCA morphine requirements and patient age. (Adapted with permission from Macintyre PE, Jarvis DA. 1996. *Pain* **64**(2): 357–64. Copyright International Association for the Study of Pain.)

The enormous variation (eightfold to tenfold) in dose requirements in each age group means that although the initial dose of opioid should be based on the age of the patient, subsequent doses still need to be titrated to effect for each patient.

There are a number of reasons why the dose of opioid required for pain relief decreases with patient age. These include age-related changes in pharmacokinetics (how the individual handles the drug, e.g., drug distribution, metabolism, and elimination) and pharmacodynamics (how the individual responds to the drug). However, it is the latter changes (i.e., pharmacodynamics) that are thought to play the largest part in the age-related decrease in opioid requirements (Macintyre and Upton, 2008).

Other factors that may affect opioid requirements are gender, genetic differences, and psychological factors—in particular, anxiety and pain catastrophizing (ANZCA and FPM, 2010). However, as yet, the evidence remains inconsistent and none can be used as a reliable basis for opioid dose alteration (ANZCA and FPM, 2010).

4.4 Titration of opioid dose

For an opioid to be effective it must reach a certain blood level (this applies to systemically administered opioids and not to epidural and intrathecal opioids, which are discussed in Chapter 9). The effective range of blood concentrations varies widely between patients. The amount of opioid that each patient requires will also vary according to the severity of the pain stimulus. Thus titration is needed in order to individualize treatment.

The lowest concentration of opioid that will produce analgesia is known as the *minimum effective analgesic concentration* (MEAC). This MEAC varies widely between patients, but also within the individual patient depending on severity of pain. MEAC should therefore not be regarded as a static number, but more as a concept. Below the MEAC a patient will experience poor pain relief and above it there will be increasing analgesia, but also an increasing possibility of side effects. In reality, the boundaries are somewhat blurred and side effects may occur before good pain relief is obtained. The therapeutic range of blood levels (where analgesia is achieved without significant side effects) is often colloquially referred to as the "analgesic corridor" (see Chapter 7). For each patient the aim of titration is to find and then maintain the effective blood level within this "corridor." A change in pain intensity may shift the corridor and require an increase or decrease in opioid dose.

To enable opioid analgesia to be titrated to optimal effect for each patient, appropriate doses and dose intervals need to be ordered. In addition, endpoints that indicate adequate or excessive doses need to be monitored repeatedly.

4.4.1 Dose and dose interval

The dose of systemic opioid prescribed and the frequency with which it may be safely administered will depend on its route of administration. For more detail, see Chapter 7.

4.4.2 Titration to pain relief, sedation, and other side effects

When titrating any drug, ongoing monitoring of endpoints that indicate "how much is enough" and "how much is too much" is needed. The best way to monitor

the former is to use a pain score and functional assessment. The most serious consequence of excessive opioid dose is OIVI, and the best early clinical indication of this is increasing sedation. Although respiratory rate has been traditionally monitored as an indicator, a normal respiratory rate can coexist with hypercapnia and significant OIVI. For more details on assessment of pain and OIVI, see Chapter 3.

The aim of pain treatment is to make the patient comfortable while keeping the sedation score below 2. If the patient does become sedated, subsequent doses should be reduced. If the patient is uncomfortable and not sedated, a larger dose may be required. Although many guidelines suggest that the respiratory rate should be maintained at above 8 breaths per minute, there may be occasions when a lower rate can be tolerated, provided the patient has a sedation score of less than 2.

Nausea and vomiting or lightheadedness may also indicate a slightly excessive dose. For more detail on assessment and monitoring, see Chapter 3.

4.5 Commonly used opioid agonists

For the half-lives and equianalgesic doses of these drugs, see Table 4.2.

4.5.1 Codeine

Codeine is metabolized in the liver and its active metabolite is morphine. This accounts for all the analgesic effect of codeine, as the drug itself has a very low affinity for opioid receptors. It should therefore be regarded as an ineffective *prodrug* of morphine. Metabolism to morphine involves the enzyme CYP2D6, an isoenzyme of the cytochrome P450 system.

Genetic variability in CYP2D6 is common and results in significant differences in enzyme activity. Based on this genetic variation, individuals may be classed as ultrarapid, extensive, intermediate, or poor metabolizers, meaning that very different plasma levels of morphine for a given codeine dose may be seen (Vuilleumier et al., 2012). Around 7–11% of the Caucasian populations are poor metabolizers (i.e., are unable to metabolize codeine to morphine) and will obtain no pain relief from codeine (Vuilleumier et al., 2012). Conversely, ultrarapid metabolizers (up to 7% of Caucasians) will have much higher blood concentrations of morphine for a given dose of codeine (Smith and Muralidharan, 2012). There are large interethnic variations in the proportion of individuals in each of these four groups. For example, up to 21% and 29% of individuals from Ethiopia and Saudi Arabia, respectively, are said to be ultrarapid metabolizers (Vuilleumier et al., 2012).

Ultrarapid metabolizers are therefore at increased risk of opioid-related side effects with recommended codeine doses. Fatalities in children (Racoosin et al., 2013) and in breastfed babies of mothers who were ultrarapid metabolizers (Smith and Muralidharan, 2012) have led to warnings about the use of codeine in these patient groups.

Codeine is usually given for the treatment of mild-to-moderate pain by IM or oral routes. There are a number of oral formulations that combine codeine with nonopioid analgesics such as paracetamol (acetaminophen) or aspirin; not all combinations show increased analgesic efficacy.

4.5.2 Diamorphine

Diamorphine (medical heroin) does not bind to opioid receptors and has no analgesic activity. It is a *prodrug* and is rapidly hydrolyzed to 6-monoacetylmorphine

(a potent analgesic) and then morphine. Both diamorphine and 6-monoacetylmorphine are more lipid soluble than morphine and will cross the blood–brain barrier more rapidly (ANZCA and FPM, 2010). It has not been shown to have any clinical advantage over morphine when administered parenterally, but there may be a more rapid onset of effect with spinal administration. Diamorphine is available for medical use only in the United Kingdom.

4.5.3 Fentanyl and its analogues

Fentanyl is a highly lipid-soluble synthetic opioid that does not cause histamine release. It has a more rapid onset of action than morphine and single doses have a short duration of action because of rapid distribution to tissue from plasma (Grape et al., 2010).

It is primarily metabolized in the liver by CYP3A4 to inactive norfentanyl and it is therefore a good choice of opioid in patients with renal impairment (Grape et al., 2010). It may be that genetic variability in the activity of CYP3A4 can alter the amount of fentanyl required for acute pain management (Smith and Muralidharan, 2012), but any differences will be difficult to detect in general populations given the already large inter-patient variation in the dose of opioids required for pain relief.

For the treatment of acute pain, fentanyl can be administered intravenously (e.g., by PCA), epidurally or intrathecally. Transmucosal oral ("lollipop" or buccal patch) and nasal (nasal spray) administration is used widely to treat breakthrough pain in cancer patients (Grape et al., 2010). True oral administration is not effective because of the very high first-pass effect. The high lipid solubility of fentanyl makes it suitable for transdermal administration (see Chapter 7).

Alfentanil is very lipid-soluble although less so than fentanyl, whereas sufentanil has a higher lipid solubility. They have a more rapid onset and shorter duration of action than fentanyl. This makes them very suitable for administration by IV infusion during anesthesia. Both have been used in PCA and either alone, or in combination with local anesthetic agents, for neuraxial analgesia (ANZCA and FPM, 2010). Both drugs are primarily eliminated by the liver.

Remifentanil has very rapid onset. It also has an ultra-short duration of action owing to its metabolism by nonspecific blood and tissue esterases. It is mainly used in clinical practice as an infusion during anesthesia, but has also been used by PCA.

4.5.4 Hydrocodone

Hydrocodone is available for oral administration in the United States, usually in combination formulations with nonopioid analgesics such as paracetamol or aspirin (Vallejo et al., 2011), which limits the amount of the opioid that can be given.

4.5.5 Hydromorphone

A semisynthetic opioid (a direct derivative of morphine), hydromorphone is available in oral (both IR and slow-release [SR]), parenteral and suppository forms and can also be used for epidural analgesia. It has no active (analgesic) metabolites. However, the metabolite hydromorphone-3-glucuronide shows similar neurotoxic effects to morphine-3-glucuronide (M3G) and its excretion is dependent on renal function. Hydromorphone is around five times as potent as morphine.

4.5.6 Methadone

A synthetic opioid developed during World War II, methadone has a much longer and much more variable half-life than other opioids and therefore a much longer duration of action. This makes methadone more suitable for the management of chronic and cancer pain, or for a patient with an opioid substance abuse disorder, than for the treatment of acute pain. Single doses have been used intraoperatively to improve postoperative pain control and decrease postoperative opioid requirements (Gottschalk et al., 2011). However, the very long and very variable half-life of methadone—average 20 hours; range 4–190 hours (ANZCA and FPM, 2010)—means that it may act like a "background infusion" and the effect of any additional opioid will be even less predictable. If a patient has been taking another opioid for some time and is changed to methadone, methadone doses should start at about 10% of the calculated equianalgesic dose for single administration and then be titrated to effect (Vallejo et al., 2011). This particular opioid rotation is best left to experienced practitioners as the inappropriate use of methadone carries an increased risk of OIVI (Centers for Disease Control and Prevention, 2012).

Methadone has complex metabolic pathways which include several CYP450 enzymes, and the coadministration of other drugs that induce (e.g., St John's Wort, carbamazepine) or inhibit (e.g., grapefruit juice, antifungal agents, some selective serotonin reuptake inhibitors) these enzymes may lead to lower or higher than expected drug levels (ANZCA and FPM, 2010). It has no active metabolites. Methadone is a weak NMDA receptor antagonist (see Chapter 6) and an inhibitor of monoamine (5-HT and norepinephrine [noradrenaline]) uptake. It may be of use in the treatment of neuropathic pain (see Chapter 12).

It can be given by oral, SC, IM, IV, and epidural routes.

Prolongation of QT intervals has been reported in patients given methadone, which could lead to *torsades de pointes* and cardiac arrest. These risks are not common but more likely when higher doses of methadone are used or, when other risk factors, such as coadministration of other drugs that can prolong the QT interval, or preexisting prolonged QT interval, are present (ANZCA and FPM, 2010; Spevak et al., 2012).

4.5.7 Morphine

Morphine is the least lipid-soluble of all opioids in common use. It is metabolized principally in the liver and less than 10% is excreted unchanged by the kidneys.

The main metabolites of morphine, morphine 6-glucuronide (M6G) and M3G have longer half-lives than morphine and are primarily excreted via the kidney. Morphine 6-glucuronide is a μ-receptor agonist which is more potent than morphine and may contribute significantly to its analgesic effect, particularly in patients taking long-term oral morphine, and has similar side effects (ANZCA and FPM, 2010). In patients with reduced renal function the half-life of morphine is not significantly increased. However, there may be an apparent prolongation of its effect (and its adverse effects) due to accumulation of M6G and an increased risk of OIVI in patients with impaired renal function. Genetic polymorphisms of enzymes responsible for the metabolism of morphine have been described, but there is, as yet, no good evidence to show that these have any significant clinical relevance (Smith and Muralidharan, 2012).

Morphine 3-glucuronide has no analgesic activity. There is some evidence that it may be responsible for some of the neurotoxic side effects sometimes seen with

long-term, high-dose morphine treatment, such as myoclonus, seizures, hyperalgesia, and allodynia (ANZCA and FPM, 2010).

Morphine can be given by IV, IM, SC, oral, transmucosal, rectal, epidural, and intrathecal routes. Dose ranges and dose intervals will vary according to the route of administration.

Slow-release (also called controlled-release, sustained-release, or extended-release) preparations of oral morphine are available and often used in the treatment of chronic and cancer pain. They only need to be given one to two, sometimes three times a day. The slower onset (4 hours or longer) and prolonged duration of action of these formulations make fast titration of the drug impossible; these preparations are usually unsuitable for the treatment of acute pain, at least in the initial stages.

4.5.8 Oxycodone

Oxycodone has been in clinical use since 1917 and is a derivative of thebaine. Because it was first introduced in some countries in oral formulations combined with paracetamol or aspirin, it was often considered suitable for the treatment of mild–to-moderate pain only. However, like all pure opioid agonists it has no ceiling effect for analgesia and oxycodone can be used as any other full opioid agonist for the treatment of even severe pain.

The major metabolite of oxycodone is noroxycodone, which has only minimal analgesic activity and is renally excreted. Oxymorphone, another metabolite, possesses significant analgesic activity. However, it is present only in very low concentrations and contributes little to the pain-relieving effect of oxycodone (ANZCA and FPM, 2010). Oxymorphone itself is now available as both IR and SR tablets (Vallejo et al., 2011), but experience with this drug in the acute pain setting is limited. The formation of oxymorphone, but not noroxycodone, depends on CYP2D6 (see codeine above). However, genetic differences in this enzyme do not appear to significantly alter the analgesic effect of oxycodone in the postoperative setting (Zwisler et al., 2010).

Oxycodone can be given by parenteral, oral, rectal, and epidural routes. An SR formulation of oral oxycodone is also available. As with morphine, the slower onset (4 hours or longer) and prolonged duration of action (Vallejo et al., 2011) makes it unsuitable for the initial treatment of acute pain. The original SR drug was reformulated to reduce the risk of abuse by injection or the intranasal route and approved by the FDA in 2010.

4.5.9 Pethidine

Pethidine (meperidine) was first synthesized just prior to World War II as a potential substitute for atropine. In addition to its analgesic effect, pethidine has some atropine-like actions that may lead to a dry mouth or slight tachycardia, and some local anesthetic activity. This latter effect has allowed intrathecal pethidine to be used as the sole agent for spinal anesthesia. In patients taking monoamine oxidase inhibitors, hyperpyrexia, convulsions, coma and hypertension or hypotension have been reported following the administration of pethidine. While there is still a widespread belief that pethidine is better than other opioids such as morphine for the treatment of renal or biliary colic, there is no evidence to show that it is more effective (Latta et al., 2002).

Pethidine is primarily metabolized in the liver and the metabolites are excreted by the kidney. One of the main metabolites is norpethidine (normeperidine), which has a long half-life of 15–20 hours. Accumulation of this metabolite, more likely if larger doses have been administered or if the patient has renal impairment, can lead to norpethidine toxicity with signs of CNS excitation including anxiety, mood change, tremors, twitching, myoclonic jerks, and even convulsions (Smith, 2011).

There is no specific treatment for norpethidine toxicity. Pethidine should be discontinued and another opioid substituted. Naloxone should not be given, as it will antagonize the sedative effect of pethidine but not the excitatory effects of norpethidine, and will therefore only exacerbate the problem. However, the best treatment is prevention and the use of pethidine for the treatment of pain is discouraged (Latta et al., 2002; ANZCA and FPM, 2010).

4.5.10 Propoxyphene

Structurally similar to methadone, only the dextrorotatory (*R* isomer) form has any analgesic activity (dextropropoxyphene). Often administered in an oral formulation in combination with paracetamol or aspirin, these preparations may be no more effective than paracetamol or aspirin alone (ANZCA and FPM, 2010). Toxicity, with hallucinations, delusions, and confusion, may occur with accumulation of the renally excreted active metabolite norpropoxyphene, particularly in the older patient or in patients with renal impairment (Barkin et al., 2006; Smith, 2011). Cardiotoxicity has also been reported, with prolongation of the QT interval and the risk of *torsades des pointes* and death. In view of these significant disadvantages and risks, and limited analgesic efficacy, the use of dextropropoxyphene should be discouraged (Barkin et al., 2006). It has been or is being withdrawn from the market in many countries.

4.5.11 Tramadol

Tramadol is a centrally acting synthetic analgesic agent. It has some μ-opioid receptor activity, mediated mainly through its main metabolite *O*-desmethyltramadol (M1) and also inhibits the reuptake of norepinephrine and serotonin (5-HT) at nerve terminals. These mechanisms account for about 40%, 40%, and 20%, respectively of its activity. The latter effect, inhibition of norepinephrine and serotonin reuptake, is similar to the mechanism of action of tricyclic antidepressant agents (TCAs) and may explain the efficacy of tramadol in neuropathic pain (see Chapter 12).

The main advantages over equianalgesic doses of other conventional opioids are less sedation and OIVI and less constipation; the incidence of nausea and vomiting is similar (ANZCA and FPM, 2010). In addition, the abuse potential of tramadol is less than with other opioids (although diversion and abuse is increasing in some countries) and it is therefore not a controlled drug. A history of epilepsy is often said to be a relative contraindication to its use as seizures have been reported. However, the incidence is probably similar to other opioids (ANZCA and FPM, 2010).

While the combination of tramadol with selective serotonin reuptake inhibitors or TCAs may theoretically increase the risk of serotonin syndrome, this complication is rarely seen in the doses commonly used clinically. Tramadol should not be given in combination with monoamine oxidase inhibitors.

Tramadol is available in oral (IR and SR) and parenteral forms. Product information sheets limit the total oral and parenteral daily doses to 400 mg and 600 mg, respectively, although much higher doses have been used successfully worldwide. There is no advantage in neuraxial administration of tramadol and this route should be avoided as neurotoxicity data are incomplete (Schug and Gandham, 2006).

As noted above, the main active metabolite of tramadol is *O*-desmethyltramadol (M1), which is excreted by the kidney. M1 is a more potent μ-receptor agonist than tramadol itself, thereby contributing to its analgesic efficacy. The formation of M1 depends on the enzyme CYP2D6. Therefore, in poor metabolizers the analgesic effect of tramadol may be reduced and in ultrarapid metabolizers the effects may be increased (Smith and Muralidharan, 2012).

Accumulation of M1 in renal failure has been described as the cause of OIVI with tramadol, as it is excreted by the kidney (ANZCA and FPM, 2010), although respiratory arrest has also been reported in patients with normal renal function who took large overdoses (Hassanian-Moghaddam et al., 2013).

4.5.12 Tapentadol

Tapentadol is a centrally acting oral analgesic agent which acts at μ-opioid receptors and inhibits norepinephrine reuptake. In contrast to tramadol, it has been classified as a controlled drug in many countries, although its abuse potential appears to be less than that of oxycodone and close to that of tramadol (Dart et al., 2012).

Its analgesic effect is similar to oxycodone or morphine, but with fewer GI side effects (Frampton, 2010). It is metabolized to inactive metabolites which are excreted renally (Frampton, 2010). Compared with tramadol, tapentadol's analgesic effect being independent of CYP2D6 activity and its lack of renally excreted active metabolites and effect on serotonin reuptake may be an advantage in some patients.

4.6 Agonist–antagonists

Agonist–antagonist drugs derive their analgesic actions principally from the activation of one opioid receptor while acting as antagonists at another. All behave as partial agonists, meaning that they do not have the intrinsic activity of full agonists (Rosow and Dershwitz, 2011). There is therefore a "ceiling" to both their analgesic and adverse effects, and once a certain dose level is reached administration of further doses will not improve analgesia or worsen side effects.

The drugs in this class are either partial μ or partial κ agonists (Rosow and Dershwitz, 2011). Buprenorphine is said to be a partial μ agonist and κ antagonist, while pentazocine, nalbuphine, and butorphenol are μ antagonists (meaning they can reverse the effects of pure μ-agonist opioids) and partial κ agonists.

4.6.1 Buprenorphine

Buprenorphine, is derived from the opium alkaloid thebaine and is available in parenteral, sublingual, and transdermal formulations. It is highly lipid soluble and is absorbed well by the sublingual route. It has high affinity for and dissociates slowly from the μ-opioid receptor (Foster et al., 2013) leading to concerns that

it may block the analgesic effects of pure agonist opioids. This is probably not the case even when given in high doses (Macintyre et al., 2013).

Although it is said to be a partial μ-agonist, a ceiling effect for analgesia has not been demonstrated in humans in the doses commonly used for pain relief. That is, it appears to act as a pure μ-agonist opioid (Foster et al., 2013). This may even be the case in the higher doses used in opioid-substitution programs (see Chapter 14) (Foster et al., 2013; Macintyre et al., 2013). Concerns that administration of buprenorphine may antagonize the effects of other opioids when given at the same time may not be well-founded (Macintyre et al., 2013).

There is, however, a ceiling effect for OIVI and other effects such as euphoria (Foster et al., 2013). Therefore, it is less likely to lead to OIVI than other opioids, even in the larger doses. If buprenorphine-related OIVI does occur, it can be reversed by naloxone.

Unlike other opioids, most of the drug is excreted unchanged, mainly in feces; the remainder is converted primarily into norbuprenorphine, a weakly active metabolite with little clinical effect (Foster et al., 2013).

Buprenorphine can be administered intravenously and sublingually for the management of acute pain (Foster et al., 2013). It is increasingly used sublingually as an opioid substitute in the management of patients with an opioid addiction (see Chapter 14). In this setting it is usually given as a combination with naloxone, which is minimally absorbed via the sublingual route. However, if the preparation is injected the naloxone will reverse the effects of the buprenorphine and can precipitate withdrawal. It is also available as a transdermal preparation for the treatment of chronic and cancer pain.

4.6.2 Pentazocine

Pentazocine was the first drug of the agonist–antagonist class to become established in clinical practice. It can be given orally or parenterally. The high incidence of dysphoria associated with the drug has limited its use.

4.6.3 Nalbuphine

Chemically related to naloxone, nalbuphine is available as a parenteral preparation. It may be effective in reversing some of the side effects of μ-agonist drugs, such as OIVI and pruritus, and may precipitate withdrawal if given to patients taking other opioids on a regular basis (Vallejo et al., 2011). Its clinical use as an analgesic is limited.

4.7 Opioid antagonists

These drugs are antagonists at all receptor sites. The most commonly used is naloxone.

4.7.1 Naloxone

Naloxone is the opioid antagonist most commonly used to treat opioid overdose. Its half-life of about 60 minutes is much shorter than those of the drugs listed above. As a result, if naloxone is required to antagonize the effects of most opioid

agonists, repeated doses or an infusion may be needed. By titrating the dose of naloxone carefully, it is possible to reverse opioid-related OIVI, while still retaining reasonable analgesia. However, this balance may be more difficult to obtain when opioids are being administered by other than epidural or intrathecal routes.

For the treatment of OIVI and excessive sedation, 40–100 μg of naloxone should be given IV and repeated every few minutes as required. If there is no venous access available, naloxone can be given in larger doses (e.g., 400 μg) by SC or IM injection. Smaller doses may be more suitable if naloxone is used to reverse other side effects of opioids such as pruritus. If a patient is on long-term opioid therapy, it is especially important to titrate naloxone in order to avoid precipitation of withdrawal signs and symptoms.

While some cardiovascular stimulation (hypertension, tachycardia) or nausea and vomiting may be seen after administration of naloxone, especially after rapid reversal of analgesia, serious side effects such as pulmonary edema and arrhythmias are rare.

Naloxone is absorbed following oral administration and antagonizes opioid receptors in the GI tract. It has therefore been combined with SR oxycodone to reduce the incidence of opioid-related constipation (ANZCA and FPM, 2010). It is, however, almost completely inactivated by the liver after absorption and less than 3% of the oral dose reaches the systemic circulation. Naloxone is also poorly absorbed sublingually.

Naloxone has been added to oral opioid preparations (e.g., buprenorphine or SR oxycodone) to make them less attractive for parenteral abuse.

4.7.2 Naltrexone

Unlike naloxone, naltrexone is effective when given orally. It has a half-life of 2–4 hours and its main metabolite is 6-naltrexol, a weaker μ-opioid antagonist but with a half-life of more than 13 hours (Rosow and Dershwitz, 2011). Naltrexone (either orally or in the form of a long-acting SC implant) has been used in the treatment of opioid addiction where the effects of a 50 mg oral dose may last up to 24 hours (ANZCA and FPM, 2010) (see Chapter 14). As it is a pure opioid antagonist, it should be stopped at least 24–48 hours before surgery if opioid analgesia is likely to be needed. Caution is required as there is some evidence to suggest that, after cessation, patients may become very sensitive to opioids (ANZCA and FPM, 2010). It has also been used in the treatment of alcoholism.

Methylnaltrexone does not penetrate the blood–brain barrier and so does not enter the CNS and will not reverse central opioid effects (Rosow and Dershwitz, 2011). It acts on opioid receptors in the GI tract wall and has been used to treat opioid-induced constipation.

4.7.3 Alvimopan

Alvimopan is a μ-receptor antagonist which was developed for the prevention and/or treatment of opioid-induced ileus and constipation subsequent to bowel resection. It shows very limited oral bioavailability and also no penetration of the blood–brain barrier. Its main effect is on opioid receptors in the gut wall, where it has a higher affinity than naloxone. It has an adverse effect profile similar to placebo, but accelerates recovery of GI function after surgery (ANZCA and FPM, 2010). In view of an increased risk of myocardial infarction, the FDA has limited its use to short-term under strict precautions (Food and Drug Administration, 2013).

Key points

1. In general, at equianalgesic doses, no one μ-agonist opioid is capable of producing better pain relief or fewer side effects than another, although an individual patient may be more sensitive to a particular opioid(s).
2. In opioid naive adult patients, the best clinical predictor of opioid requirements is patient age, although the very wide inter-patient variation means that opioid doses must be titrated to effect.
3. Opioid-induced ventilatory impairment (a better term than respiratory depression) is best detected clinically by increasing sedation. If the patient is snoring, this could indicate upper airway obstruction due to the opioid.
4. The risk of OIVI is increased with coadministration of other CNS sedative drugs or alcohol.
5. The use of pethidine and dextropropoxyphene is discouraged because of limited benefit and the risk of significant adverse effects.
6. A number of drugs are effective for the treatment of nausea and vomiting. Combinations of drugs from different classes of antiemetics will be more effective than a single drug.
7. The mechanisms underlying the development of pruritus following administration of an opioid are likely to include activation of the μ-opioid receptor. Antihistamines will offer little benefit and may increase the risk of sedation.

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CHAPTER 5

Pharmacology of local anesthetics

Cocaine was the first local anesthetic introduced into medical practice in 1884 by the ophthalmologist Koller, who described its use for topical anesthesia of the cornea (Brown and Fink, 2009). Subsequently it was used in local infiltration anesthesia, nerve conduction blockade and, in 1898, by Bier for spinal anesthesia. Cocaine became the precursor of a series of ester local anesthetics such as procaine, synthesized by Einhorn in 1905.

Lidocaine (lignocaine), synthesized by Löfgren and Lundqvist in 1943, heralded the beginning of the development of amide compounds, which are the local anesthetics in common use today (Brown and Fink, 2009). Subsequent developments led to the enantiomer-specific amide local anesthetics, with an increased margin of safety, and most recently, the introduction of long-acting liposomal bupivacaine (Chahar and Cummings, 2012).

5.1 Mechanism of action

Local anesthetics block sodium channels in cell membranes (Salinas and Auyong, 2011). They prevent the influx of sodium ions into cells and thereby the generation of action potentials and the conduction of nerve impulses (see Figure 5.1). Local anesthetics may also modify a number of other neuronal membrane channels or even receptors, contributing to their effect (Salinas and Auyong, 2011).

However, sodium channel blockade is the main mechanism of action. The initiation and subsequent propagation of an action potential involves the opening of sodium channels in the nerve cell membrane. This process leads to a massive flow of sodium ions from the outside to the inside of the cell membrane, which depolarizes the membrane. Immediately after depolarization the membrane is actively repolarized by ion pumps back to its resting membrane potential. It is then available for another depolarization.

Local anesthetics do not have a specific analgesic effect, but can block all nerve conduction in all sensory and motor fibers (Salinas and Auyong, 2011; Becker and Reed, 2012). Blockade of sympathetic nerve fibers will also occur, which may be beneficial after peripheral vascular or plastic surgery, as it leads to increased blood flow. However, with epidural analgesia, postural (orthostatic) hypotension remains a potential risk.

The degree of blockade is dependent on a number of factors. It is therefore useful to briefly look at the different types of nerve fibers, their size and function (Table 5.1). It is commonly believed that smaller-diameter nerve fibers are more easily blocked than those with a larger diameter, but diameter is not the only factor (Salinas and Auyong, 2011). The ease with which a nerve fiber is blocked by a local anesthetic drug also depends on the length of nerve fiber that must be exposed to the drug in order to block conduction. This length is shorter for unmyelinated than for myelinated fibers. Nerve blockade is also frequency dependent—active nerve fibers are more easily blocked than inactive ones.

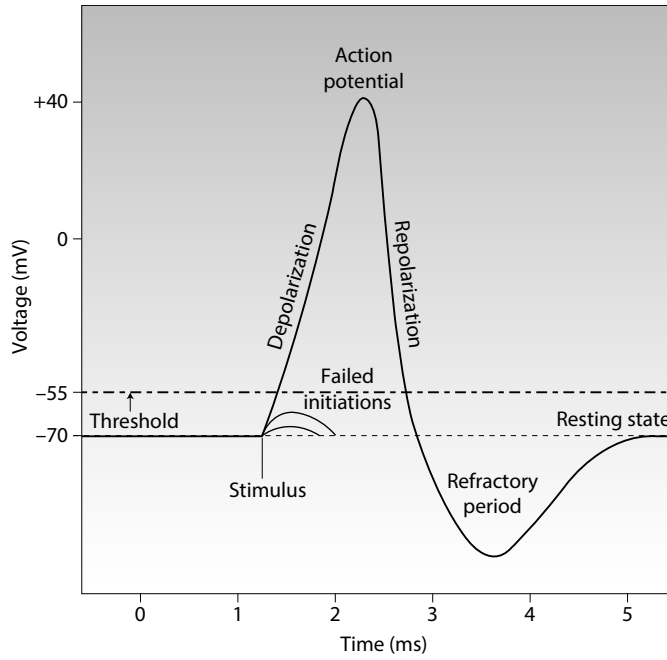

Figure 5.1 The changes of the membrane potential during an action potential and during failed initiations due to local anesthetic effects.

The onset and regression of a nerve block usually progresses in a certain order, but this may vary a little between patients and different drugs (Salinas and Auyong, 2011). Overall, sympathetic blockade, with a feeling of warmth reported by the patient and vasodilation observed by the operator, usually occurs first, followed by block of nociception and temperature sensation. Motor block is commonly the last to be complete.

As the effect of a nerve block is wearing off, recovery of movement (larger fibers) may precede recovery of sensory function and pain perception or

Table 5.1 Nerve fiber class, size, and function

Class	Size	Function
Myelinated fibers		
A-alpha (Aα)	Largest	Motor, proprioception (position sense)
A-beta (Aβ)		Touch, pressure
A-gamma (Aγ)		Muscle spindle tone
A-delta (Aδ)		Pain, temperature, touch
B		Preganglionic autonomic (sympathetic)
Unmyelinated fibers		
C	Smallest	Pain/temperature
		Postganglionic autonomic (sympathetic)

sympathetic nerve function (smaller fibers). This is of particular importance following epidural or spinal anesthesia, when a patient may have normal motor function but incomplete return of sensation, and a residual sympathetic block that could lead to postural hypotension.

The higher the concentration of local anesthetic solution used, the more likely nerves of all sizes are to be blocked. Low concentrations can therefore be used in an attempt to block the smaller sensory fibers only (*differential nerve block*) (Mather and Tucker, 2009). This approach is commonly utilized with local anesthetic infusions given via epidural and peripheral nerve catheters and aims to allow the patient to move the affected limb while still receiving good pain relief. However, there may be differences in response due to interindividual variability and catheter position. Some patients may still have some degree of motor block even with low concentrations.

The blockade of sodium channels explains not only the effects but also the adverse effects of local anesthetics, which occur primarily due to interference with action potential generation and conduction in the heart and central nervous system (CNS). However, mitochondrial effects may also play a role (Neal et al., 2010).

5.2 Efficacy of local anesthetics

The potency and therefore efficacy of a local anesthetic increases primarily with its lipid solubility, whilst the duration of action is dependent to some extent on the degree of protein binding at the site of action (Becker and Reed, 2012). However, the situation is complicated by other factors which affect the removal of the drug from the site, such as the blood supply and addition of vasoconstrictors.

Just as opioids have equianalgesic doses, local anesthetic drugs given in equal volumes have equieffective anesthetic concentrations (Table 5.2) (Mather and Tucker, 2009). However, the total dose administered is also an important determinant of effect. The issue of relative potency becomes even more complex when lower doses and concentrations are used to provide analgesic rather than

Table 5.2 Equieffective anesthetic concentrations

Local anesthetic drug	Concentration (%)
Lidocaine (lignocaine)	1
Bupivacaine	0.25
Ropivacaine	0.35–0.5[a]
Levobupivacaine	0.25
Prilocaine	1
Chloroprocaine	2
Procaine	2
Mepivacaine	1
Etidocaine	0.25

Source: Information obtained from multiple sources including Mather LE, Tucker GT. 2009. *Neural Blockade in Clinical Anesthesia and Pain Medicine*. Cousins MJ, Carr DB, Horlocker TT, Bridenbaugh PO (eds). Philadelphia: Wolters Kluwer, Lippincott, Williams and Wilkins. p. 48–95.

[a] Results vary according to different studies.

anesthetic effects for patients in labor or in the postoperative period. Titration studies done to determine a minimum local anesthetic concentration (MLAC)—an analogy to an effective dose in 50% of patients (ED_{50}) for other drugs—reflect pharmacological differences, which may not be clinically relevant, and so there is a high risk of misinterpretation (Graf et al., 2005).

5.3 Adverse effects of local anesthetics and their management

The adverse effects that may follow administration of a local anesthetic agent can be a result of the physiological consequences of blocking the function of certain nerves, local tissue toxicity or systemic toxicity. Physiological effects are most commonly due to blockade of the sympathetic nervous system and are most relevant following epidural and spinal anesthesia or analgesia (see Chapter 9).

5.3.1 Local tissue toxicity

All local anesthetics are neurotoxic in high concentrations (Selander, 1993). *In vitro,* lidocaine and tetracaine have been shown to be neurotoxic even in concentrations used clinically. However, in clinical practice, local anesthetic agents have an enviable safety record with regard to neurotoxicity and rarely if ever cause localized nerve damage.

An exception to this has been a series of reports of cauda equina syndrome following intrathecal administration of local anesthetics. These cases reflect the effects of local anesthetics given via very thin ("micro") intrathecal catheters accumulating near lumbosacral nerve roots in high concentrations due to insufficient mixing with cerebrospinal fluid (Salinas and Auyong, 2011).

"Transient radicular irritation" (TRI) is another phenomenon, initially thought to be a result of neurotoxicity and first described in 1993. The terminology was later changed to "transient neurologic symptoms" (TNS) and is no longer regarded as a neurotoxic effect (Pollock, 2003). It presents as a temporary pain syndrome affecting the gluteal region and the lower extremities following spinal anesthesia. While this has also been attributed to other local anesthetics, lidocaine has the highest propensity to cause TNS (Zaric and Pace, 2009). Therefore, although the cause of TNS remains unclear, continued use of lidocaine for spinal anesthesia has been questioned. It is of interest that surgical position is a contributing factor to the risk of TNS; potential causes under discussion are musculoskeletal strain and stretching of the sciatic nerve.

Local anesthetics can also cause skeletal muscle toxicity (Zink and Graf, 2004). *In vitro*, intramuscular injections of these drugs can result in reversible myonecrosis, in particular when bupivacaine is used. Clinical cases of such complications are exceedingly rare. Very few case reports describe myopathy after continuous infusions into peripheral nerve sheaths, infiltration of wound margins and, in particular, after eye blocks.

A more serious clinical concern is chondrotoxicity, mainly described as chondrolysis after intraarticular local anesthetic infusions (primarily bupivacaine) into the shoulder joint in particular (Borgeat and Aguirre, 2010). This has led to recommendations to avoid intraarticular bupivacaine infusions (ANZCA and FPM, 2010). The FDA has also issued a warning about use of this technique (Food and Drug Administration, 2010).

5.3.2 Systemic toxicity

High blood concentrations of local anesthetic drugs can lead to signs and symptoms of local anesthetic systemic toxicity (LAST) (Neal et al., 2010; Wolfe and Butterworth, 2011). LAST results from the effects of local anesthetic drugs on the CNS and the cardiovascular system. This can occur if an otherwise safe dose is inadvertently injected directly into a blood vessel, excessive doses of local anesthetic agents are given (by injection or long-term infusion), relatively high amounts are injected into highly vascular areas (e.g., intercostal space) or rarely, if the metabolism of the drugs is reduced by severe hepatic impairment. The higher the blood concentration the more severe will be the signs and symptoms (Table 5.3). Not all will necessarily occur in every patient and with every drug.

A number of factors may influence the blood concentrations of local anesthetic agent reached after injection (Mather and Tucker, 2009; Salinas and Auyong, 2011):

- *Dose of drug*: "Recommended" or "safe" doses may be excessive if injected directly into blood vessels or tissues with a rich vascular supply.
- *Site of injection*: The rate of absorption of local anesthetics depends to a large extent on the vascularization of the site; the order, from most to least rapid absorption, is interpleural > intercostal > caudal > epidural > brachial plexus > sciatic/femoral nerves > subcutaneous.
- *Vasoconstrictor*: With some local anesthetics (lidocaine and mepivacaine) the addition of a vasoconstrictor such as epinephrine (adrenaline) may decrease the rate of absorption, thus prolonging duration of action and leading to lower blood concentrations; little difference is seen if a vasoconstrictor is added to prilocaine or ropivacaine.
- *Speed of injection*: The more rapid the rate of injection the more rapid the rise in plasma concentration of the drug; in a general ward a continuous infusion of local anesthetic solution may be the safest method of administration.

These considerations make it obvious that the current concept of a universally applied maximum recommended dose for local anesthetics has little relevance for clinical practice. Useful recommendations would need to be specific

Table 5.3 Signs and symptoms of systemic local anesthetic toxicity

Ventricular fibrillation, cardiac arrest	
Cardiovascular depression and arrhythmias	↑
Respiratory arrest	
Coma	
Convulsions	*Increasing blood concentrations*
Unconsciousness	
Drowsiness	
Muscular twitching	
Tinnitus, visual disturbances	
Circumoral numbness and numbness of tongue	
Lightheadedness	

to the type of block and take into account patient variables such as advanced age, weight, and medical comorbidities (including cardiovascular and liver disease and low plasma protein concentrations), all of which may also have an effect on the blood concentration of local anesthetic agent reached after injection, in addition to the factors listed above (Mather and Tucker, 2009; Neal et al., 2010).

5.3.2.1 Central nervous system toxicity

Signs and symptoms of CNS toxicity (Table 5.3) are generally seen at lower blood concentrations than those leading to cardiovascular toxicity (Neal et al., 2010; Wolfe and Butterworth, 2011). Premonitory signs of CNS toxicity are best detected by maintaining verbal contact with the patient who, as the blood concentration of the drug rises, may complain of numbness around the mouth and tongue, a feeling of lightheadedness, and ringing in the ears. Slurring of speech and muscle twitching will follow and the patient may become drowsy. If the blood level continues to rise, a generalized convulsion (usually brief) will occur due to initial blockade of inhibitory pathways. At even higher blood concentrations respiratory arrest will ensue. Occasionally, seizures will occur without evidence of the other, usually earlier, signs and symptoms of CNS toxicity (Neal et al., 2010; Wolfe and Butterworth, 2011).

Hypoxia, hypercarbia, and acidosis decrease the convulsive threshold of the drug, increasing the risk of convulsions at lower blood levels. Conversely, hyperventilation and administration of oxygen will lower $PaCO_2$ levels, improve any hypoxia, and help raise the seizure threshold, shortening the duration of the seizure.

5.3.2.2 Cardiovascular toxicity

In general, higher doses are required to produce cardiovascular toxicity than CNS toxicity and cardiovascular toxicity is usually preceded by premonitory CNS symptoms (Neal et al., 2010; Wolfe and Butterworth, 2011). However, with the more potent local anesthetic agents bupivacaine and etidocaine, life-threatening arrhythmias (which may be resistant to treatment) have occurred without preceding CNS signs. A CNS mechanism may contribute to the cardiotoxicity.

Local anesthetic drugs can directly affect the muscles of the heart and peripheral blood vessels and toxicity may result in alterations to myocardial contractility, conductivity, and rhythmicity. Arrhythmias caused by high systemic concentrations of local anesthetics usually involve ventricular ectopy, which may progress to more malignant arrhythmias such as ventricular tachycardia, *torsades de pointes*, and ventricular fibrillation, but can also present as conduction delay, complete heart block, sinus arrest, or asystole (Wolfe and Butterworth, 2011).

Bupivacaine in particular can lead to severe cardiotoxicity, which is often refractory to aggressive and appropriate resuscitation, including defibrillation. Such cases may require prolonged maintenance of resuscitation efforts (sometimes necessitating temporary extracorporeal circulation) to avoid fatalities. The enantiomer-specific long-acting local anesthetics, in particular ropivacaine but also levobupivacaine, offer safety advantages in this regard (Zink and Graf, 2008).

The higher potential for cardiac toxicity with bupivacaine has been demonstrated in animal studies and in healthy volunteers using surrogate outcomes of toxicity (e.g., ECG changes) (ANZCA and FPM, 2010). The animal studies have shown that resuscitation after circulatory collapse following administration of large doses of local anesthetics was significantly more successful after

enantiomer-specific agents were given compared with bupivacaine (Wolfe and Butterworth, 2011). These results are confirmed by published case reports of accidental toxic overdoses in patients, which suggest better outcomes and response to resuscitation after ropivacaine and levobupivacaine than bupivacaine.

Acidosis, hypercapnia, and hypoxia will also markedly enhance the cardiac toxicity of local anesthetic agents.

5.3.3 Management of systemic toxicity

The main goals of treatment of LAST are to prevent cerebral and myocardial hypoxia, so oxygenation, ventilation, and circulatory support are the first priorities (Neal et al., 2010).

In the case of seizures, small doses of an anticonvulsant (preferably a benzodiazepine) should be given intravenously by trained staff; overmedication of early signs of toxicity needs to be avoided. Intubation of the patient may be necessary if mask ventilation is difficult, the patient is apneic or there is a need to protect the airway.

Treatment of malignant arrhythmias caused by local anesthetic overdose should follow established guidelines for advanced cardiac life support, including early defibrillation and the use of the antiarrhythmic amiodarone. However, the dose of epinephrine should be reduced as it may increase the risk of arrhythmias.

The discovery of lipid emulsion as a "sink" for local anesthetics (and other lipophilic toxins) has revolutionized the treatment of LAST (Weinberg, 2012). Current recommendations for the management of LAST published as guidelines by the Association of Anaesthetists of Great Britain and Ireland (AAGBI) (Association of Anaesthetists of Great Britain and Ireland, 2010) and the American Society of Regional Anesthesia (ASRA) (Neal et al., 2010) include the use of a 20% lipid emulsion once airway management and ventilation have been established, with an initial bolus dose of 1.5 mL/kg at the first signs of LAST (Neal et al., 2010). The infusion of lipid emulsion should be continued, but in case of failure of all resuscitative measures, cardiopulmonary bypass should be considered, if available. Useful online checklists are provided by the AAGBI (http://www.aagbi.org/sites/default/files/la_toxicity_2010_0.pdf) and ASRA (http://www.asra.com/checklist-for-local-anesthetic-toxicity-treatment-1-18-12.pdf).

5.4 Commonly used local anesthetic drugs

Local anesthetic agents are classified according to the nature of the linkage between the lipid-soluble and water-soluble parts of the molecule (Mather and Tucker, 2009; Becker and Reed, 2012). The two types of linkage are *amides* and *esters* (see Table 5.4). The clinical differences between the two classes involve the mechanisms by which they are metabolized and their potential for producing allergic reactions.

5.4.1 Esters

Ester local anesthetic drugs are metabolized in plasma (and to a lesser extent the liver) by pseudocholinesterases, thus their half-lives in the circulation are shorter than amide local anesthetic drugs (Mather and Tucker, 2009; Becker and Reed, 2012). These drugs have a greater potential to cause allergic reactions as they are

Table 5.4 Classes of local anesthetic drugs

Amides	Esters
Lidocaine (lignocaine)	Procaine
Bupivacaine	Chloroprocaine
Ropivacaine	Cocaine
Levobupivacaine	Tetracaine (amethocaine)
Mepivacaine	Benzocaine
Etidocaine	
Prilocaine	
Dibucaine (cinchocaine)	
Articaine	

metabolized to para-amino benzoic acid, which acts as a hapten. They are also less stable in solution than amide local anesthetics. For these reasons, they are no longer widely used and are more of historical interest. In particular, they play no role in the treatment of acute pain and will therefore only be discussed briefly.

5.4.1.1 Cocaine

In addition to its local anesthetic action, cocaine also causes general stimulation of the CNS and blocks reuptake of catecholamines at adrenergic nerve endings, thus potentiating the effects of sympathetic nervous system stimulation. Because of its potential for toxicity, the use of cocaine is restricted to topical administration, usually at the nasal mucosa, where its local vasoconstrictor effect helps to reduce intraoperative bleeding. Doses should be kept within recommended limits to avoid the risk of side effects.

5.4.1.2 Chloroprocaine

Because of its rapid onset, rapid metabolism, and short duration of action, chloroprocaine has been primarily used in obstetric epidural analgesia or regional anesthetic techniques for day surgery. Neurotoxicity, with motor and sensory deficits, has followed accidental subarachnoid injection; the antioxidant sodium bisulfite in the anesthetic solution has been implicated as the cause. This has been replaced by ethylenediaminetetraacetic acid, usually abbreviated as EDTA, in recent formulations, which seems to carry a very low risk of TNS (Goldblum and Atchabahian, 2013).

5.4.2 Amides

Amide local anesthetic drugs are metabolized in the liver and the elimination half-lives vary from about 1.5 to 3.5 hours. These drugs rarely, if ever, cause true allergic reactions although patients may be allergic to the antioxidants and preservatives contained in some local anesthetic solutions (Becker and Reed, 2012). These were a particular problem with multi-dose vials, which have been discontinued in most countries. Some patients reporting an "allergy" to these drugs may have experienced effects due to the systemic absorption of epinephrine

(Becker and Reed, 2012), or an allergic reaction to an ester local anesthetic, or had a vasovagal response to the injection.

A differentiation between short-acting amide (e.g., lidocaine) and the long-acting amide agents (bupivacaine, levobupivacaine, and ropivacaine), which are most often used for longer lasting blocks and continuous techniques to provide analgesia, is clinically useful.

5.4.2.1 Lidocaine

Lidocaine (lignocaine) is the most widely used short-acting local anesthetic worldwide. Absorption can be reduced, and therefore length of action increased and the risk of toxicity decreased, by the addition of vasoconstrictors to the solution. Although often used to establish regional and local anesthetic blocks for operative procedures, it is not commonly used in the ongoing management of acute pain. The reasons for this include the development of acute tolerance and tachyphylaxis as well as the propensity to cause a greater degree of motor block for a given degree of sensory block than the long-acting local anesthetics (Mogensen, 1995).

Lidocaine is available in a number of preparations: ointments, jelly, topical solutions including a spray, and formulations for injection. It has also been administered by nebulizer to obtain topical anesthesia of the upper airway and intravenously for the treatment of cardiac arrhythmias, neuropathic pain, and to improve postoperative recovery of gastrointestinal function (Borgeat and Aguirre, 2010) (see Chapter 12).

A mixture of lidocaine and prilocaine (2.5% of each), called EMLA™ cream (eutectic mixture of local anesthetics), can be used as a topical local anesthetic agent for skin (ANZCA and FPM, 2010). Applied under an occlusive dressing or as a patch, it takes 30–60 minutes to have its full effect. It has been used prior to the insertion of intravenous cannulae or other needles (especially in children) and for local procedures such as superficial skin surgery and skin grafting.

A topical lidocaine patch is also available in some countries and is recommended as first-line treatment of localized neuropathic pain (e.g., postherpetic neuralgia) (ANZCA and FPM, 2010).

5.4.2.2 Bupivacaine

Bupivacaine is commonly used for the management of acute pain outside the operating room and a number of different infusion solutions are available for provision of continuous epidural and regional analgesia.

A more recent development is the formulation of liposomal bupivacaine, which aims to increase its duration of effect. It has been used primarily for local wound infiltration, and while this could be promising for the treatment of acute pain, current studies show no consistent benefit compared with plain bupivacaine (Chahar and Cummings, 2012).

As outlined above, bupivacaine is more cardiotoxic than other local anesthetic drugs and any cardiovascular collapse that does occur may be more difficult to treat. Bupivacaine is a racemic mixture of two enantiomers, *S*-(–) and *R*-(+). These enantiomers have the same structural formula, but a different three-dimensional configuration of atoms, resulting in two molecules which are mirror images (Sidebotham and Schug, 1997; Mather and Tucker, 2009). This leads to different biological activities with the *R*-(+)-enantiomer of bupivacaine being more toxic to the heart and CNS.

In response to these findings, the enantiomer-specific local anesthetics ropivacaine and levobupivacaine have been developed (Zink and Graf, 2008). They have a lower potential for CNS and cardiac toxicity.

5.4.2.3 Ropivacaine

Ropivacaine is the *S*-(–)-enantiomer of the propyl analogue of bupivacaine (Simpson et al., 2005). It is said to have a comparable potency compared with bupivacaine, with a similar onset, duration, and degree of sensory block, when given in equivalent doses, although in some studies it appears to be less potent. Another advantage over bupivacaine is said to be a greater differential block (less motor block for the same degree of sensory block); however, in acute pain management, when low concentrations of bupivacaine are commonly given by infusion, the difference in degree of motor blockade between the two drugs is not always apparent.

5.4.2.4 Levobupivacaine

Levobupivacaine is the *S*-(–)-enantiomer of bupivacaine (Sanford and Keating, 2010). Compared with racemic bupivacaine, it has similar anesthetic properties, but, like ropivacaine, has a lower potential for cardiac toxicity and therefore offers similar advantages.

5.4.2.5 Mepivacaine

Mepivacaine has a similar anesthetic profile to lidocaine with a relatively rapid onset and a moderate duration of action. Unlike lidocaine, mepivacaine is effective as a topical agent only in large doses and should not be used for this indication.

5.4.2.6 Prilocaine

Prilocaine has a similar clinical profile to lidocaine (lignocaine), but is the least toxic of the amide local anesthetic drugs. This makes it a most suitable choice for intravenous regional anesthesia (Bier's block).

The initial step in the metabolism of prilocaine forms orthotoluidine. The administration of large doses of prilocaine may lead to the accumulation of this metabolite, which, in turn, leads to an increase in the oxidation of hemoglobin to methemoglobin (Becker and Reed, 2012). If the level of methemoglobin becomes excessive, the patient may appear cyanotic. This metabolic toxicity limits the use of prilocaine in anemic patients and leads to the recommendation to avoid repeat injections or infusions, thereby limiting its use in acute pain therapy.

5.4.2.7 Dibucaine (cinchocaine)

Dibucaine is used widely to provide topical analgesia, for example, in creams and ointments. The injectable preparation is used primarily for spinal analgesia.

5.4.2.8 Etidocaine

Etidocaine is as long acting as bupivacaine and has been associated with similar problems with respect to cardiac toxicity. It is noted for its profound motor blockade and therefore not used to provide analgesia.

Key points

1. Local anesthetics do not have a specific analgesic effect, but can block all nerve conduction in sensory, motor, and autonomic fibers.
2. The mechanism of action of local anesthetics is sodium channel blockade, which also explains their adverse effects on the cardiovascular and central nervous system.
3. Local anesthetic systemic toxicity is a rare, but serious complication of use of these compounds; treatment should follow established guidelines and include the use of lipid emulsion.
4. Among the long-acting local anesthetics most commonly used for analgesia, bupivacaine has a much higher cardiotoxicity than the enantiomer-specific agents ropivacaine and bupivacaine.

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CHAPTER 6

Nonopioid and adjuvant analgesic agents

Drugs other than opioids and local anesthetics play an important role in the treatment of acute pain. While they can be used as the sole analgesic agent, they are more commonly given in combination with opioids as important components of multimodal or balanced analgesia. The combination of medications with different mechanisms or sites of action aims to improve acute pain relief and is often opioid sparing, which may reduce the incidence and severity of opioid-related adverse effects. This may lead to improved recovery with less nausea and vomiting, earlier oral intake, quicker return of bowel function and more successful functional rehabilitation. In addition, such medications can play an important role in the management of acute neuropathic pain, acute pain in opioid-tolerant patients and procedural pain, as well as improve pain relief on mobilization.

The drugs discussed in this chapter include the traditional nonopioid analgesics, that is, paracetamol (acetaminophen) and nonsteroidal antiinflammatory drugs (NSAIDs), the inhalational agents nitrous oxide and methoxyflurane, and a large group of drugs commonly called adjuvant analgesic agents or coanalgesics. These were often developed for other indications (e.g., antidepressants, anticonvulsants, anesthetic drugs), but are very useful in the management of pain, including neuropathic pain, and central sensitization (see Chapter 12).

The information given below relates to the systemic use of nonopioid and adjuvant medications. However, some are also given in combination with drugs used for neuraxial and other regional analgesia (see Chapters 9 and 10).

6.1 Paracetamol

The development of paracetamol started with the discovery of the fever-lowering effect of acetanilide, a finding that resulted in the manufacture of phenacetin by Bayer. Its active metabolite, paracetamol, was first used clinically by von Mehring in 1893.

Although paracetamol is often classified as an NSAID, this is incorrect, as it shows only very limited antiinflammatory activity. Paracetamol is mainly an analgesic and antipyretic agent.

6.1.1 Mechanism of action

Despite its common and long history of use, the mechanisms underlying the antinociceptive effects of paracetamol are still not well understood. Originally believed to have only central effects, paracetamol is now thought to act both centrally and peripherally (Graham et al., 2013). It reduces prostaglandin synthesis from arachidonic acid via inhibition of the cyclooxygenase isoenzymes COX-1 and COX-2, but appears to be more selective for COX-2. However, it should not be termed a selective COX-2 inhibitor as it may inhibit COX-1 when arachidonic acid levels are low, and it also inhibits other oxidases (possibly COX-3 and/or

peroxidase). Other possible mechanisms of action of paracetamol include an effect on central serotonergic (5-HT) pathways, a component of the descending inhibitory system of pain control, and on both the opioid and endocannabinoid systems (Graham et al., 2013). A potential role in the inhibition of nitric oxide synthetase with effects on the NMDA receptor is also debated. None of these hypotheses have been confirmed and the definitive mechanism of action underlying the analgesic effect of paracetamol remains unknown.

The antipyretic effect of paracetamol may result from inhibition of prostaglandin synthesis in the hypothalamus.

6.1.2 Clinical efficacy and use

Paracetamol should be regarded as the first-line analgesic for mild-to-moderate pain and as a component of multimodal analgesia in the treatment of moderate and severe pain. Clinically, its analgesic efficacy is comparable to aspirin, but it is less effective than other NSAIDs (Graham et al., 2013). It has become the first-line choice worldwide for pain relief across a wide range of indications and a wide range of patients and patient ages. Reasons for this popularity include its relative effectiveness in many pain conditions, its high tolerability, even for patients in whom other nonopioid drugs are contraindicated, and the minimal risk of serious adverse effects.

Paracetamol is usually given by oral or rectal routes. After oral administration, peak plasma concentrations are reached within about an hour. Time-to-peak plasma concentration and bioavailability are much less reliable when the rectal route is used (ANZCA and FPM, 2010).

The use of paracetamol has been facilitated by the introduction of an intravenous (IV) preparation, now available in many countries. Intravenous administration results in higher central nervous system (CNS) concentrations of the drug and faster-onset analgesia compared with the oral and in particular the rectal routes of administration.

Coadministration of an NSAID with paracetamol is synergistic and the combination provides better pain relief than either drug alone (Ong et al., 2010). This is also true for combinations with various opioids including codeine, oxycodone, and hydrocodone (Graham et al., 2013) as well as tramadol. The addition of paracetamol to opioid treatment regimens results in "opioid-sparing," but only limited additional benefits in terms of analgesia or the incidence of opioid-related adverse effects (Maund et al., 2011).

The discussion about a reasonable therapeutic dose continues. Although a dose limit of 4 g/day for adults is often suggested, higher doses may be more effective in the acute pain setting (ANZCA and FPM, 2010). For a short period at least and provided there is no contraindication, most adults with normal body weight may benefit from treatment with 1 g 4-hourly up to a maximum dose of 6 g/day. Longer-term use of paracetamol should continue with a maximum of 1 g given four times a day.

6.1.3 Adverse effects

Many of the misconceptions about the risks of paracetamol have resulted from widely reported severe and sometimes fatal liver damage. However, these cases are generally the result of intentional or unintentional overdose. Taken in suggested therapeutic doses, paracetamol is very well tolerated by most patients with minimal adverse effects.

Hepatotoxicity following overdose is caused by a metabolite of paracetamol, *N*-acetyl-*p*-benzoquinone imine (NAPQI), a highly reactive radical that leads to hepatic cell necrosis. The small amounts of NAPQI resulting from paracetamol intake are normally inactivated by combination with glutathione, resulting in harmless compounds that undergo renal excretion. However, excessive doses of paracetamol may exhaust the liver's glutathione stores and NAPQI can then cause dose-related liver damage. It has been suggested that patients who have low levels of glutathione (e.g., associated with starvation, malnutrition, HIV, chronic liver disease, and regular high alcohol intake) or already impaired liver function may be more susceptible to paracetamol-associated hepatotoxicity. However, none of these factors seem to place patients at increased risk, as long as recommended doses only of paracetamol are used (ANZCA and FPM, 2010). Only overdoses of paracetamol in such patients may result in an increased risk of and more severe liver damage.

Renal toxicity, historically linked to phenacetin, rarely occurs with paracetamol despite its apparent COX-2 inhibitory effect (Graham et al., 2013). It is specifically recommended for use in patients with renal impairment. Paracetamol hypersensitivity and allergies are unlikely, but it can increase the risk of asthma in some patients with aspirin-exacerbated respiratory disease (AERD). Compared with NSAIDs, paracetamol causes little or no gastrointestinal toxicity and it does not have a significant effect on platelet function (Graham et al., 2013), although it can enhance the effect of warfarin (ANZCA and FPM, 2010). It can lead to hemolysis if given to patients with the extremely rare glucose-6-phosphate dehydrogenase (G6PD) deficiency.

6.2 Nonselective nonsteroidal antiinflammatory drugs

The analgesic and antiinflammatory properties of the bark of the willow and other plants have been known for centuries. The active ingredient in willow bark is salicin and it was first described in the nineteenth century (Wick, 2012). Subsequently, the chemist Hoffmann, trying to improve the gastric tolerability of salicylic acid for his father, synthesized acetylsalicylic acid, the well-known aspirin. Aspirin became the prototype NSAID and attempts to improve on this compound resulted in the many different NSAIDs now available worldwide.

The discovery of two isoenzymes of cyclooxygenase, COX-1 and COX-2, led to the rapid development of a series of COX-2 selective inhibitors (coxibs) which were marketed with great success, as they have a lower risk of the adverse effects commonly associated with the nonselective NSAIDs (nsNSAIDs)—see below.

The differences in adverse effects make it useful to look at nsNSAIDs and coxibs separately.

6.2.1 Mechanism of action

Nonselective NSAIDs exhibit a spectrum of analgesic, antiinflammatory, antiplatelet, and antipyretic actions, although the degree to which these are seen may vary between different drugs. In 1971 Vane, who later won a Nobel Prize for his discovery, identified the mechanism of action of aspirin as inhibition of the enzyme responsible for prostaglandin synthesis (Vane, 1971). This enzyme was later called cyclooxygenase (Vane and Botting, 1998). It metabolizes arachidonic acid to a large number of eicosanoids, including prostaglandins, prostacyclins, and thromboxane A_2. This mechanism of action also explains the wide range of adverse effects

of nsNSAIDs, as the eicosanoids have protective homoeostatic functions in the intestinal mucosa and the kidney and are linked to platelet function.

The antiinflammatory effect is related to the reduction of prostaglandins such as PGE_2 and prostacyclin, which act as mediators of inflammation. The analgesic effect is the result of reduced prostaglandin synthesis in the periphery, leading to decreased sensitization of nociceptors. In addition, inhibition of cyclooxygenase in the CNS reduces the formation of prostaglandins in the spinal cord and the brain, and thereby central sensitization. The antipyretic effect is the result of a decrease in prostaglandin concentrations in the hypothalamus.

6.2.2 Clinical efficacy and use

NSAIDs may be used as the sole method of treatment for mild-to-moderate pain (Moore et al., 2011). They can lead to better analgesia than the so-called "weak opioids" such as codeine, tramadol, and propoxyphene. When NSAIDs are used instead of these drugs, a significant reduction in side effects is seen.

However, they are not sufficiently effective as the sole agent after major surgery or injury in most patients, and are best used as an integral component of multimodal analgesia in combination with other drugs such as opioids. When used in combination with opioids, NSAIDs lead to a significant reduction in opioid requirements (i.e., they are "opioid-sparing") and a reduction in the incidence of nausea and vomiting (Maund et al., 2011).

There is a "ceiling effect" to the analgesia produced by NSAIDs, when further increases in dose do not result in additional pain relief, but may lead to an increase in adverse effects. There appears to be little, if any, difference in analgesic efficacy between the different NSAIDs (Moore et al., 2011), although differences may exist in their antiinflammatory activity and in the incidence of side effects. While concurrent use of two NSAIDs is not recommended, pain relief is improved by the combination of paracetamol with an NSAID (Ong et al., 2010).

Most NSAIDs are given orally or rectally. After oral administration they are rapidly absorbed from the upper gastrointestinal tract, primarily from the stomach, and peak plasma concentrations are usually reached in about 2 hours. Some (e.g., ketorolac, tenoxicam, and diclofenac) can be given by injection. Oral administration is very effective and there is little evidence that other routes offer significant advantages in terms of analgesic efficacy or side effects, except in treatment of acute renal colic (ANZCA and FPM, 2010). However, parenteral administration permits use in patients who are unable to take oral medications.

NSAIDs are commonly metabolized in the liver and their metabolites excreted by the kidney. Clearance is reduced in elderly patients and in those with renal impairment. Most NSAIDs have half-lives of around 2–3 hours, although some, like piroxicam and tenoxicam, are much longer (50–60 hours). NSAIDs with longer half-lives seem to be associated with a higher risk of adverse effects.

6.2.3 Adverse effects

The nsNSAIDs can produce a variety of undesirable adverse effects, so the potential risk of using these drugs should always be weighed against possible benefits. The comments in this section refer to the commonly used nsNSAIDs that show both COX-1 and COX-2 inhibition, although the degree of inhibition of each isoenzyme may vary between drugs.

6.2.3.1 Gastrointestinal

Reductions in prostaglandin levels by inhibition of COX-1 may lead to erosions of the gastrointestinal mucosa, especially in the stomach, but also the small intestine (Lim and Chun, 2013). This is due to a reduction in the prostaglandin-mediated protective functions of mucus production, maintenance of mucosal blood flow, and inhibition of gastric acid secretion. Thus, contrary to widespread belief, the problem is not a local one and erosions will not be avoided by using parenteral or rectal routes of administration. Limited prophylaxis against gastric, but not small intestine ulceration is possible. Prostaglandin analogs (e.g., misoprostol) and proton pump inhibitors (e.g., omeprazole) are far more effective than H_2 antagonists (e.g., cimetidine, ranitidine) (Conaghan, 2012).

Gastric irritation, dyspepsia, and ulceration (which may be silent in approximately 50% of patients until a bleed or perforation occurs) may develop at any time. While the risk of gastrointestinal side effects increases with long-term treatment, there is a significant risk of ulcer formation even after a short course of treatment in the perioperative setting (ANZCA and FPM, 2010). Other risk factors are increasing age, alcohol, history of peptic ulcer disease and/or gastric bleeding, high doses, and concurrent use of anticoagulants (including heparin used for thromboprophylaxis) or steroids. Of the nsNSAIDs, ibuprofen and diclofenac appear to have the lowest rates of gastrointestinal side effects while piroxicam and ketorolac are associated with the highest rates (Conaghan, 2012).

Other gastrointestinal complications include esophagitis and a diffuse intestinal inflammation known as NSAID enteropathy and colitis.

6.2.3.2 Renal

Renal toxicity related to the use of nsNSAIDs is the result of COX-1 and COX-2 inhibition, as both isoenzymes produce vasodilatory prostaglandins that help to maintain renal blood flow and glomerular filtration rate. This detrimental effect on the kidney will therefore occur in patients in whom vasodilatory renal prostaglandins are needed in order to maintain renal perfusion. This includes those patients whose effective circulating blood volume is decreased (e.g., as a result of hypovolemia, dehydration, hypotension, sepsis, or excessive use of diuretics) or patients with congestive cardiac failure or hepatic cirrhosis (ANZCA and FPM, 2010). Acute postoperative renal failure due to NSAIDs has been reported even in healthy young patients when risk factors such as hypovolemia are present. As many factors in the perioperative period may adversely affect renal blood flow, it may be wise to delay administration of nsNSAIDs until the patients is normovolemic and normotensive in the postoperative period.

Preexisting renal impairment will increase the risk of renal complications with nsNSAIDs as will concurrent administration of some other drugs; these include angiotensin-converting enzyme (ACE) inhibitors, potassium-sparing diuretics, aminoglycoside antibiotics (e.g., gentamicin), methotrexate, and cyclosporine.

However, concerns about renal toxicity should not result in a complete avoidance of NSAIDs in the perioperative period. Adults with normal preoperative renal function show only clinically insignificant and transient decreases in creatinine clearance with perioperative use of these medications (Lee et al., 2007). However, any relevant increase in plasma urea or creatinine or low urine output should lead to a discontinuation of NSAIDs.

With longer-term use, NSAIDS can also cause sodium, potassium, and water retention, which may lead to edema in some patients and may reduce the effectiveness of antihypertensive therapy. Interstitial nephritis and nephrotic syndrome have also been reported.

6.2.3.3 Platelet function

Platelet aggregation requires the presence of thromboxane A_2, a product of COX-1. Therefore, nsNSAID-induced inhibition of COX-1 results in prolonged bleeding times (ANZCA and FPM, 2010). This increases the risk of perioperative blood loss in some situations and leads to a higher reoperation rate for bleeding after tonsillectomies.

Aspirin is the only nsNSAID that irreversibly inhibits COX-1 and, therefore, effectively prolongs bleeding time for the life of the platelet (4–8 days). Recovery depends exclusively on the production of new platelets. This is the reason why low-dose aspirin is used in the secondary prevention of myocardial infarction and stroke. All other nsNSAIDs reversibly inhibit platelet COX-1 as their antiplatelet effect is limited by the duration of effect of the drug.

6.2.3.4 Respiratory

Aspirin-exacerbated respiratory disease (AERD) refers to the onset of bronchospasm following the administration of aspirin and other nsNSAIDs in some patients with asthma. Up to 10–15% of adult asthmatic patients have AERD (ANZCA and FPM, 2010) and these drugs should therefore be used with caution in patients with asthma. It is worth asking asthmatic patients whether they have taken nsNSAIDs before, as many will have done so without any worsening of their symptoms.

6.2.3.5 Other effects

Headache, anxiety, depression, confusion, dizziness, somnolence, hypertension, and cardiac failure have all been reported following administration of nsNSAIDs, as have a variety of skin reactions and blood dyscrasias. Cardiac complications have been reported in association with long-term use of nsNSAIDs—see 6.3.3.1.

Abnormalities in liver function tests may be seen, but these are usually transient. Rarely, hepatotoxicity occurs (Conaghan, 2012). A specific form of hepatotoxicity called Reye's syndrome is linked to the intake of aspirin during febrile viral illnesses (e.g., an upper respiratory tract infection or chicken pox) in children. While causation remains unclear, these children may develop cerebral inflammation and edema in addition to the liver failure and the results may be fatal. Therefore, the FDA recommends that aspirin should be avoided in children and adolescents under 19 years of age.

There is experimental evidence that NSAIDs, by inhibiting prostaglandin synthesis, impair osteoblast activity. However, there is no evidence for any clinically relevant effect of NSAIDs on fracture healing (Kurmis et al., 2012).

NSAIDs may also affect the actions of other drugs that are dependent on the kidney for excretion, such as the aminoglycoside antibiotics (e.g., gentamicin) and digoxin.

6.2.4 Precautions and contraindications

An evidence-based report by the Royal College of Anaesthetists considered the use of NSAIDs in the postoperative period and suggested certain precautions

Table 6.1 Possible precautions and contraindications to the use of NSAIDS for acute pain management

NSAIDs should be avoided in the following clinical situations:

- Preexisting renal impairment (elevated plasma creatinine levels)
- Hyperkalemia
- Dehydration, hypovolemia, or hypotension from any cause
- Cardiac failure
- Severe liver dysfunction
- Uncontrolled hypertension
- Aspirin-exacerbated respiratory disease (aspirin-exacerbated asthma)
- History of gastrointestinal bleeding or ulceration
- Known hypersensitivity to aspirin or other NSAIDs

NSAIDs should be used with caution in the following clinical situations:

- Impaired hepatic function, diabetes, bleeding or coagulation disorders, vascular disease
- Operations where there is a high risk of intraoperative hemorrhage (e.g., cardiac, major vascular, and hepatobiliary surgery)
- Operations where an absence of bleeding is important (e.g., eye surgery, neurosurgery, and cosmetic surgery)
- Other forms of asthma
- Concurrent use of other, ACE inhibitors, potassium-sparing diuretics, anticoagulants, methotrexate, cyclosporin, and antibiotics such as gentamicin
- Children less than 16 years old
- Pregnant and lactating women
- Advanced age (renal impairment is likely in patients older than 65 years, even if creatinine levels are normal)

Source: Adapted from the Royal College of Anaesthetists. 1998. *Guidelines for the Use of Nonsteroidal Antiinflammatory Drugs in the Perioperative Period.* London: Royal College of Anaesthetists.

Note: Many perioperative factors may adversely affect renal blood flow and it may be wise to delay administration of NSAIDs until the postoperative period and until the patient is normovolemic and normotensive. If a patient is already receiving an NSAID, it should be discontinued if there is any increase in plasma urea or creatinine levels, or if urine output is low.

and contraindications (Royal College of Anaesthetists, 1998). These are summarized in Table 6.1.

6.3 COX-2 selective inhibitors (coxibs)

The discovery of two isoenzymes of cyclooxygenase, COX-1 and COX-2, rapidly resulted in the development of a new class of analgesic and antiinflammatory drugs, the so-called selective COX-2 inhibitors or coxibs (Conaghan, 2012). COX-2 is found in inflammatory cells, sites of inflammation and tissue damage, synovia of joints, endothelium and the CNS, and was the logical choice as the target of a new class of drugs that might avoid classical nsNSAID-related adverse effects.

6.3.1 Mechanism of action

The isoenzyme COX-1 is a constitutively expressed cyclooxygenase found in the gastrointestinal tract, kidney, and platelets. It maintains gastric cytoprotection, renal sodium and water balance, and normal platelet aggregation. The isoenzyme COX-2 was initially regarded as an enzyme only inducible by inflammatory cytokines such as interleukins. However, it is also a constitutive enzyme in the brain, kidney, ovary, uterus, and endothelium.

The discovery of a hydrophilic side pocket in the wider COX-2 isoform of the enzyme enabled the development of larger molecules with a side chain that fitted COX-2 and its side pocket, but not the slimmer COX-1 isoenzyme.

6.3.2 Clinical efficacy and use

Within a very short time of discovery of the two isoenzymes of cyclooxygenase, rofecoxib and celecoxib were developed and marketed for use in patients with osteoarthritis and rheumatoid arthritis. Subsequently, other coxibs such as valdecoxib and its parenterally administered prodrug parecoxib, as well as etoricoxib and lumiracoxib became available (Conaghan, 2012).

Coxibs are as effective as NSAIDs for the treatment of arthritic pain and moderate-to-severe postoperative pain (ANZCA and FPM, 2010). Combined with opioids as a component of multimodal analgesia, they result in opioid sparing, but may not lead to a reduction in the incidence of opioid-related adverse effects (Maund et al., 2011).

Parecoxib, the only injectable coxib, is particularly suitable for acute pain management as it can be given as an IV or intramuscular injection. It provides rapid onset of effective analgesia within 10–15 minutes and lasts 12–24 hours.

6.3.3 Adverse effects

In the treatment of acute pain, coxibs can offer significant advantages over nonselective NSAIDs with regard to adverse effects (ANZCA and FPM, 2010).

6.3.3.1 Gastrointestinal, respiratory, and renal

While even short-term use of nsNSAIDs (such as naproxen and ketorolac) is associated with a high incidence of gastrointestinal ulceration, there is no increase in risk related to administration of parecoxib compared with placebo. Coxibs do not impair platelet function and therefore do not increase the risk of postoperative bleeding, and they do not induce bronchospasm in patients with AERD. They are thought to have a similar adverse effect on renal function and should be used with the same precautions as nsNSAIDs, although a large epidemiological study has suggested that the risk of renal toxicity may be less with coxibs (Lafrance and Miller, 2009).

A comparative table of the adverse effects associated with short-term use of nsNSAIDs and coxibs is provided in Table 6.2.

6.3.3.2 Cardiac

The withdrawal of rofecoxib from the market in September 2004, because of reports of an increased incidence of thromboembolic complications (i.e.,

Table 6.2 Comparison of potential adverse effects with short-term use of nonselective NSAIDs and coxibs

Adverse effect	nsNSAID	Coxib
Upper gastrointestinal	+	–
Lower gastrointestinal	+	–
Bleeding	+	–
Aspirin-sensitive asthma	+	–
Renal toxicity	+	+ (Possibly less risk compared with nsNSAIDs)

+ Increased compared with placebo.
– Identical to placebo.

myocardial infarction, stroke) associated with its long-term use, initiated debate about a potential "class effect" of coxibs (Conaghan, 2012). This hypothesis was based on the concept that selective inhibition of the COX-2 isoenzyme would lead to an imbalance between endothelial prostacyclin production and lack of thromboxane A_2 formation in platelets. Such an imbalance could have a prothrombotic effect. However, it is now obvious that the increased incidence of thromboembolic complications is a class effect of all NSAIDs and not just coxibs. Individual drugs have specific risk profiles irrespective of their COX-2 selectivity. For example, the risk of cardiovascular events appears to be lowest with naproxen and highest with diclofenac and coxibs (Bhala et al., 2013).

Short-term use of any NSAIDs (e.g., perioperatively) does not carry an increased risk of serious cardiovascular adverse events after noncardiac surgery (ANZCA and FPM, 2010). However, use of any NSAID after coronary bypass graft surgery has been shown to increase the incidence of cardiovascular and cerebrovascular events and their use in patients after this type of surgery is now contraindicated. The risk is most likely due to the shear stress induced on platelets by the roller pumps used for cardiopulmonary bypass.

Key points for nonopioid analgesic drugs

1. Paracetamol is an effective nonopioid analgesic for acute pain with minimal adverse effects as long as correct doses are used.
2. Nonselective NSAIDs and coxibs are nonopioid analgesics of similar efficacy in acute pain.
3. Combined use of paracetamol and NSAIDs provides better pain relief than either drug alone.
4. Paracetamol and NSAIDs are useful components of multimodal analgesia.
5. While NSAIDs can lead to renal impairment in at-risk patients (e.g., hypovolemia, preexisting renal disease, other nephrotoxic medications), their use in selected patients with careful monitoring rarely leads to perioperative renal failure.
6. The risk of adverse effects other than renal impairment with coxibs is reduced in comparison with nsNSAIDs.
7. The use of coxibs for short-term treatment of postoperative pain is not associated with an increased risk of cardiovascular complications after noncardiac surgery. All NSAIDs are contraindicated after cardiac surgery.

6.4 NMDA receptor antagonists

Surgery or trauma leading to tissue damage and subsequent inflammatory responses causes nociceptive stimuli to be carried along peripheral sensory nerves to the spinal cord. The CNS responds to this persistent input from the periphery with adaptive processes commonly described as neuroplasticity. This leads to the development of spinal cord hyperexcitability, a process referred to as central sensitization (Woolf, 2011). Features of this process include an increased sensitivity and exaggerated response to further pain stimuli (hyperalgesia). The increased sensitivity may also extend to stimuli that would not normally be regarded as painful (e.g., touch), but because of these changes, result in the sensation of pain (allodynia). Thus, central sensitization leads to alterations in the nature, intensity, and duration of the pain perceived. It is further increased by a reduction in descending inhibitory transmission in the spinal cord.

Underlying phenomena are somewhat similar to those of memory generation. Among the excitatory processes, wind-up, where spinal cord neurons show a progressively greater response to repetitive stimuli, also plays an important role. Subsequent processes that are involved include long-term potentiation, recruitment leading to expansion of the receptive fields of these neurons, afterdischarge and increased spontaneous neuronal activity. The increased excitability is primarily the result of increased excitatory amino acid (EAA) release, in particular glutamate. It is mediated by glutamate activation of *N*-methyl-D-aspartate (NMDA) receptors in the dorsal horn neurons of the spinal cord.

These changes happen in all patients after acute injury and therefore central sensitization contributes significantly to the pain experience after trauma or surgery. In most patients central sensitization lessens as the injury heals and acute pain resolves. However, in some patients, central sensitization persists beyond healing and can then contribute to persistent pain states (see Chapter 12). Of note is that the mechanisms underlying the development of tolerance to opioids and opioid-induced hyperalgesia are similar to central sensitization (see Chapter 4).

These processes explain the pivotal importance of EAAs and their binding site, the NMDA receptor, in both nociceptive and neuropathic pain. Medications that either decrease EAA release (e.g., gabapentin and pregabalin; see Section 6.7) or act as antagonists at their receptors reduce the risk of development of wind-up and central sensitization and downregulate hyperexcitability after sensitization has taken place. Therefore, NMDA receptor antagonist drugs show effects that are best described as "anti-allodynic," "anti-hyperalgesic," and "tolerance-protective" rather than as simply analgesic (ANZCA and FPM, 2010).

The use of NMDA receptor antagonist drugs, mainly ketamine, has become increasingly common in the management of acute and chronic pain states.

6.4.1 Ketamine

The most important NMDA receptor antagonist in clinical use is ketamine, a compound which was initially developed as a dissociative anesthetic agent.

It is commonly available as a racemic mixture of *R*-(–)- and *S*-(+)-isomers. The *S*-(+)-isomer, available as an enantiomer-specific product in some countries only, is the more potent analgesic (twofold) with a shorter duration of action and it is said to produce fewer side effects than the racemic mixture. Ketamine acts at a

number of receptors including NMDA and opioid receptors, although interactions at receptors other than the NMDA receptor appear to be of limited clinical importance.

The terminal elimination half-life of racemic ketamine is 2–3 hours. The drug is metabolized by the liver and the metabolites are excreted by the kidney. The primary metabolite, norketamine, is also an NMDA receptor antagonist and contributes to its analgesic effect, although it is less potent than ketamine itself.

6.4.1.1 Clinical efficacy and use

Ketamine is widely used to provide anesthesia in out-of-hospital settings and in Third World countries, but it is also commonly used in the management of pain. The doses given will vary according to the indication for the drug.

The use of anesthetic doses requires appropriate training and familiarity with the drug and its adverse effects, although it is the only anesthetic agent that results in no or only minimal opioid-induced ventilatory impairment (OIVI) or airway compromise.

In acute pain management, lower doses are usually administered as an adjunct to other analgesic interventions to improve the quality of pain relief, reduce the amount of opioid needed, and decrease the incidence of opioid-related side effects such as nausea and vomiting (Laskowski et al., 2011).

Ketamine is particularly useful for the treatment of pain that is poorly responsive to opioids, including pain in opioid-tolerant patients, acute neuropathic pain, and ischemic pain (ANZCA and FPM, 2010). Ketamine also has a preventive effect and can limit the progression from acute to persistent pain (Chaparro et al., 2013)—see Chapter 12.

Ketamine is usually administered by the intravenous (IV) or, less commonly, by the subcutaneous (SC) route. There is also increasing interest and evidence of efficacy for nonparenteral routes of administration (intranasal, transmucosal, transdermal).

Ketamine can improve analgesia by its inhibitory effects on central sensitization when given in subanesthetic (analgesic) and even less than analgesic doses. These effects of ketamine have been described with infusion rates as low as 100–200 mg/day (run as 4–8 mg/h) in an average adult. Some centers alter the dose based on the weight of the patient and use an initial infusion rate of 0.1 mg/kg/h (i.e., 7 mg/h for the average adult). Adjustments to the rate of infusion should be made according to effect and adverse effects. In the older patient, it may be appropriate to start with even lower doses (e.g., 50 mg/day or 2 mg/h) and increase as needed. It may be useful to give a small loading dose (e.g., 5 mg increments up to a total of 15–25 mg in the average adult patient) prior to the start of the infusion, with lower doses used in older patients. Single bolus doses in this dose range can also be used to treat pain that has not responded well to large doses of opioid, even if an infusion is not required.

In some centers, ketamine is added to the opioid used in patient-controlled analgesia (PCA), so that the patient receives both opioid and ketamine with every demand. However, large interindividual variations in opioid requirements mean that patients are likely to receive widely varying doses of ketamine. This could lead to inadequate therapy in some patients and an increased risk of adverse effects in others. Therefore, a separate infusion of ketamine is preferred.

Last, but not least, in higher doses (but still in subanesthetic doses), ketamine is widely used to treat pain in emergencies, in out-of hospital settings, disaster

Table 6.3 Possible uses for the NMDA receptor antagonist drug ketamine

"Low-dose" pain setting use

- Prevention of central sensitization and reduction of developed central sensitization
- Attenuation of tolerance and hyperalgesia
- Indications:
  - Treatment of poorly opioid-responsive pain
    - Neuropathic pain
    - Ischemic pain
    - Pain in opioid-tolerant patients
  - Attenuation of tolerance in opioid-tolerant patients
  - Preventive analgesia in patients at increased risk of developing persistent pain
    - After nerve injury (surgical, traumatic, or other cause)
    - In patients with previous persistent pain (e.g., previous CRPS)

"Higher-dose" pain setting use

- Treatment of acute pain
  - Procedural pain (dressing changes, emergency department procedures)
  - Prehospital setting

Anesthetic doses

scenarios, and during transport and transfer (Jennings et al., 2011). It has also been used for pain relief during procedures including dressing changes (e.g., in burns, plastic surgery, or venous ulcers) and fracture reductions. In these situations, doses can be titrated in 10–20 mg steps (or less in the older patient). A benzodiazepine such as midazolam may be needed to reduce the incidence of psychotomimetic adverse effects. Alternatively, bolus doses of 10 mg ketamine with 0.5 mg midazolam and a 5-minute lockout via PCA pumps have proven to be very effective with high patient acceptance. The major advantage with the use of such higher doses is that airway protection and respiratory function are maintained.

Possible uses for ketamine in the acute pain setting are summarized in Table 6.3.

6.4.1.2 Adverse effects

One of the main problems with ketamine is that its use may be associated with psychotomimetic side effects. These are dose-dependent effects and include dreaming and nightmares (pleasant or unpleasant), hallucinations and dysphoria. Other adverse effects that have been described include nystagmus, blurred vision, and diplopia (Laskowski et al., 2011). These side effects may be reduced by the concurrent administration of benzodiazepines.

In the low doses required to reduce central sensitization, ketamine-related adverse effects are probably negligible, and at doses of less than 200 mg/day in the average adult patient, adverse effects occur infrequently. In the rare cases of such adverse events, doses should be reduced and/or low doses of a benzodiazepine (e.g., midazolam) may be added if dysphoria or hallucinations are of concern.

While ketamine in anesthetic doses causes hypertension and tachycardia, in the low doses used for analgesia clinically relevant cardiovascular effects have not been reported. Ketamine alone does not increase the risk of OIVI in patients also receiving opioids, but the risk will be increased if a benzodiazepine is also used.

Ketamine is a drug of abuse and is widely used as a recreational drug. It is therefore a scheduled (controlled) drug in many countries. Appropriate precautions against abuse or diversion therefore need to be taken, including the use of a lockable infusion pump for all infusions.

6.4.2 Dextromethorphan

Dextromethorphan is widely available as an over-the-counter cough suppressant. It is not in common clinical use as an analgesic adjuvant agent and results from clinical trials in the postoperative setting have been disappointing.

6.4.3 Magnesium

As NMDA receptors are "plugged" by magnesium ions, there has been interest in the role of magnesium in the treatment of pain. Although not commonly used in clinical practice, perioperative use of IV magnesium may lead to reduced opioid consumption and improved analgesia, but no reduction in opioid-related adverse effects (Albrecht et al., 2013; Murphy et al., 2013).

Key points for NMDA receptor antagonist drugs

1. NMDA receptors play an important role in the process of central sensitization, which contributes to hyperexcitability and increased pain experience after trauma and surgery.
2. The clinically most relevant NMDA-receptor antagonist is ketamine, and used in low doses perioperatively it reduces pain intensity, opioid consumption, and the incidence of some adverse effects of opioids.
3. Low-dose ketamine is in particular useful in settings of poorly opioid-responsive pain, for example, neuropathic pain and pain in opioid-tolerant patients.
4. Low-dose ketamine has also a preventive effect and reduces the risk of persistent pain development.
5. Higher doses of ketamine have analgesic effects and are useful in the setting of prehospital and emergency care as well as for procedural pain relief.

6.5 Alpha-2-adrenergic agonist drugs

Alpha-2-adrenoreceptors (or α_2-receptors) are located on peripheral sensory nerve terminals and in the spinal cord and brain stem. While the mechanisms and relevance of the peripheral and supraspinal effects continue to be debated, the spinal effects are well described. Peripherally and centrally, α_2-agonism has an inhibitory effect on pain transmission. Endogenous activation is by norepinephrine (noradrenaline), which explains some of the analgesic effect of norepinephrine reuptake inhibitors such as tramadol and antidepressants. These receptors in the spinal cord are thought to be primarily responsible for the analgesic effects of α_2-adrenergic agonist drugs such as clonidine and

dexmedetomidine (Blaudszun et al., 2012). Alpha-2-adrenergic agonists are usually used in combination with other analgesic drugs such as local anesthetics or opioids.

6.5.1 Clonidine

Clonidine is the α_2-agonist most commonly used in clinical practice. It is available in multiple forms and can be given by multiple routes of administration including oral, parenteral, transdermal, perineural, epidural, and intrathecal. Most of the drug, which has a half-life of 5–13 hours, is excreted unchanged by the kidney.

Introduced initially as a nasal decongestant and used as an antihypertensive for many years, clonidine is also an effective analgesic—less so on its own than in combination with other analgesics. In acute pain management, systemic administration of clonidine in combination with opioid analgesia can lead to improved pain relief and a reduction in opioid requirements and early nausea (but not vomiting) (Blaudszun et al., 2012).

Clonidine may be effective in the treatment of neuropathic pain. It has also been used in the management of withdrawal from opioids, benzodiazepines, and alcohol, where it can reduce the severity of withdrawal symptoms. Abrupt cessation of clonidine after long-term treatment can itself lead to a withdrawal syndrome, the signs and symptoms of which may include restlessness, headache, nausea, insomnia, rebound hypertension, and cardiac arrhythmias. The extent to which this may be a problem when the lower doses commonly used in the acute pain setting are given (often just 75–150 mg a day in divided doses given orally or by SC injection) are unknown.

The routine use of clonidine in acute pain management has been limited by side effects, particularly hypotension and sedation. Other possible side effects include bradycardia, dizziness, dry mouth, and decreased bowel motility.

6.5.2 Dexmedetomidine

Dexmedetomidine is a more specific α_2-agonist than clonidine with a shorter duration of effect. Despite these promising pharmacological properties, it is only indicated for sedation, particularly in intensive care units. Used in this setting it results in a significant decrease in opioid requirements (ANZCA and FPM, 2010).

There is limited evidence relating to the perioperative use of dexmedetomidine, but, like clonidine, it appears to be opioid sparing, improves pain relief, and reduces the risk of nausea (Blaudszun et al., 2012).

Key points for alpha-2 agonist drugs

1. The α_2 agonists clonidine and dexmedetomidine may improve postoperative analgesia and lead to reductions in opioid requirements and nausea. However, the data on dexmedetomidine are still limited and recommendations for clinical use as an analgesic cannot be made.
2. The adverse effects of these agents, including sedation and hypotension, limit their clinical usefulness.

6.6 Antidepressant drugs

Selected antidepressants are commonly used as first-line agents in the treatment of neuropathic pain and have been shown to be effective in a variety of neuropathic and centrally mediated pain states. The analgesic effect of these drugs is distinct from their effect on mood, as pain relief can be obtained in the absence of depression.

The effect on pain is based on the strengthening of inhibitory pathways of pain control and achieved by inhibition of reuptake of monoamines into nerve terminals in the spinal cord. Those antidepressants which inhibit both reuptake of norepinephrine and serotonin (5-hydroxy-tryptamine, 5HT)—tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs)—are much more effective in the treatment of neuropathic pain (O'Connor and Dworkin, 2009) than those which inhibit serotonin reuptake only—selective serotonin reuptake inhibitors (SSRIs) (ANZCA and FPM, 2010).

Other effects that may contribute to the pain relief resulting from the use of antidepressant drugs include blockade of NMDA and α-adrenergic receptors, and various ion channels.

6.6.1 Tricyclic antidepressant drugs

6.6.1.1 Clinical use

Tricyclic antidepressants (TCAs) have been shown to be effective in the treatment of a number of chronic neuropathic pain conditions (ANZCA and FPM, 2010). Amitriptyline is the most widely studied TCA, however, other TCAs including nortriptyline (the major metabolite of amitriptyline), doxepin, desipramine, and imipramine are also effective (Moulin et al., 2007).

Evidence for the use of TCAs in acute neuropathic pain is limited to acute zoster (ANZCA and FPM, 2010), where amitriptyline may have some preventive effect. However, they are commonly recommended as one of the first-line agents for the treatment of acute neuropathic pain in general (O'Connor and Dworkin, 2009). A role in the treatment of acute nociceptive pain has not been demonstrated.

Adverse effects of TCAs are common but dose dependent. As tolerance develops to both the anticholinergic and sedative effects of TCAs (see below), it is better to start with low, single daily doses which can be increased every few days as tolerated and needed. Recommended starting doses for amitriptyline are 10–25 mg (5–10 mg in older patients) and these may be increased every 3–7 days if required and no unacceptable adverse effects develop (Moulin et al., 2007). A satisfactory response usually occurs at levels between 25 and 150 mg. Benefits may be seen within a few days, but TCAs should be continued for 6–8 weeks at the maximum tolerated dose before a definitive decision is made about their effectiveness (O'Connor and Dworkin, 2009). As TCAs may cause drowsiness, especially in the early stages of treatment, doses are best given at night. This may also help to "normalize" sleep patterns, which are often disturbed in patients with pain.

Alternative TCAs include nortriptyline and desipramine, which cause fewer side effects.

6.6.1.2 Adverse effects

The side effects of TCAs result mainly from their anticholinergic actions and include dry mouth, increased heart rate, blurred vision, constipation, and urinary

retention (O'Connor and Dworkin, 2009). Narrow-angle glaucoma may be aggravated and postural (orthostatic) hypotension and dizziness may also occur due to an effect on α-adrenergic receptors. Impairment of cardiac conduction due to sodium channel effects leading to QT interval prolongation has been reported and TCAs may be contraindicated in patients with preexisting cardiac conduction abnormalities and cardiovascular disease. Sedation is reasonably common and primarily caused by histaminergic effects. Elderly patients may be more at risk of TCA-related adverse effects, in particular postural hypotension, dysphoria, agitation, confusion, and urinary retention as well as sedation. Other more serious side effects are rare, but include bone marrow depression, skin rashes, and hepatic dysfunction.

Combinations of TCAs, especially in higher doses, with SSRIs, SNRIs, and tramadol may increase the risk of serotonin syndrome.

6.6.2 Serotonin norepinephrine reuptake inhibitors

Serotonin norepinephrine reuptake inhibitors including venlafaxine, duloxetine, and milnacipran are also effective in the treatment of a variety of chronic neuropathic pain states and are commonly listed in evidence-based guidelines, together with TCAs and gabapentinoids, as suggested first-line treatments for chronic neuropathic pain (O'Connor and Dworkin, 2009). They are also commonly recommended as first-line agents for the treatment of acute neuropathic pain (O'Connor and Dworkin, 2009).

SNRIs have a better adverse event profile than TCAs, but should also be titrated slowly. As they are not sedating, they can be given in the morning. The starting daily doses are 30 mg for duloxetine (these can be increased to 60 or even 120 mg if needed) and 75 mg for venlafaxine (maximum suggested daily dose of 225 mg) (O'Connor and Dworkin, 2009). A common adverse effect with initiation is nausea, which often subsides after a few days.

Key points for antidepressant drugs

1. Tricyclic antidepressants (TCAs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are first-line treatments for chronic neuropathic pain and are more effective than selective serotonin reuptake inhibitors (SSRIs), which show only very limited efficacy.
2. It is reasonable to also use these medications in the treatment of acute neuropathic pain, given the lack of other more specific evidence.
3. As TCAs have a higher incidence of adverse effects, SNRIs may be preferable in certain patients; treatment should start with low doses with slow titration.

6.7 Anticonvulsant drugs

Anticonvulsant drugs have been shown to be effective in a variety of neuropathic (usually chronic) pain states. Of the anticonvulsants that are available, only the gabapentinoids (gabapentin and pregabalin) are effective for the management of neuropathic pain in general (Wiffen et al., 2013) and they are universally recommended for first-line treatment of neuropathic pain (O'Connor and Dworkin, 2009). Others have only limited indications (such as carbamazepine in patients

with trigeminal neuralgia), are only third- or fourth-line treatments, or are not effective at all. In particular, the effectiveness of sodium valproate (valproic acid), topiramate, lacosamide, lamotrigine, phenytoin, and levetiracetam in the treatment of neuropathic pain in general is not supported by current clinical data. Therefore, only gabapentinoids, carbamazepine, and clonazepam will be discussed in this chapter.

Anticonvulsants are often used on their own in the management of chronic neuropathic pain, but they also play a role in combination with other first-line treatments such as TCAs or SNRIs or second-line treatments such as opioids and tramadol (see Chapter 12).

6.7.1 Gabapentinoids

Gabapentin and pregabalin are the two anticonvulsants commonly recommended as first-line treatment for the management of neuropathic pain (O'Connor and Dworkin, 2009). This is in part due to their well-documented efficacy, but also because the incidence and severity of adverse effects is significantly less than with other anticonvulsants. These drugs have been used successfully in a wide variety of neuropathic pain conditions.

Pregabalin has also been recommended for use as first-line treatment of generalized anxiety disorder (Baldwin et al., 2013).

6.7.1.1 Mechanism of action

The effect of gabapentin and pregabalin is based on binding to the $\alpha_2\delta$-subunit of neuronal voltage-gated calcium channels (Thorpe and Offord, 2010). They therefore modulate but do not block these channels and thus reduce the influx of calcium ions in hyperexcitable neuronal states. As intracellular calcium concentrations control the release of EAAs such as glutamate, these drugs reduce synaptic glutamate concentration and subsequent NMDA receptor activation. This explains their efficacy in reducing central sensitization.

6.7.1.2 Clinical use

Gabapentin and pregabalin have the same mechanism of action, but differ in potency and pharmacokinetics (Bockbrader et al., 2010). Gabapentin, the older of the two substances, relies on an active transport mechanism for uptake through the gut wall and therefore shows saturation kinetics, that is, a nonlinear dose–response relationship. This and its low potency make titration over a wide dose range (300–3600 mg daily) necessary. The short half-life requires commonly eight-hourly dosing for it to be effective.

Pregabalin was subsequently developed specifically for the treatment of neuropathic pain. It has a linear dose–response relationship, longer half-life and higher oral bioavailability and potency. Commonly recommended daily doses are 150–600 mg (given in two divided doses), although starting doses of 25 mg are recommended in elderly and frail patients. Adverse effects and efficacy should govern titration to higher doses.

6.7.1.3 Treatment of neuropathic pain

The gabapentinoids have been shown to be effective in a number of chronic peripheral and central neuropathic pain states including postherpetic neuralgia,

diabetic polyneuropathy, mixed neuropathic pain, and spinal cord injury pain (ANZCA and FPM, 2010).

Their fast onset of effect and low rate of serious adverse events make them a reasonable first-line choice for the treatment of acute neuropathic pain—see Chapter 12.

6.7.1.4 Use in the perioperative setting

Gabapentinoids have been shown to reduce postoperative pain, opioid requirements, and some opioid-related adverse effects such as nausea and vomiting, but there is a higher incidence of sedation and visual disturbances (ANZCA and FPM, 2010; Zhang et al., 2011). This and their anxiolytic effects have resulted in their use as premedication before anesthesia in a number of hospitals. Optimal dosing and duration of treatment are still unclear; however, benefits have been achieved with a single preoperative dose. In addition, some patients are given gabapentinoids in a wide variety of dose regimens for the continuation of treatment after surgery.

While the potential preventive effect of perioperative gabapentinoids, shown in a number of RCTs, is still being debated—see Chapter 12—a Cochrane meta-analysis has concluded that neither gabapentin nor pregabalin reduce the incidence of persistent postoperative pain (Chaparro et al., 2013).

6.7.1.5 Adverse effects

Severe adverse effects are uncommon. However, minor adverse effects, including drowsiness and sedation, dizziness and disturbance of balance, can have significant consequences for quality of life and function. Therefore, dose increases in an outpatient setting need to be done slowly and carefully, so that tolerance to these adverse effects can develop. Other adverse effects are unexplained peripheral edema (primarily in the lower legs) and weight gain.

As gabapentin and pregabalin are excreted unchanged by the kidney, renal impairment requires dose adjustment. Pregabalin is cleared extensively by dialysis, gabapentin to a lesser extent (ANZCA and FPM, 2010) and patients commonly require a postdialysis "booster" dose.

6.7.2 Carbamazepine

The best documented indication for carbamazepine is trigeminal neuralgia, where it seems to have a specific effect (Hepner and Claxton, 2013). Its use in other neuropathic pain states is not well supported in the literature, and in view of the significant and potentially severe adverse effects it is not recommended as a first-line treatment in conditions other than trigeminal neuralgia (O'Connor and Dworkin, 2009).

It is often commenced at low doses (e.g., 50–100 mg orally 12-hourly) and increased after a few days in 200 mg steps if required and if there are no side effects, up to a maximum of 1200 mg/day.

As with many of the older anticonvulsants, adverse effects are very common and potentially severe. The most frequently reported side effects are blurred vision, drowsiness, ataxia, vertigo, and nausea as well as leukocytosis and thrombocytopenia (Hepner and Claxton, 2013). Enzyme induction requires care with other medications. Other potentially adverse effects include blood dyscrasias (agranulocytosis or aplastic anemia), hepatic dysfunction and skin reactions including the

life-threatening Steven–Johnson syndrome. In a number of countries oxcarbazepine is available as an alternative with a better adverse effect profile.

6.7.3 Clonazepam

Clonazepam is a benzodiazepine anticonvulsant. It is the only benzodiazepine that may play a role in the treatment of neuropathic pain. In doses between 0.5 and 2 mg at night it has good efficacy with adverse effects being limited to sedation. However, as a benzodiazepine, it carries the risk of development of tolerance, dependence and abuse, and of OIVI if given to a patient also requiring opioids.

Key points for anticonvulsant drugs

1. Gabapentinoids are effective anticonvulsants with minor adverse effects in the treatment of chronic neuropathic pain.
2. The efficacy and speed of onset of effect in chronic neuropathic pain suggests that they have a role in the treatment of acute neuropathic pain.
3. Perioperative gabapentinoids are a useful component of perioperative multimodal analgesia.
4. Anticonvulsants other than gabapentinoids play no role in acute pain management.

6.8 Membrane stabilizing drugs

Membrane stabilizing drugs are primarily used as antiarrhythmics or local anesthetics and are thought to work by blocking sodium channels, thereby stabilizing cell membranes and reducing ectopic discharges (see also Chapter 5). Such ectopic discharges are thought to be a major contributor to neuropathic pain states.

6.8.1 Lidocaine

6.8.1.1 Clinical use

6.8.1.1.1 Neuropathic pain

The systemic use of lidocaine (lignocaine) has been shown to be effective in the treatment of chronic neuropathic pain, especially for the management of pain due to peripheral nerve trauma and central pain including pain from spinal cord injury (ANZCA and FPM, 2010). The use of lidocaine for the treatment of acute neuropathic pain can only be extrapolated from this information. As it has a fast onset of action, it may be particularly useful in this setting (see Chapter 12). However, in a comparative trial, ketamine had a higher responder rate and better response than IV lidocaine (Kvarnstrom et al., 2003).

A single dose of IV lidocaine (given as a 1–2 mg/kg as a bolus dose over a few minutes) can be given to treat acute neuropathic pain in an emergency situation or to test the effectiveness of this drug. Analgesia from a single dose may exceed the known pharmacological duration of action of the drug by days or weeks. When pain returns, the single dose may be followed by an IV or subcutaneous infusion. Suppression of ectopic impulses generated by damaged

nerves appears to occur at concentrations of the local anesthetic that are lower than those normally required to block nerve impulses. The plasma concentrations reached are therefore low and there is disagreement on the question of whether continuous ECG monitoring is required.

6.8.1.1.2 As a component of multimodal analgesia

Perioperative infusion of lidocaine has been shown to improve postoperative analgesia, reduce opioid consumption and nausea and vomiting, and lead to faster return of bowel function and a shorter duration of hospital stay (Vigneault et al., 2011). These benefits were seen mainly after abdominal surgery.

There are also data supporting a preventive effect of lidocaine in this setting, with the beneficial effect of lidocaine significantly outlasting the expected duration of the drug (Barreveld et al., 2013).

6.8.1.2 Adverse effects

Adverse effects may include dizziness, perioral numbness and, less frequently, metallic taste, tremor, dry mouth, insomnia, allergic reactions, and tachycardia. Serious adverse events, such as local anesthetic systemic toxicity including cardiac arrhythmias and hemodynamic instability are rare but may occur with larger doses.

6.8.2 Mexiletine

Mexiletine is an antiarrhythmic drug that is structurally related to lidocaine, but it can be given orally. While it was thought to be useful as an oral analogue of lidocaine, its efficacy in neuropathic pain is very poor and not predicted by the response to lidocaine. However, it can be very useful in the treatment of neuropathic pain caused by erythromelagia, a rare genetic disorder of $NaV_{1.7}$ sodium channels, where attacks of acute neuropathic pain occur.

Adverse effects include nausea, sedation, and tremor. Care should be taken in patients with ischemic heart disease or cardiac arrhythmias as sudden cardiac death has been described in susceptible patients. The use of medication might require monitoring of ECG (QT interval measurement) and plasma concentrations.

Key points for membrane stabilizing drugs

1. Intravenous lidocaine plays a limited role in the treatment of acute neuropathic pain states.
2. It is an effective component of multimodal analgesia with beneficial effects on pain relief, opioid consumption, adverse effects, and other outcomes.

6.9 Inhalational agents

Inhalational agents were initially developed for use in anesthesia. However, lower concentrations of two inhalational agents, nitrous oxide and methoxyflurane, are widely used to provide prehospital and procedural analgesia in ambulance services, emergency departments, and on hospital wards including burns units.

6.9.1 Nitrous oxide

Nitrous oxide (N_2O) is one of the oldest inhalational anesthetics available. It is not a very potent anesthetic agent, but has analgesic properties in subanesthetic concentrations and has therefore become a widely used inhalational analgesic.

6.9.1.1 Clinical efficacy and use

Owing to its physicochemical properties, nitrous oxide has a rapid onset and short duration of action—some effect will be seen after four or five deep breaths. Offset of effect is also rapid so analgesia can only be maintained by repeated inhalations. It is therefore suitable for the provision of analgesia during labor and during painful procedures such as dental surgery, endoscopy, dressing changes, biopsies and venous cannulation, as well as in the prehospital setting (ANZCA and FPM, 2010). It will often be used in combination with opioid or other analgesic therapies. In some institutions, concerns about environmental nitrous oxide levels have limited the use of nitrous oxide in general wards.

Nitrous oxide is commonly used in some countries as a combination of 50% nitrous oxide and 50% oxygen in premixed cylinders (Entonox®). In other countries, the use of a mixing valve permits a variety of nitrous oxide/oxygen combinations to be given.

A one-way demand valve allows delivery of the gas when the patient inspires, providing there is an airtight fit between face and mask or mouthpiece. The technique is inherently safe as it is self-administered, and if the patient becomes too drowsy the mask will fall away from the patient's face. As it causes minimal respiratory depression, it can be used without the presence of medically trained staff, as long as unconsciousness is avoided.

6.9.1.2 Adverse effects

6.9.1.2.1 Air-containing spaces

Gases equilibrate across permeable membranes so that the concentrations on both sides of the membrane become equal: nitrous oxide equilibrates rapidly and nitrogen much more slowly. If a patient breathes a mixture containing oxygen and nitrous oxide, the concentration of nitrous oxide in any air-containing space will rise rapidly while the concentration of nitrogen will fall only slowly. If the space cannot expand, there can be a marked increase in pressure in that space. Nitrous oxide is therefore contraindicated in patients with a pneumothorax, pneumocephalus, bowel obstruction or obstruction of the middle ear or sinus cavities, or in patients who have had recent vitreoretinal surgery with use of gas, or a recent gas embolism (e.g., divers) (ANZCA and FPM, 2010).

6.9.1.2.2 Toxicity

Nitrous oxide oxidizes vitamin B_{12} and thereby inactivates the enzyme methionine synthetase, which is essential for the synthesis of DNA and RNA (Sanders et al., 2008). This may lead to bone marrow depression (resulting in a megaloblastic anemia) and a reduction in the synthesis of myelin (resulting in a rapidly progressive myeloneuropathy). The clinical features resemble those of vitamin B_{12} deficiency. However, vitamin B_{12} levels may be normal, as the problem is due to a reduction in *active* vitamin B_{12} levels and not necessarily total body levels.

Bone marrow toxicity is progressive, but also reversible and almost completely preventable by administration of folinic acid (ANZCA and FPM, 2010).

Neurotoxicity resulting from nitrous oxide use is rare, but it can develop rapidly and may be irreversible. The clinical features are the same as those seen with a vitamin B_{12} deficiency—subacute combined degeneration of the spinal cord leading to numbness, paresthesia, ataxia, and spasticity. The risk of this complication is significantly increased in patients with a preexisting vitamin B_{12} deficiency (e.g., those who are vegetarians or elderly), and the deficiency may be subclinical, that is, detectable only by measuring vitamin B_{12} blood levels (Sanders et al., 2008).

It was commonly thought that these complications might only follow prolonged or repeated administration of nitrous oxide. However, severe irreversible neurotoxicity has been reported after single, short-term exposure in susceptible patients.

An evidence-based approach to the prevention or treatment of complications due to nitrous oxide-related inactivation of vitamin B_{12} cannot be provided, as most information is derived from case reports or laboratory studies. Only suggestions extrapolated from such information can be made (ANZCA and FPM, 2010). It may be reasonable to:

- Avoid the use of nitrous oxide in patients with a known or suspected vitamin B_{12} deficiency, or in the early stages of pregnancy.
- Limit use to the shortest possible time (with supervised access to the gas supply as abuse has been reported).
- Prophylactically administer methionine, vitamin B_{12}, and folinic or folic acid if nitrous oxide exposure is likely to be repeated.
- Monitor for signs and symptoms of neuropathy.

6.9.2 Methoxyflurane

Methoxyflurane was initially developed as an inhalational anesthetic, but then withdrawn due to concerns about nephrotoxicity and hepatotoxicity. In view of its analgesic properties it is now used, mainly in Australia and New Zealand, to provide short-term analgesia for painful procedures and in the prehospital setting (Grindlay and Babl, 2009). Administration is via a dedicated single-use inhaler dispensing 0.2–0.4% methoxyflurane.

The limited data on efficacy suggest that methoxyflurane administered as a single dose as described above provides effective analgesia resulting in high patient satisfaction with no evidence of toxicity (Grindlay and Babl, 2009).

There is no good evidence regarding the safety of repeated doses, for example, for analgesia during daily dressing changes.

Key points for inhalational agents

1. Nitrous oxide and methoxyflurane are effective analgesics for short-term use in painful procedures and in the prehospital setting. Nitrous oxide is also used to provide analgesia during labor.
2. Nitrous oxide is contraindicated in patients with air-containing spaces (e.g., pneumothorax, pneumocephalus, bowel obstruction) or a recent gas embolism.
3. Nitrous oxide can cause rare but serious complications related to myeloneuropathy and bone marrow suppression. These complications are increased in patients with vitamin B_{12} deficiency and may be reduced by limiting time of exposure to the nitrous oxide and prophylactic administration of methionine, vitamin B_{12}, and folinic or folic acid.

6.10 Calcitonin

Calcitonin is a peptide hormone, which regulates calcium homeostasis, but also has analgesic properties in certain settings. These are most likely mediated by modulation of serotonergic mechanisms; therefore, it is partially antagonized by 5-HT_3-antagonistic antiemetics (ANZCA and FPM, 2010). It may also act as a neurotransmitter in its own right in the CNS.

Salmon calcitonin, which has a higher potency than human calcitonin, is used clinically. Initial indications were for the treatment of hypercalcemia (e.g., in patients with a malignancy and bone metastases) and to increase the calcium content of bones in patients with Paget's disease and osteoporosis. However, when used for these reasons, an analgesic effect was also observed.

It has proven efficacy in the treatment of acute but not chronic phantom limb pain (ANZCA and FPM, 2010), and in acute but not chronic pain due to vertebral body fractures (Knopp-Sihota et al., 2012).

While calcitonin is available in some countries for intranasal administration, it is most commonly given by IV infusion or, more conveniently, by SC injection. Most reports use daily doses in the range of 100–200 I.U. of salmon calcitonin for a treatment series of a number of days.

Nausea and vomiting are the most common adverse effects and premedication with an antiemetic (other than ondansetron and other 5-HT_3 inhibitors but preferably metoclopramide) can prevent this to a large extent. Flushing and drowsiness are other side effects, and all support the hypothesis of a serotonergic effect. Allergic reactions and hypocalcemia occur rarely, if ever.

Key point for calcitonin

1. Salmon calcitonin is an effective treatment for acute pain caused by osteoporotic vertebral crush fractures and for acute phantom limb pain.

6.11 Glucocorticoids

Perioperative glucocorticoids, primarily a single dose of dexamethasone, have a well-documented effect on reducing nausea and vomiting and are widely used for this indication.

Subsequently there were observations that this use may result in additional benefits in terms of improved analgesia, reduced analgesic requirements and even reduced postoperative fatigue (ANZCA and FPM, 2010). A meta-analysis concluded that administration of dexamethasone leads to a small but statistically significant reduction in postoperative pain and opioid requirements (Waldron et al., 2013). There was no increase in wound infections or delayed wound healing, but blood glucose levels were increased.

Key point for glucocorticoids

1. Perioperative dexamethasone not only reduces the risk of postoperative nausea and vomiting, but may lead to slightly lower pain scores and opioid consumption.

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CHAPTER 7

Systemic routes of opioid administration

Opioids can be administered via a number of systemic routes. The choice of route will depend on multiple factors including site and severity of the pain; patient factors such as age, cognitive ability, and willingness to accept a technique; and organizational factors including cost, staff education, and the level of monitoring and supervision available.

The use of more sophisticated methods of opioid administration, such as patient-controlled and epidural analgesia, has improved the management of acute pain for many patients. However, the majority of patients in most institutions will still receive opioids using one of the more traditional methods of systemic administration—generally intermittent doses given orally, or by subcutaneous (SC) or intramuscular (IM) injection. Surveys continue to show that these methods of opioid delivery frequently result in inadequate analgesia (Dolin et al., 2002; Chang et al., 2010; Murnion et al., 2010). To a large extent, this remains a consequence of deficiencies in their application and a lack of flexible dose regimens, rather than limitations associated with the route of administration.

Frequently, these more traditional opioid regimens make inadequate allowances for the enormous interpatient variation in opioid requirements (eightfold to tenfold) that result from the unpredictable differences in pharmacodynamic factors (how the individual responds to the drug) and pharmacokinetic factors (how the individual patient handles the drug—that is, how it is absorbed, distributed, metabolized, and excreted). It is also known that the same dose of opioid given to different patients can result in a fourfold to fivefold difference in peak blood concentration reached, and that the same dose of opioid when repeated may result in significant within-patient differences in peak blood concentration (ANZCA and FPM, 2010).

Added to this has been the still-common lack of appropriate education of medical and nursing staff, unfounded fears about the risks of side effects and addiction, and a lack of assessment of pain and the patient's response to treatment—both analgesic effect and side effects. It is therefore hardly surprising that traditional regimens for pain relief may be less than successful.

Regardless of the route chosen, the key to making opioid analgesia more effective is to individualize treatment regimens for each patient. As outlined in Chapter 4 (Section 4.4), blood levels of an opioid need to reach the minimum effective analgesic concentration (MEAC), which varies widely between patients, before any relief of pain is perceived. The only way to achieve good acute pain relief is therefore to titrate the dose of opioid for each patient.

Regardless of the route of administration, titration of opioids requires the prescription of an appropriate initial dose (which should be age-based in opioid-naive adult patients) and dose interval, followed by monitoring of the effectiveness of analgesia and signs indicating an excessive dose, so that subsequent alterations to doses and frequency of administration can be made. Table 7.1

Table 7.1 Basic requirements for opioid titration

For each route of opioid administration, safe and effective titration requires:

- Initial prescription of the appropriate age-related dose range (for opioid-naive patients)
- Use of a dose interval (the interval where additional doses should not be given) appropriate to the route of administration
- Regular monitoring of pain, sedation, and FAS
- Monitoring for the presence of other adverse effects
- Alteration of subsequent doses according to patient response (pain relief, excessive sedation, and other adverse effects)

Titration should aim for

- Patient comfort (not necessarily pain free) and good functional activity
- Sedation score <2
- Respiratory rate <8 breaths/min (in most cases)

summarizes the requirements for titration; details of assessment of pain and functional activity scores (FAS) and sedation scores are in Chapter 3.

In this chapter, the doses of opioids listed are those that have been suggested for use in opioid-naive patients. Opioid requirements in opioid-tolerant patients may be higher and even more variable—see Chapter 14.

The aim of a dose interval, the interval prescribed between intermittent doses of an opioid, is to allow for the full effect of the previous dose to be seen before another is given. It is determined mainly by the speed of onset of effect of the drug. While the time taken for an opioid to reach a maximum blood concentration depends primarily on the route of administration, the time taken to then achieve maximum effect depends on the rate at which the drug crosses to the central nervous system (CNS) and opioid receptors. Factors that determine the rate of transfer to the CNS include the lipid solubility of the drug, the degree of ionization of the drug molecule, the proportion of the drug that is unbound (i.e., not bound to protein), and the concentration gradient across the blood–brain barrier. The effect of lipid solubility and degree of ionization on the times to onset of effect and peak effect is most noticeable, and of most clinical relevance when bolus doses of the different intravenous (IV) opioids are given (see Section 7.3.1).

The dose interval is also used inappropriately by some to give an indication of the expected duration of action of the drug and is frequently based on its elimination half-life. However, choosing dosing intervals based on this parameter will not allow effective titration as the half-life of a drug is simply the time taken for the blood concentration to change by 50%. It gives only an indication of the rate at which the body metabolizes and excretes the drug. As well as elimination half-life, the duration of action of any given dose of opioid will depend on a number of other factors including amount given, route of administration, and the pharmacokinetic characteristics of the drug such as absorption, rate of distribution to different tissues (including opioid receptors), rate of dissociation from receptors, and lipid solubility.

The implementation of ongoing education programs for medical and nursing staff, and the use of simple guidelines that include treatment and monitoring algorithms, can lead to major improvements in the titration of opioids regardless of route of administration.

7.1 Oral

In the absence of any contraindications, the oral route is the route of choice for opioid administration, unless a patient has severe acute pain. It is simple, effective, and well tolerated by most patients (ANZCA and FPM, 2010).

Limitations to the use of the oral route include delayed gastric emptying, which is common after surgery and injury, and nausea and vomiting. If emptying is delayed, opioids will not pass through to the small intestine where they are absorbed. If several doses are given before normal gastric motility is reestablished, accumulated doses may enter the small intestine at the same time when normal emptying resumes ("dumping" effect). This could result in the patient receiving an unexpectedly large dose with an increased risk of adverse effects.

A patient with delayed gastric emptying and not permitted to take anything orally should be distinguished from a patient who is fasting because an "empty stomach" is required (e.g., before elective surgery or other procedure). In the latter case, gastric emptying is not delayed and oral opioids can usually be given as normal, as can other oral medications.

Larger doses are usually required when opioids are given orally compared with doses required for parenteral administration. Their oral bioavailability depends on the first-pass effect where a proportion of an orally administered drug is metabolized by the liver and/or bowel wall after absorption from the gastrointestinal tract. This affects the amount of unchanged drug that reaches the systemic circulation. These differences are reflected in the equianalgesic doses of the oral and parenteral forms of each opioid (see Table 4.2).

7.1.1 Immediate-release and slow-release formulations

The rate of absorption of orally administered opioids will depend primarily on the formulation of the drug: immediate-release (IR) tablet, capsule, or liquid, or slow-release (SR) tablet, capsule, or suspension.

Immediate-release oral opioid preparations such as those of oxycodone, morphine, and hydromorphone are preferred for the initial and early management of acute pain. In most cases their peak effect will be obtained within about 45–60 minutes (ANZCA and FPM, 2010). As the patient's opioid requirements will not be known at the time the oral IR opioid is commenced, and as the dose required may vary according to the pain experienced and will usually decrease at least a little each day, IR opioids are commonly prescribed on a PRN (*pro re nata* meaning "as the circumstances require" or "according to need") basis.

Slow-release preparations (also referred to as controlled-, sustained-, or extended-release) of opioids such as morphine, oxycodone, and hydromorphone as well as tramadol are commonly used in the treatment of chronic and cancer pain and usually only need to be given once, twice, or sometimes three times a day at fixed time intervals. They should not be ordered on a PRN basis. The slower onset (it may take 4 hours or more to reach peak effect) (ANZCA and FPM, 2010) and longer duration of action of SR formulations make short-term adjustments and rapid titration of the drug impossible. They are therefore unsuitable for the treatment of acute pain, at least in the early stages. As acute pain improves and opioid requirements decrease, dose tapering will be required, complicating the situation further. However, they may become useful in situations of sustained opioid requirements where they may reduce excessive on-demand usage.

Although methadone has a relatively quick onset of action, its long and very variable half-life makes it more difficult to titrate rapidly without risking accumulation of the drug. It is therefore unsuitable for the routine management of acute pain. Specialist advice should be sought before commencing a patient on methadone.

If acute pain patients with sustained opioid requirements are prescribed SR opioids, they should also be ordered an IR opioid for "breakthrough" analgesia. The amount of IR opioid required can be used as a guide to adjusting the dose of the SR drug, which is usually given in doses that are 50% or less of their total daily opioid requirements.

7.1.2 Titration of oral immediate-release opioids

7.1.2.1 Dose range

Initial doses of an oral IR opioid should be based on the age of the patient (see the doses section in Figure 7.1) as well as severity of the pain. If the patient has been receiving parenteral opioids, particularly via patient-controlled analgesia (PCA), the parenteral opioid requirement can be used as a guide to the dose of oral opioid that is likely to be needed. If a dose—especially one based on prior parenteral requirements—appears to have no effect, a delay in gastric emptying should be suspected and consideration given to returning to parenteral opioids.

If a combination formulation is used, where an IR opioid is combined with paracetamol (acetaminophen) or an NSAID, limits placed on the doses of these nonopioids will limit the total amount of opioid that can be given. It is therefore often more appropriate to provide background analgesia with regular oral paracetamol and/or NSAID and add PRN doses of the IR opioid than to use the combination preparations.

Recommended total daily doses of oral IR tramadol are usually limited to 400 mg, while 600 mg is the recommended daily limit for parenteral tramadol (lower doses are recommended for older patients). This advice conflicts with what is known about the oral bioavailability of the drug and, in practice, daily oral doses of 600 mg or more are usually well-tolerated—in nonelderly patients and patients with normal renal function at least.

7.1.2.2 Dose interval

As noted earlier, oral IR opioids are commonly ordered on a PRN basis, although sometimes fixed-interval dose regimens are used.

Prescriptions of opioids PRN have been the mainstay of acute pain management (albeit often inadequate pain management) for years. There are both drawbacks and advantages to the PRN system. It should mean that opioid is given when the patient needs it. However, there are frequently long delays between the return of discomfort and the actual administration of another dose. For a variety of reasons a patient may be reluctant to request another dose, at least until pain is severe. In addition, there are the inevitable delays that follow such a request in many hospitals, as opioids are kept in locked cupboards and extra nurses may be required to check the drug and dose before it is given. Following administration there is yet another delay while the drug takes effect. Unless the patient is offered pain relief frequently, which should ideally be the case, or asks for and is given another dose as soon as the pain starts to become uncomfortable, the PRN system will fail.

The main advantage of a PRN regimen is that, titrated properly, it can provide the flexibility needed to cover the changes in pain intensity that occur within

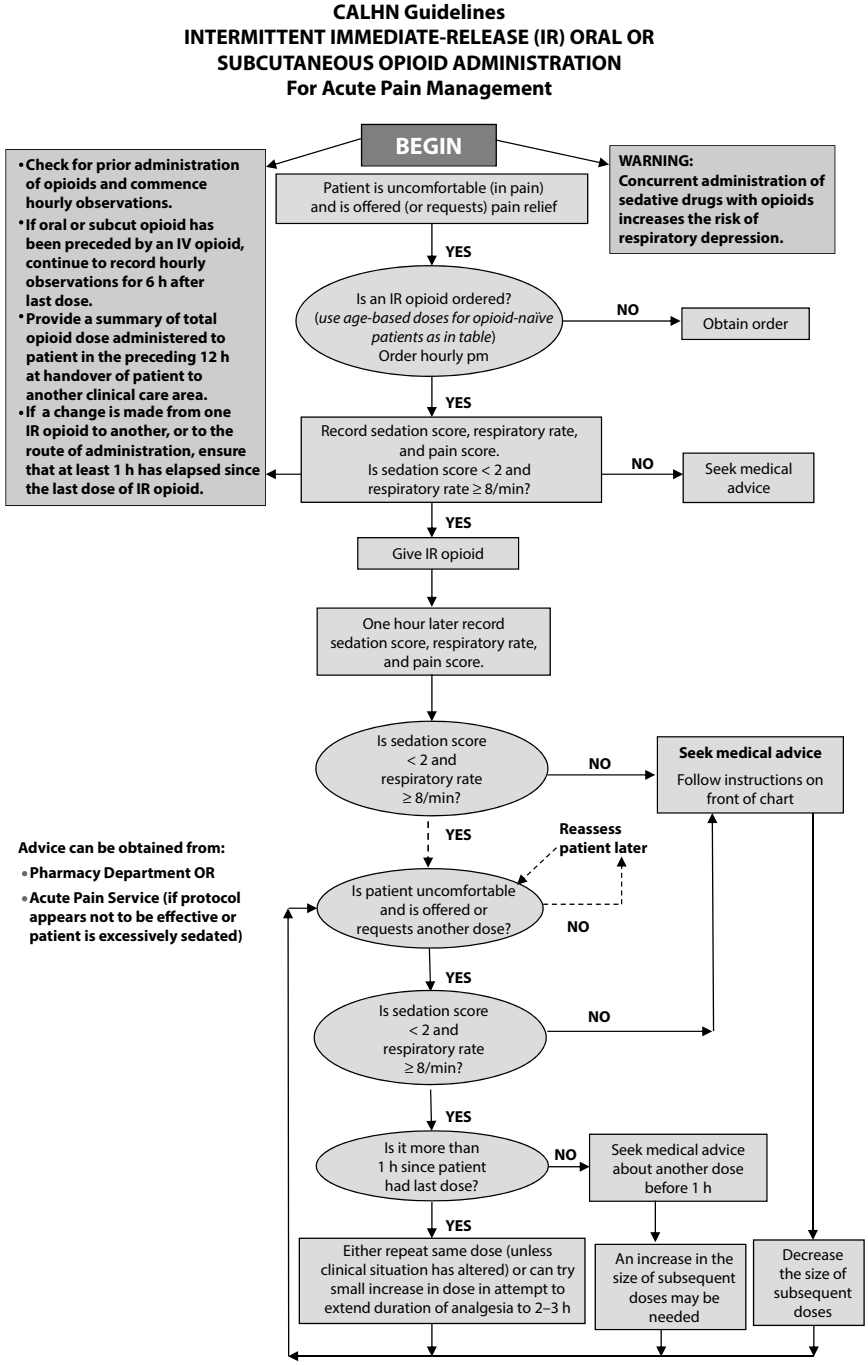


Figure 7.1 An example of an intermittent PRN immediate-release oral and SC/IM opioid administration guideline. (Reproduced with permission of the Royal Adelaide Hospital and Central Adelaide Local Health Network.)

AGE-BASED IMMEDIATE-RELEASE OPIOID DOSES FOR ACUTE PAIN MANAGEMENT

The doses below are suggested initial doses only for opioid-naïve inpatients with moderate to severe acute pain.

- Lower opioid doses are more appropriate in patients with less pain and/or if treatment is not initial.
- Opioid-tolerant patients (patients taking opioids long-term) may require higher doses.
- Consideration should be given to dosage amendment in differing clinical situations.

Age (yrs)	Subcut MORPHINE or OXYCODONE (mg) *	Subcut FENTANYL (microg) *	Oral OXYCODONE (mg) *
< 15	seek advice		
15 – 39	7.5 – 12.5	100 – 200	10 – 25
40 – 59	5 – 10	75 – 150	10 – 20
60 – 69	2.5 – 7.5	40 – 100	5 – 15
70 – 85	2.5 – 5	40 – 75	5 – 10
> 85	2 – 3	30 – 50	2.5 – 5

Recommended dose interval: 1 hourly prn ↓ dose if pain not severe*

- Order recommended dose of immediate-release opioid hourly prn (Note: this is for inpatients only; suggest 4 hourly prn otherwise).
- Suggest start in middle of dose range.
- Doses may be given hourly if needed but frequency of subsequent doses will depend on response to previous dose; can increase dose given in attempt to extend duration of analgesia to 2-3 h or more as long as sedation score is less than 2.
- Upper limit of dose range can be increased if analgesia is inadequate, sedation score is less than 2 and respiratory rate greater than 7 breaths/min (first check that doses are correct/ have been given).
- Oxycodone and fentanyl can be given to patients with renal impairment.
- Note that the equianalgesic dose (same analgesic efficacy) for subcut oxycodone is equal to that of subcut morphine but is half the oral oxycodone dose. That is 10 mg subcut oxycodone = 10 mg subcut morphine = 20 mg oral oxycodone.
- If a decision is made to give subcut fentanyl note that 10 mg morphine = 150 microg fentanyl. Note also that 150 microg fentanyl = 3 mL, which is a large volume for subcut injection, and can be very painful unless given slowly.
- Some patients may require a prescription for oral oxycodone at discharge.
  - if patient was already taking long-term opioids on admission or has a history of substance abuse this may not be appropriate – seek advice.

IMPORTANT NOTES

- **Slow-release (SR) opioids such as OxyContin, MS Contin and Kapanol, as well as fentanyl or buprenorphine patches, are not suitable or safe for routine management of acute pain.**

MONITORING OF THERAPY IS ESSENTIAL IF OPIOIDS ARE TO BE TITRATED SAFELY FOR EACH PATIENT

Figure 7.1 (*continued*) An example of an intermittent PRN immediate-release oral and SC/IM opioid administration guideline. (Reproduced with permission of the Royal Adelaide Hospital and Central Adelaide Local Health Network.)

each patient with acute pain. As noted earlier, a dose interval really only has to ensure that the dose of opioid has had its maximum effect before another is given and, in most patients, this would occur within 60 minutes following oral administration of an IR opioid. Therefore, if a patient is in pain, there is no need to wait 4–6 hours before giving the next dose. In hospitals where staffing and monitoring permit, IR opioids are sometimes ordered 1-hourly PRN, so that the total amount

the patient needs can be rapidly adjusted. In other institutions longer dose intervals may be safer, albeit possibly less effective. Once the patient leaves hospital however, longer dose intervals may be considered more appropriate.

Knowledge of a patient's prior opioid requirements (e.g., if a patient is switching from PCA to oral analgesia) makes calculation of oral opioid doses much easier as it gives a good guide to the patient's likely 24-hour oral requirement. Ideally, the patient should be allowed to choose the dose of opioid from the range ordered based on the effect of previous doses. This range needs to take into account the fact that acute pain intensity will often decrease rapidly over the first few days in most patients.

Immediate-release tramadol can be given on a PRN or fixed-interval basis (e.g., strictly every 4 hours) because excessive sedation is unlikely, and therefore both titration and fixed-interval dosing are safer compared with opioids. SR tramadol should always be given at fixed time intervals.

7.1.2.3 Monitoring

As outlined in Chapter 3, monitoring of pain scores, FAS scores, sedation scores (used as the better early clinical indicator of opioid-induced ventilatory impairment [OIVI]), and respiratory rate will give an indication of adequacy of analgesia and whether the dose is excessive. These should be monitored on a regular basis and include assessment at the time an IR opioid is given and again about an hour later, that is, at around the time the peak effect of the drug is likely to occur. Subsequent doses can be adjusted according to these assessments.

As with all opioids the aim is to keep the patient comfortable and with good functional activity while their sedation score is less than 2 (see Table 7.1).

7.1.2.4 Selection of subsequent doses

Although the dose range ordered and the initial dose given should be based on the age of the patient, subsequent doses need to be titrated to suit each patient. All too often subsequent doses are chosen because "that was the dose given before" and not on the basis of patient assessment.

An example guideline for titration of oral IR oxycodone, including age-based doses (for opioid-naive patients) and monitoring requirements, is outlined in Figure 7.1. An example of a "standard order" form for PRN IR oral opioid analgesia (similar to those used for PCA and epidural analgesia) is in Appendix 7.1. This form incorporates the opioid prescription, orders for the recognition and management of adverse effects, other general orders (e.g., caution regarding coadministration of sedatives), and monitoring requirements and documentation.

Where possible, patients should be allowed some input into the size and timing of subsequent doses. They can be instructed to ask for a larger subsequent dose if analgesia was inadequate or a smaller dose if they felt sleepy or nauseated. "Patient control" should not be confined to PCA pump systems.

7.2 Subcutaneous and intramuscular

Although morphine was first given by SC injection in the early 1850s, the IM route became the more common route of administration, possibly in the mistaken belief that absorption was slower from subcutaneous sites. The SC route is still

often used for opioids given to patients with cancer pain, but has become increasingly popular in the management of acute pain.

A plastic cannula or narrow-gauge "butterfly" needle is inserted into subcutaneous tissue, for ease of access often just below the clavicle, and covered with a transparent dressing. To ensure that the needle is placed correctly and not too superficially, a generous fold of skin and subcutaneous tissue should be held in one hand and the cannula or needle inserted at the base of this fold (at an angle of 30–45° to the patient) with the other. Injections can be administered through a cap or one-way valve on the indwelling cannula. Advantages of using this route over the IM route include improved patient comfort and patient preference and a reduced risk of needle stick injury as once the indwelling needle or cannula is in place, all other needles can be avoided.

If the injection through the indwelling needle is painful it may be that the rate of injection is too rapid (each dose needs to be given over 1–2 minutes) or that the needle has been inserted too superficially. The insertion site should be changed if pain on injection persists or if any redness or swelling develops at the site. Normally, the indwelling needle will only need to be replaced every 3–4 days, although some institutions may require all indwelling cannulae to be changed at more frequent intervals.

Subcutaneous opioids should be given in solutions concentrated enough to avoid the need for large volumes as this can be another source of tissue irritation and pain.

The rates of uptake of the commonly used opioids into the circulation after injection into subcutaneous tissue are similar to the uptake following an IM injection (Gupta et al., 2011). The time to peak blood concentrations following SC administration of morphine (ANZCA and FPM, 2010), oxycodone (Krishnamurthy et al., 2012), and fentanyl (Capper et al., 2010) have all been shown to be around 15–20 minutes. Note that this is not the same as the time-to-peak effect.

Traditionally, IM opioids have been ordered 4-hourly PRN. A reluctance to give them more frequently has played a major role in the lack of effectiveness of IM regimens. Even if pain returns before the end of this period (which is not uncommon), patients are often made to wait until the 4 hours has elapsed before they are "allowed" another injection.

Figure 7.2 is a hypothetical representation of what could happen to the blood concentrations of a typical opioid with a half-life of about 3 hours (e.g., morphine) if a fixed IM dose is repeated at 4-hourly intervals.

After absorption from the injection site the first dose may result in a blood level that only just enters the "analgesic corridor" (range of therapeutic blood concentrations) for that patient, leading to very little if any pain relief. The second two doses may result in higher blood levels and better pain relief for longer periods. Fourth and subsequent doses may increase blood concentrations to a level that, as well as giving pain relief, start to produce side effects.

Two things are obvious from Figure 7.2:

- The amount of opioid required to make a patient comfortable in the first instance may not be the same as the amount required to maintain comfort.
- While peaks and troughs in the blood concentrations of opioid are an inevitable consequence of this type of regimen, the aim of treatment should be to reduce the extent of this variation so that the peaks and troughs occur predominantly within the "analgesic corridor." For example, giving a little less opioid more often can result in the same overall daily dose, but less variability in blood concentrations between doses.

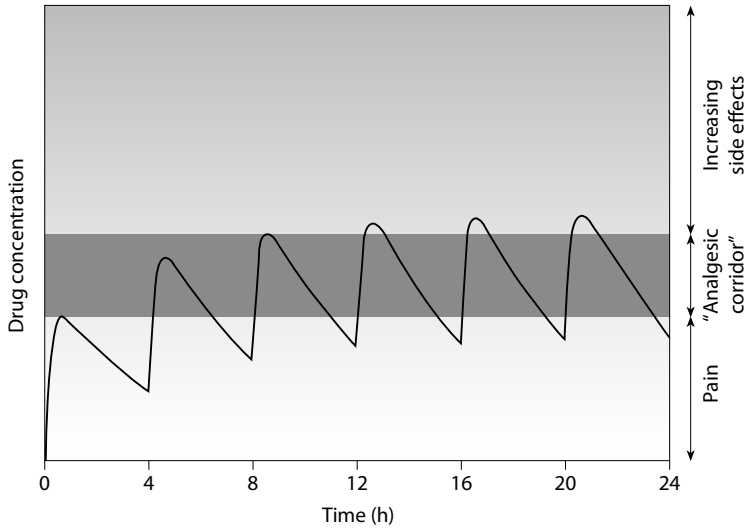


Figure 7.2 Intermittent intramuscular opioid analgesia.

7.2.1 Titration of intermittent SC or IM opioids

The principles of titration of SC and IM opioids are very similar to those for oral opioids. An example guideline for titration of SC/IM morphine, oxycodone, and fentanyl, is outlined in Figure 7.1. An example of a "standard order" form used for both IR oral and SC opioids is in Appendix 7.1.

7.2.1.1 Dose range

As for any route, an age-related range of doses should be prescribed initially. Suggestions for initial dose ranges (based on Figure 4.1) are listed in the doses section of Figure 7.1. Note that these values were obtained from opioid-naive patients using morphine by PCA after major surgery. Dose requirements may be lower if pain is less severe or higher for patients with a history of prior opioid use. Variations may also occur with different patient populations.

Staff are often tempted to start at the lower limit of any prescribed range, but these ranges should allow them the ability to decrease as well as increase subsequent doses as needed. Unless there is a contraindication (e.g., the patient has severe pain or is a little sleepy) and provided the range ordered is appropriate, it is reasonable to start in the middle of the dose range in most cases.

7.2.1.2 Dose interval

As with oral opioid regimens, SC and IM opioids can be ordered as PRN or fixed-interval doses, and the same comments made above relating to oral opioid analgesia apply. A PRN regimen is commonly used in the acute pain setting because of the rapidly changing nature of acute pain, but analgesic efficacy will be very dependent on the patient getting the appropriate dose truly when needed. As most of the effect of an SC or IM opioid dose will be seen well within 45–60 minutes,

dose intervals of just 1 hour are possible, providing there is proper ongoing monitoring and assessment of the patient. A delay in absorption may be seen where there is poor perfusion, such as in hypovolemic or hypothermic states. This delay may lead to late onset of analgesia and late absorption of the drug when perfusion is restored. In such situations, IV administration is preferred.

7.2.1.3 Monitoring and selection of subsequent doses

Pain scores, FAS, sedation scores, and respiratory rate should be monitored on a regular basis. For intermittent SC and IM regimens as with oral opioids, these assessments should be done at the time injection is given and again about an hour later.

An example protocol for titration of intermittent oral, IM, or SC opioids, including age-based doses and monitoring requirements is outlined in Figure 7.1. Similar algorithms have been shown to lead to significant improvements in pain relief. An example of a "standard order" form for intermittent SC/IM opioids is in Appendix 7.1.

Again, where possible, patient input into the size and timing of subsequent doses based on the effectiveness of the prior dose and any adverse effects may be appropriate.

7.3 Intravenous

Many books and guidelines still suggest that IV opioids can be given in doses similar to those administered by IM injection and at similar dose intervals. Figure 7.3 is a hypothetical representation of what might happen to opioid blood levels if the *same dose* of opioid administered by IM injection in Figure 7.2 were given by IV injection every 4 hours. This regimen would result in large variations in blood concentrations of the drug, and higher peak blood concentrations

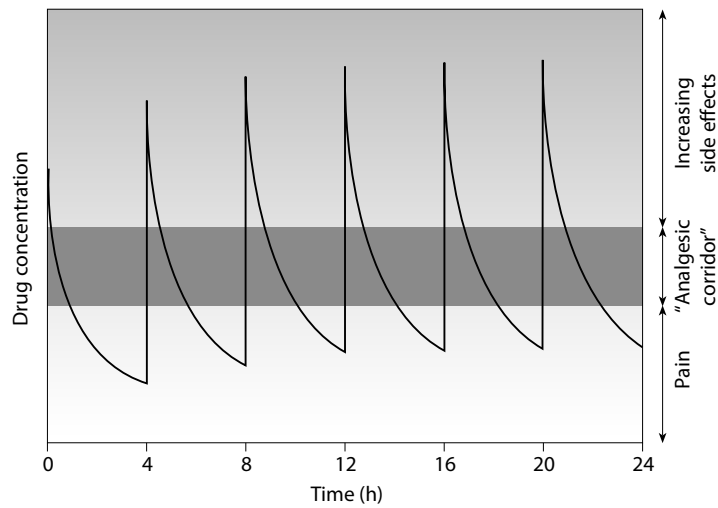


Figure 7.3 Intermittent intravenous opioid analgesia.

leading to an increased risk of adverse effects. It is a potentially less effective and, more importantly, a less safe way to administer opioids. If sustained pain relief is to be obtained without side effects, much smaller doses have to be given IV and much more often.

The smaller the dose and the more often it can be administered, the less variability there will be in the blood concentration of the opioid and the easier it will be to titrate the drug to suit each patient and differing pain stimuli. This is the rationale behind PCA and one of the reasons why PCA has been so effective. However, it would be a major logistical and staffing problem if intermittent IV doses of opioid had to be given by nursing staff to large numbers of patients, so this method of analgesia is not recommended for routine maintenance of pain relief in general wards. This technique is, however, the best way to obtain rapid analgesia and should be used to

- Obtain initial pain relief if pain is severe (e.g., immediately after an operation), that is, "load" the patient so that blood levels rapidly reach the MEAC for that patient.
- Provide analgesia for patients who are hypovolemic or hypotensive, when uptake of drug from muscle or subcutaneous tissue is poor.
- Cover episodes of "incident pain" (e.g., dressing changes, physiotherapy) or inadequate analgesia.

In an attempt to avoid the "peaks and troughs" in blood concentration associated with intermittent administration, continuous intravenous infusions of opioid are sometimes used. While it may be possible to maintain reasonably constant blood concentrations using this technique, it is difficult to predict what level will be needed for a particular patient or what dose is needed to achieve it. Also, acute pain is not constant and the amount of opioid required by a patient will vary in response to different pain stimuli. For the reasons outlined below, alterations of infusion rate alone will often mean there is a considerable delay in matching the amount of opioid delivered to the amount actually needed. There are also possible risks that blood concentrations of the drug continue to rise after analgesia has been obtained.

If an infusion of any drug is ordered at a fixed rate, it takes five half-lives of the drug to reach 95% of final steady-state concentration. The half-life of morphine is around 3 hours (Gupta et al., 2011), so it may take up to 15 hours for blood levels to reach a plateau (steady-state concentration). It is this plateau that needs to be in the "analgesic corridor."

It can be seen from the hypothetical representation in Figure 7.4 of a continuous infusion of an opioid with a half-life of 3 hours (e.g., morphine) that analgesia has been obtained within 3 hours of starting the infusion. If this infusion continues at the same rate, the blood concentration will continue to rise for some hours, and side effects (including OIVI) may result. It will also take hours for each alteration made to the infusion rate to have its full effect, that is, to reach the new steady-state concentration.

A patient who becomes sedated while using PCA (PCA mode only) will not press the demand button and further doses of opioid will not be delivered. Equipment used for continuous infusions of opioid will continue to deliver the drug regardless of whether the patient is sedated or not. For this reason continuous intravenous opioid infusions are probably the *least safe* way to administer opioids in a general ward.

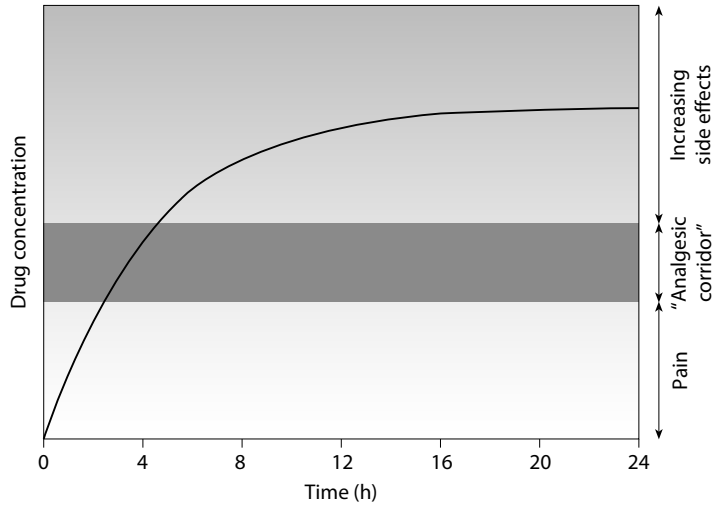


Figure 7.4 Continuous intravenous opioid infusions.

7.3.1 Titration of intermittent IV opioids

When opioids are administered intravenously, peak blood concentrations of the drug will be reached quickly. However, the time for the drug to then take effect will depend on the rate at which it crosses to the CNS and opioid receptors. As noted earlier, factors that determine the rate of transfer to the CNS include the lipid solubility of the drug and the degree of ionization of the drug molecule. This means that there can be significant differences in the time-to-peak effect (or latency-to-peak effect) for different opioids after they have been given as an IV bolus dose.

The latency-to-peak effect of alfentanil and remifentanil, both highly lipid soluble and, compared with other opioids, present in greater proportion in a non-ionized form, is short (under 2 minutes) (Gupta et al., 2011). Their rapid onset but short duration of effect makes them more suited to situations where short duration but intense analgesia is needed.

Morphine, oxycodone, fentanyl, and hydromorphone will be used more commonly in the acute pain setting. Fentanyl and sufentanil are also very lipid soluble and their peak effects will be seen about 4–5 minutes after a bolus dose has been given (Gupta et al., 2011). Morphine is the least lipid soluble and has the longest latency-to-peak effect. While about two-thirds of the full effect of a given dose may be reached after about 5 minutes, it may take up to 20 minutes or more following an IV bolus dose for the maximum effect to be achieved (Gupta et al., 2011). The lipid solubility of hydromorphone is only slightly greater than morphine.

Single doses of IV methadone have been used intraoperatively to improve postoperative pain control and decrease postoperative opioid requirements (Gottschalk et al., 2011). However, the long and very variable half-life of methadone means that it may act like a continuous infusion and the effect of any repeated doses, or doses of any other opioid that may be given, will be even less predictable and less safe. Such use is not recommended, at least in opioid-naive patients.

Large IV bolus doses of tramadol given rapidly can result in a high incidence of emetic symptoms. Slower delivery of the drug, the use of smaller but more

frequent doses, or, in the surgical setting, giving it before the patient emerges from general anesthesia, will usually reduce risk of this side effect (ANZCA and FPM, 2010).

7.3.1.1 Dose range

As before, dose ranges should be based on the age of the patient. Suggested doses for morphine, oxycodone, fentanyl, and tramadol are listed in Figure 7.5.

7.3.1.2 Dose interval

While the peak effect of a bolus dose of fentanyl will be seen within 5 minutes after IV administration, it may take 20 minutes or more for a less lipid-soluble drug such as morphine to exert its maximum effect on the CNS. However, this latter interval is too long if analgesia is to be obtained rapidly. A reasonable balance between absolute safety (ensuring one dose has had its peak effect before another dose is given) and efficacy is to use a dose interval of about 5 minutes for all the commonly used opioids. This has proved safe and effective, as long as staff monitor the patient closely and are aware that this interval may not represent the true time-to-peak effect, especially after morphine has been given.

7.3.1.3 Monitoring and selection of subsequent doses

A guideline that has been widely used for the administration of intermittent IV bolus doses of opioid is reproduced in Figure 7.5. It is managed by nursing staff, usually in the postanesthesia recovery units or other specialized areas such as intensive care, emergency medicine, and burns units. There is no limit to the total amount of opioid that can be given as long as the patient's sedation score remains below 2.

While this protocol is in use and for 15 minutes after cessation of the protocol, a nurse should remain close to the patient.

7.3.1.4 Subsequent analgesic regimens

The aim of IV titration of an opioid is to achieve good pain relief in a short time. Once comfortable, patients can be changed to an alternative opioid analgesic regimen.

7.3.2 Titration of continuous IV opioid infusions

7.3.2.1 Dose range

In view of the variable time taken from the commencement of a continuous infusion to the onset of pain relief, analgesia will be obtained more rapidly if IV bolus doses (as in Figure 7.5) are administered to "load" the patient in the first instance, and the infusion commenced once the patient is comfortable. It has been said that the rate of the infusion can then be based on this loading dose—half the loading dose being required during each elimination half-life. However, half-lives vary between patients; various opioid doses may have been given during surgery; pain immediately after surgery may differ from pain later in the ward (e.g., shoulder tip pain after laparoscopy or abdominal colic may have abated); sedation after anesthesia may have limited the amount

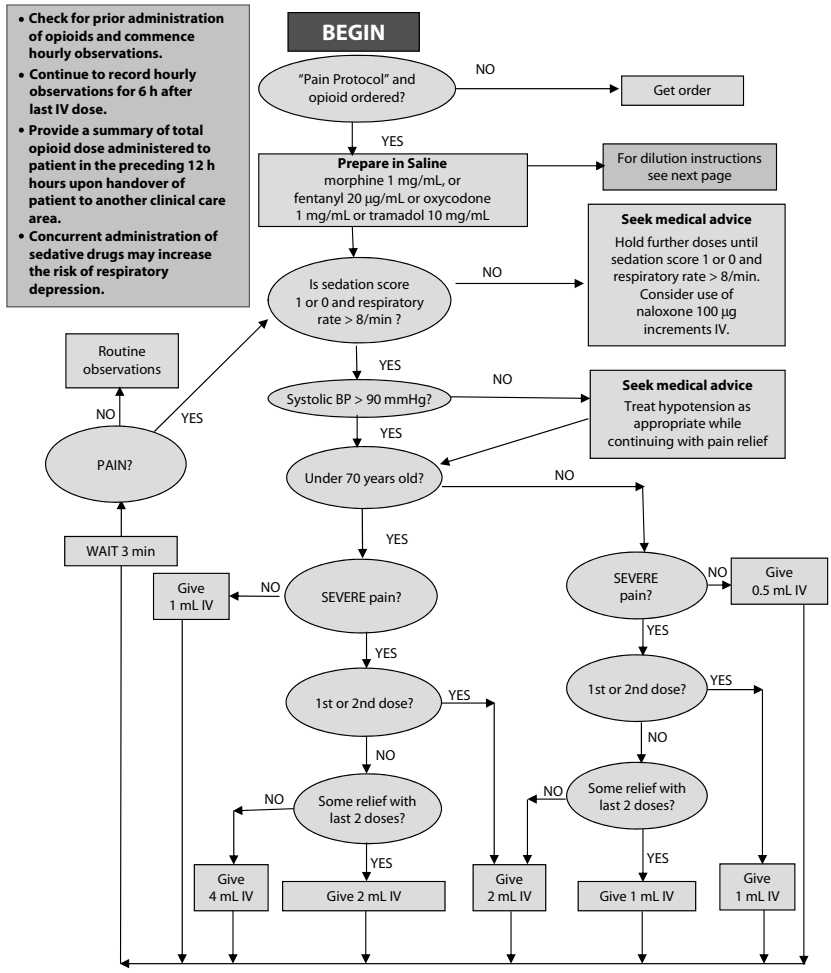
CALHN Guidelines

INTERMITTENT INTRAVENOUS OPIOID ADMINISTRATION

For Acute Pain Management

USE OF THESE GUIDELINES IS RESTRICTED TO THE POST-ANESTHESIA RECOVERY UNIT

- **Only to be used by staff who have been instructed in this technique**
- **Note that the peak effect of an intravenous dose may not occur for over 15 minutes, therefore all patients should be observed closely during this time**
- **All patients receiving repeated doses of IV opioids should be ordered oxygen**



Approved by the CALHN Drug and Therapeutic Committee January 2014

Review date: January 2016

Figure 7.5 An example of an intermittent IV opioid administration guideline. (Reproduced with permission of the Royal Adelaide Hospital and Central Adelaide Local Health Network.)

of opioid given; and the volume status of the patient may have altered (hypovolemia reducing the amount of opioid needed). These and other variables make this calculation, at best, a very rough guide.

7.3.2.2 Monitoring

Pain scores, FAS, sedation scores, and respiratory rates should be monitored frequently, and hourly intervals are suggested.

7.3.2.3 Alterations of infusion rates

Because of the time taken for any alteration in infusion rate to have an effect, if analgesia is inadequate, IV bolus doses should again be used to achieve patient comfort before the infusion rate is increased.

If an infusion is stopped it also take five half-lives of the drug to return to a blood concentration of zero. Therefore, if a patient becomes oversedated, the infusion should cease until the patient is more awake (sedation score <2), not merely be reduced to a lower rate.

7.4 Rectal

The submucosal venous plexus of the rectum drains into the superior, middle, and inferior rectal veins. The drug absorbed from the lower half of the rectum will pass into the latter two veins and into the inferior vena cava, thus bypassing the portal vein and first-pass metabolism in the liver. This is one of the advantages of this route of administration. The drug absorbed through the rectal mucosa of the upper part of the rectum passes into the superior rectal vein and enters the portal system.

Rectal absorption is often variable owing to differences in the site of placement of the drug, the contents of the rectum and the blood supply to the rectum. In addition, there is not always widespread patient—or staff—acceptance of this route of administration. Patients consent should be obtained prior to rectal administration of any drug, whether given awake or under anesthesia.

Rectal administration of drugs should be avoided in patients with preexisting rectal lesions or who are immunosuppressed, and following some types of colorectal surgery.

In most instances similar doses of oral and rectal opioids are used, although there may be differences in bioavailability and rate of absorption due to the reasons outlined above. The drug may not be distributed evenly throughout the suppository and therefore doses of "half a suppository" may not deliver half of the amount of opioid in that suppository.

7.5 Transdermal

The stratum corneum of the epidermis forms a major barrier to the entry of drugs. However, opioids that are lipid-soluble may be absorbed through the skin.

Skin permeability can be affected by a number of factors such as age, skin temperature, body site, and ethnic group. Variations in these factors could lead to unpredictable rates of drug transfer across the skin. To minimize the influence of variable skin transfer, early transdermal fentanyl delivery systems incorporated

a drug reservoir and a membrane. The membrane was much less permeable than skin and was therefore the rate-controlling step, which ensured a more predictable rate of drug transfer (Lotsch et al., 2013). Rate-controlling membrane patches have largely been replaced by drug-in-matrix systems with the same bioequivalence, where the fentanyl or buprenorphine is dissolved in an inert adhesive matrix. This controls the rate of transdermal drug transfer and the amount delivered is proportional to the surface area of the patch (Lotsch et al., 2013). Delivery may also vary according to skin temperature (e.g., if the patient is febrile) or if the patch is exposed to external heat sources.

With all these systems (new and old), the skins act as a reservoir for the drug before it is absorbed into the blood stream. The effect of this reservoir can be significant, and continued absorption of opioid from the site may continue long after the patch has been removed.

7.5.1 Fentanyl patches

Transdermal fentanyl patches are available in sizes that deliver 12 (or 12.5), 25, 50, 75, and 100 μg/h. These are designed to release the drug at a constant rate over 72 hours, although rates may vary between patients. Once the patch is placed on the patient there is relatively rapid absorption of the fentanyl into the skin reservoir because of the large concentration gradient between the two. The drug is then released more slowly from the skin and it may be 24 hours or longer before peak blood concentrations are reached (Lotsch et al., 2013). Similarly, if the patch is removed, the depot of fentanyl in the skin reservoir means that blood levels will decrease only slowly (the apparent elimination half-life is around 17 hours after patch removal (Lotsch et al., 2013).

Fentanyl patches are usually replaced every 72 hours. It should be remembered that a significant amount of drug remains in the patch after removal and care must be taken with its disposal. For example, one brand of fentanyl patch that delivers 100 μg/h (7200 μg over 72 hours) contains 16,800 μg of fentanyl, so that patch may still contain about 9600 μg (or the equivalent of around 500 mg IV morphine) after it is removed from the patient. Careful disposal of fentanyl patches is therefore very important in order to prevent harm or misuse.

Transdermal fentanyl patches are commonly used in the management of cancer and chronic pain. The slow onset of action does not allow for easy titration to analgesic effect and so they are not suitable for routine acute pain management or for use in opioid-naive patients. More importantly, because of repeated reports of deaths resulting from OIVI, fentanyl patches are currently specifically contraindicated for the management of acute or postoperative pain in many countries. Serious injury, including death, of infants and children accidentally exposed to a fentanyl patch has been reported (Bailey et al., 2009; Burghardt et al., 2013).

A newer method of transdermal delivery, called *iontophoresis*, enables a more rapid transfer of drug through the skin by application of an external electric field. It is not yet in common clinical use. An iontophoretic patient-controlled transdermal delivery systems for fentanyl was introduced into practice but later withdrawn following reports of technical problems (ANZCA and FPM, 2010). It has undergone further work and may be remarketed. As with all disposable PCA devices, the size of the bolus dose of fentanyl (40 μg) will be fixed, which will limit its ability to provide good pain relief in some patients, especially those with high opioid requirements. Safe use and disposal of the patch will be important.

7.5.2 Buprenorphine patches

Transdermal buprenorphine patches are also available in a variety of sizes. The lower-dose patches, which deliver 5, 10, or 20 μg/h, are the most common. They need to be changed only every seven days. Higher-dose patches which deliver 35, 52.5, and 70 μg/h are also available in some countries and are usually changed every three and a half days. Peak blood concentrations of the lower-dose patches are reached at about 48 hours and the apparent terminal half-life is around 26 hours after removal of the patch (Plosker, 2011).

Transdermal buprenorphine patches are commonly used in the management of cancer and chronic pain. They are not considered suitable for the routine treatment of acute pain given their slow onset and offset.

7.6 Transmucosal

Transmucosal drug administration refers to drug delivery through nasal, sublingual, buccal, or pulmonary mucosal membranes. It is particularly suited to the more lipid-soluble opioids such as fentanyl, sufentanil, and alfentanil. It has the advantage of avoiding first-pass metabolism because a proportion of the dose administered enters the systemic circulation without first passing through the liver.

7.6.1 Intranasal

The intranasal (IN) route of opioid administration has become more popular in recent years. The opioids are absorbed systemically without undergoing gastrointestinal or hepatic first-pass metabolism. The nasal mucosa contains drug-metabolizing enzymes, but the extent and clinical significance of any nasal first-pass effect is unknown (Grassin-Delyle et al., 2012). It is also thought that the nasal route may allow delivery of a portion of the drug directly to the CNS via the olfactory epithelium, thus bypassing the blood–brain barrier (Grassin-Delyle et al., 2012). However, the degree to which this transport occurs, the mechanism by which it occurs, and the clinical significance of any transport through the olfactory zone are not fully understood.

As the surface area of nasal mucosa is small, it is suggested that the volume of a dose of any drug given intranasally should not exceed 150–200 μL per nostril in order to avoid excessive run-off into the pharynx (Dale et al., 2002; Grassin-Delyle et al., 2012). Therefore, IN formulations with high opioid concentrations are needed (Hansen et al., 2012).

Fentanyl, sufentanil, alfentanil, remifentanil, butorphanol, oxycodone, buprenorphine, methadone, diamorphine, hydromorphone, and morphine are among the opioids that have been administered as a nasal spray (Dale et al., 2002; Grassin-Delyle et al., 2012). The method seems best suited to the more lipid-soluble opioids such fentanyl, sufentanil, and alfentanil.

The IN opioid most commonly in the acute pain setting is fentanyl, both for in-hospital and prehospital analgesia. Most studies in the acute pain setting have shown IN fentanyl to be as effective as IV fentanyl, but with a lightly slower onset of analgesia (Hansen et al., 2012). Peak blood concentrations are reached about 7 minutes after administration. The bioavailability of IN fentanyl is said to be around 70–90%, but, in general, the studies looking at the

pharmacokinetics of IN fentanyl have involved the use of very concentrated solutions (up to 4000 μg/mL of fentanyl) (Hansen et al., 2012). These higher concentration solutions have been marketed only for the treatment of breakthrough cancer pain in patients already taking long-term opioids, and deliver a range of doses (between 50 and 400 μg) in just 100 μL.

The standard 50 μg/mL solution of fentanyl is more commonly used for IN administration in the acute pain setting. The less concentrated solution requires the volume delivered to be much larger than the suggested maximum of 150–200 μL if adequate doses are to be given, especially in adult patients. The nasal bioavailability of the 50 μg/mL solution in the volumes commonly used in adult patients is unclear and most likely highly variable.

IN fentanyl can also be administered in metered doses which can be "patient-controlled." Issues around easy and unauthorized access to some IN fentanyl techniques, which use multi-dose delivery systems such as IN PCA, remain.

7.6.2 Oral transmucosal (sublingual and buccal)

Fentanyl is equally well absorbed well after both buccal and sublingual administration (Lotsch et al., 2013). Its efficacy will depend in part on the proportion of drug that is swallowed.

Oral transmucosal fentanyl citrate (OTFC) "lollipops" are fentanyl lozenges on sticks. About 25% of the fentanyl in the lozenge is absorbed through the buccal mucosa (that portion does not undergo first-pass metabolism) and the remainder is swallowed; overall bioavailability is about 50% and peak blood concentrations are seen at about 20 minutes (Grape et al., 2010). Doses ranging from 200 to 1600 μg are available.

Fentanyl buccal tablets use an effervescent reaction and change in pH to promote absorption of the fentanyl across the buccal mucosa. Half the dose is absorbed transmucosally, the rest is swallowed, the overall bioavailability is about 65%, and the time taken to reach peak blood concentrations is around 50 minutes (Grape et al., 2010). Doses ranging from 100 to 800 μg are marketed.

More recently, soluble buccal films of fentanyl that adhere to the inside of the patient's cheek have been marketed and these are available in doses ranging from 200 to 1200 μg. They have an overall bioavailability of 79% and peak blood concentrations are seen about 1 hour after buccal placement (Lim et al., 2012).

These three formulations are approved only for the management of breakthrough cancer pain in patients already taking long-term opioids. In most countries they are specifically contraindicated for use in patients with acute pain or in any opioid-naive patient.

Sublingual sufentanil administration using a portable electronic dispenser is being investigated for the treatment of postoperative pain as an alternate to IV PCA (Minkowitz et al., 2013). It is possible that, as with other fixed-dose systems, adequate analgesia in patients with high opioid requirements may be more difficult to achieve.

Buprenorphine is used as an analgesic agent and also, increasingly, as an alternative to methadone in the treatment of opioid addiction. It has commonly been given sublingually as a tablet. However, for patients requiring the buprenorphine–naloxone combination used in opioid addition treatment programs, sublingual mucoadhesive films are now more commonly administered than sublingual tablets.

7.6.3 Pulmonary

Inhalational administration (as a nebulized aerosol) of some opioids, including morphine, diamorphine, fentanyl, and hydromorphone, has been used, primarily in palliative care for the provision of analgesia and for the symptomatic control of breathlessness. Although using newer delivery systems the bioavailability of the drugs can be quite high, the unpredictable and large variation in absorption probably makes this route unsuitable for the management of acute pain and experience in the acute pain setting is very limited.

Key points

1. Safe and effective management of acute pain using intermittent PRN oral, SC, and IM opioid administration requires individualization of treatment regimens in order to manage the very large interpatient differences in opioid requirements. This means the use of initial age-based doses (in opioid-naive patients) prescribed at appropriate dose intervals followed by titration of subsequent doses according to assessments of pain, FAS, sedation scores, and respiratory rate.
2. Patients should be offered analgesia on a regular basis—they should not always have to ask for more pain relief.
3. In the absence of contraindications or severe pain, the oral route remains the route of choice for administration for opioids.
4. If a patient has severe acute pain and the education of the staff and the monitoring and setting allow it, the most rapid way to get good relief of severe pain is to titrate IV bolus doses of opioid.
5. Continuous IV opioid infusions are the least safe way to deliver opioids in a general ward setting.
6. IN fentanyl can be used to treat acute pain and the onset can be almost rapid as an IV bolus dose. However, the bioavailability of the commonly used 50 μg/mL solution is uncertain as the volume administered to each nostril should not exceed 200 μL in order to avoid excessive run-off into the pharynx.
7. SR opioids should be given at fixed time intervals and are not suitable for the early or only management of acute pain.
8. Transdermal fentanyl patches are not suitable for the management of acute pain. In most countries use in patients with acute pain is specifically contraindicated and a caution is issued about use on opioid-naive patients.
9. Fentanyl oral transmucosal lozenges, and buccal tablets and films are not suitable for the management of acute pain. In most countries they are approved for use only for the treatment of breakthrough pain in opioid-tolerant cancer patients; use in patients with acute pain and opioid-naive patients is specifically contraindicated.

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Appendix 7.1: Example of a "standard order" form for intermittent PRN oral and SC opioid regimens

CALHN

☐ **RAH** ☐ **TQEH**

IMMEDIATE-RELEASE 'PRN' ORAL AND SUBCUTANEOUS OPIOID ORDERS FOR MANAGEMENT OF ACUTE PAIN

PATIENT LABEL

Unit Record No.: _____

Surname: _____

Given Names: _____

Date of Birth: _____ Sex: _____

OPIOID ORDERS:

1. If the patient is drinking, an oral opioid is usually given.
2. Usually order EITHER **oral** OR **subcut** (note that doses are different for each route of administration).
3. Refer to guidelines (see back of this form) for age-based doses in opioid-naïve patients; DO NOT use trailing zeros (e.g. 5 mg and not 5.0 mg); Order dose as mg or microgram.
4. There must be an interval of at least one hour between doses, regardless of route of administration.

1. **ORAL OPIOID (name):**	1. **SUBCUT OPIOID (name):**
.....	.....
2. **DOSE RANGE:** *Sign & date any change.*	2. **DOSE RANGE:** *Sign & date any change.*
..... to	..... to .....
..... to	..... to .....
3. **DOSE INTERVAL:**	3. **DOSE INTERVAL:**
..... hourly PRN	..... hourly PRN
(providing sedation score < 2)	(providing sedation score < 2)

Place label on the PRN section of the NIMC MR 90.0

For All PRN opioid orders see MR98.9

GENERAL ORDERS:

1. Supplemental oxygen (2 to 4 L/min nasal specs) may be advisable in some patients, e.g. after major surgery or trauma.
2. Note that administration of other systemic opioids or sedatives (including antihistamines) will increase the risk of respiratory depression.
3. Naloxone must be immediately available.
4. Many patients will not ask for pain relief, therefore analgesia should be offered hourly until comfortable and then at least 4 hourly, with concurrent monitoring and documentation of pain and sedation scores.
5. *Monitoring requirements: see overleaf.*
6. For inadequate analgesia or other problems related to the analgesia, contact the medical officer. Patients with two consecutive pain scores at rest > 7 and/or FAS = C must be reviewed by a doctor.
7. If respiratory rate is 8-10/min, no action is required as long as sedation score is < 2. If sedation score is 2 or 3, follow instructions below.

TREATMENT OF SIDE EFFECTS:

RESPIRATORY DEPRESSION (EXCESSIVE SEDATION):

1. If sedation score = 2 (indicates respiratory depression):
   a. medical review required within 30 mins
   b. do not give any more opioid until sedation score < 2
   c. do hourly sedation scores until sedation score < 2 for at least 2 hours
   d. reduce size of subsequent doses (e.g. half the dose)
2. If sedation score = 3 (indicates severe respiratory depression irrespective of respiratory rate) OR sedation score = 2 and respiratory rate ≤ 7 breaths/min:
   a. initiate MER call
   b. give 100 microgram NALOXONE IV stat. Repeat 2 minutely PRN up to a total of 400 microgram (if no IV access, give 400 microgram NALOXONE subcut or IM)
   c. do hourly sedation scores until sedation score < 2 for at least 2 hours

NAUSEA AND VOMITING:

Refer to hospital protocols

SIGNATURE OF MEDICAL OFFICER:..... Date:.....

(Print name.....) Designation..... Contact No.....

Cease above orders:

Signature of MO..... Date:..... Time:..... Contact No.....

IMMEDIATE-RELEASE 'PRN' ORAL AND SUBCUTANEOUS OPIOID ORDERS MR 98.9

CALHN

IMMEDIATE-RELEASE 'PRN' ORAL AND SUBCUTANEOUS OPIOID ADMINISTRATION

Observations and Record of Drug Administration

PATIENT LABEL

Unit Record No.: _____

Surname: _____

Given Names: _____

Date of Birth: _____ Sex: _____

MONITORING REQUIREMENTS:

RECORD PAIN SCORE, SEDATION SCORE, RESPIRATORY RATE AND FAS

a) At the TIME OF ADMINISTRATION of the opioid AND

b) 1 HOUR after administration AND

c) At least 4 HOURLY for any patient ordered opioids for management of their acute pain and offer* pain relief at the same time

* offer pain relief more frequently if needed; do not wait for patient request

Pain Score:	**Sedation Score:**	**Functional Activity Score (FAS):**
0 = no pain 10 = worst pain imaginable *NB: record pain scores at rest and with movement e.g. coughing*	0 = wide awake 1 = easy to rouse, can stay awake 2 = easy to rouse but cannot stay awake 3 = difficult to rouse (severe respiratory depression)	A = no limitation of (relevant) activity due to pain B = mild limitation of activity due to pain C = unable to complete activity due to pain

Record drug given, dose and route of administration, pain, sedation scores, respiratory rate and FAS below

Date	Time	Drug	Dose	Route (oral or subcut)	Pain Scores ..... X 0 2 4 6 8 10	Sed'n Score	Resp Rate	FAS	Comments	Signature RN or MO
While these orders are in effect, please follow instructions related to SEDATION and PAIN scores (including frequency of observations and responses to inadequate analgesia and excessive sedation) ON THIS FORM AND NOT ON MR 59A										
Example:										
26/3	*1100*	*Morphine*	*10mg*	*subcut*	*X X*	*0*	*12*	*B*		*J Smith*
26/3	*1200*	*(one hour later)*			*X X*	*1*	*12*	*A*		*J Smith*
					0 2 4 6 8 10					

ADVERSE DRUG REACTIONS			
Drug	Date	Details	Signature

Record drug given, dose and route of administration, pain, sedation scores, respiratory rate and FAS below

Date	Time	Drug	Dose	Route (oral or subcut)	Pain Scores ..... X 0 2 4 6 8 10	Sed'n Score	Resp Rate	FAS	Comments	Signature RN or MO
					0 2 4 6 8 10					

Not all patients will need or should be prescribed oxycodone (or any other oral opioid) when they leave hospital. If prescription for oral oxycodone is thought necessary, the following guide is suggested.

DISCHARGE PRESCRIPTIONS FOR ORAL OXYCODONE:

- Use immediate-release oxycodone (Endone®) only, not SR (OxyContin®)
- The dose of oxycodone prescribed should be based on the patient's immediate-last 24 hour requirement; suggest order 4 hourly prn for discharge
- In most patients it is suggested that doses are reduced each day after discharge and that duration of treatment is restricted to a week or less unless the patient is reviewed

Complete the following:

- Immediate-last 24 hour total dose of oxycodone required = ... mg
- Divide this daily dose by 6 to obtain the maximum 4 hourly dose; allow a range so that lower doses can be taken
- Therefore, dose of oxycodone prescribed = ... mg to ..... mg 4 hourly PRN

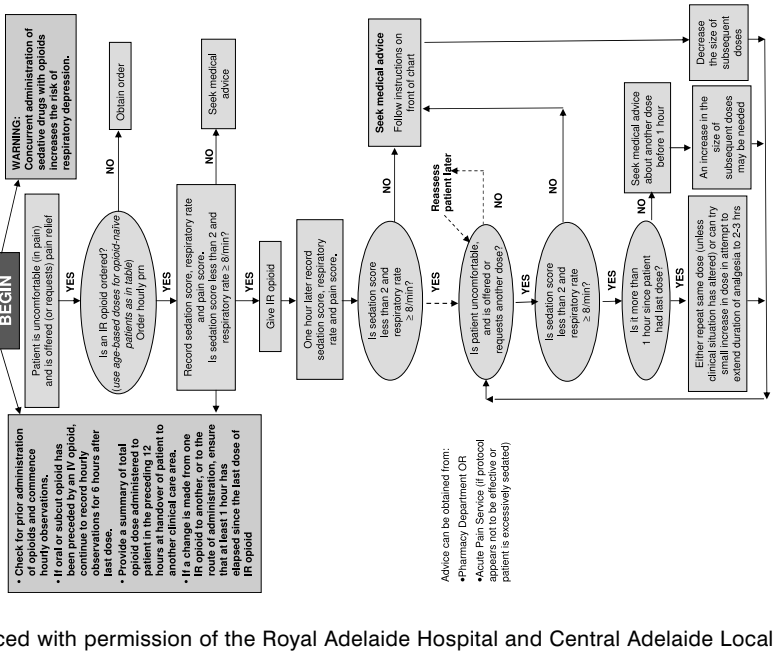
Note: *If calculated dose is 20 mg or more, seek advice before prescribing.*

- Doses and plan for dose decrease over short period included in discharge letter and communicated to patient? **Y / N**

Signature of MO..... **Date**.....

CALHN Drug Committee
Approved Nov 2013
Planned review date: Dec 2014

CALHN Guidelines
INTERMITTENT IMMEDIATE-RELEASE (IR) ORAL OR SUBCUTANEOUS OPIOID ADMINISTRATION
For Acute Pain Management



AGE-BASED IMMEDIATE - RELEASE OPIOID DOSES FOR ACUTE PAIN MANAGEMENT

The doses below are suggested initial doses only for opioid-naïve inpatients with moderate to severe acute pain.
- Lower opioid doses are more appropriate in patients with less pain and/or if treatment is not initial.
- Opioid-tolerant patients (patients taking opioids long-term) may require higher doses.
- Consideration should be given to dosage amendment in differing clinical situations.

Age (yrs)	Subcut MORPHINE or OXYCODONE (mg) *	Subcut FENTANYL (microg) *	Oral OXYCODONE (mg) *
< 15	seek advice		
15 – 39	7.5 – 12.5	100 – 200	10 – 25
40 – 59	5 – 10	75 – 150	10 – 20
60 – 69	2.5 – 7.5	40 – 100	5 – 15
70 – 85	2.5 – 5	40 – 75	5 – 10
> 85	2 – 3	30 – 50	2.5 – 5
*Recommended dose interval: 1 hourly prn**		↓ *dose if pain not severe*	

Contact WCH Drug Information Centre or WCH Department of Anaesthesia for advice on opioid doses for children <15 years

- Order recommended dose of immediate - release opioid hourly prn (Note: this is for inpatients only; suggest 4 hourly prn otherwise).
- Suggest start in middle of dose range.
- Doses may be given hourly if needed but frequency of subsequent doses will depend on response to previous dose; can increase dose given in attempt to extend duration of analgesia to 2-3 h or more as long as sedation score is less than 2.
- Upper limit of dose range can be increased if analgesia is inadequate, sedation score is less than 2 and respiratory rate greater than 7 breaths/min (first check that doses are correct/ have been given).
- Oxycodone and fentanyl can be given to patients with renal impairment.
- Note that the equianalgesic dose (same analgesic efficacy) for subcut oxycodone is equal to that of subcut morphine but is half the oral oxycodone dose. That is 10 mg subcut oxycodone = 10 mg subcut morphine = 20 mg oral oxycodone.
- If a change is made to give subcut fentanyl note that 10 mg morphine = 150 microg fentanyl. Note also that 150 microg fentanyl = 3 mL which is a large volume for subcut injection, and can be very painful unless given slowly.
- Some patients may require a prescription for oral oxycodone at discharge.
  - If patient was already taking long-term opioids on admission or has a history of substance abuse this may not be appropriate – seek advice.

IMPORTANT NOTES
- **Slow-release (SR) opioids such as OxyContin, MS Contin and Kapanol, as well as fentanyl or buprenorphine patches, are not suitable or safe for management of acute pain.**
- **At some hospitals patients can only be commenced on SR opioids and fentanyl or buprenorphine patches by the Pain Management Unit, Acute Pain Service, Cancer Centre, Spinal Injury Unit & also Consultant General Physicians and Geriatricians for prescription for patients with malignancy. Check hospital Formulary.**

MONITORING OF THERAPY IS ESSENTIAL IF OPIOIDS ARE TO BE TITRATED SAFELY FOR EACH PATIENT

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CHAPTER 8

Patient-controlled analgesia

In the broadest sense, the phrase "patient-controlled analgesia" refers to a general process that allows patients to determine when and how much analgesic medication they receive, regardless of the drug used or route of administration. However, it more commonly refers to a method of pain relief which uses electronic or disposable infusion devices and allows patients to self-administer an opioid as required.

The concept of intravenous (IV) patient-controlled analgesia (PCA) dates back to the late 1960s. Sechzer (1968) looked at the efficacy of 1 mL doses of an IV morphine or pethidine (meperidine) solution given by a nurse for postsurgical analgesia whenever the patient pressed a demand button. He went on to design the first automated patient-controlled analgesic-demand system for the management of postoperative pain (Sechzer, 1971). A number of PCA devices were then developed commercially which had adjustable parameters and better safety features. However, use of PCA in clinical practice did not become widespread until the introduction of acute pain services (APS) (Ready et al., 1988). It is now generally accepted as part of routine acute pain management practice.

This chapter deals primarily with IV PCA, although PCA via other systemic routes is also discussed. Patient-controlled epidural and other regional analgesia are covered in Chapters 9 and 10, respectively. The principles of PCA management are similar regardless of the route used.

In general, compared with "as needed" conventional opioid analgesic regimens, IV PCA provides better pain relief and greater patient satisfaction with no increase in the incidence of opioid-related side effects (other than pruritus), despite higher opioid consumption (Dolin et al., 2002; Hudcova et al., 2006).

One reason for better analgesia may be that PCA allows small and frequent IV bolus doses of opioid to be given as needed. This flexibility means that PCA is more likely to allow patients to keep blood concentrations of opioid within the "analgesic corridor" and allow rapid titration if there is an increase in pain stimulus, requiring higher blood levels of opioid in order to maintain analgesia (Figure 8.1). It is also easier to overcome the known and very wide interpatient variations in opioid requirements (see Chapter 4). Patients are also able to vary the amount of opioid delivered according to any dose-related side effects they might experience.

8.1 Equipment

There are two basic types of PCA equipment—programmable electronic pumps and disposable devices.

8.1.1 Electronic PCA pumps

Electronic PCA machines have been commercially available since the early 1970s. Over the years, improvements have included better security, the use of error-reduction programs and a choice of battery or mains power.

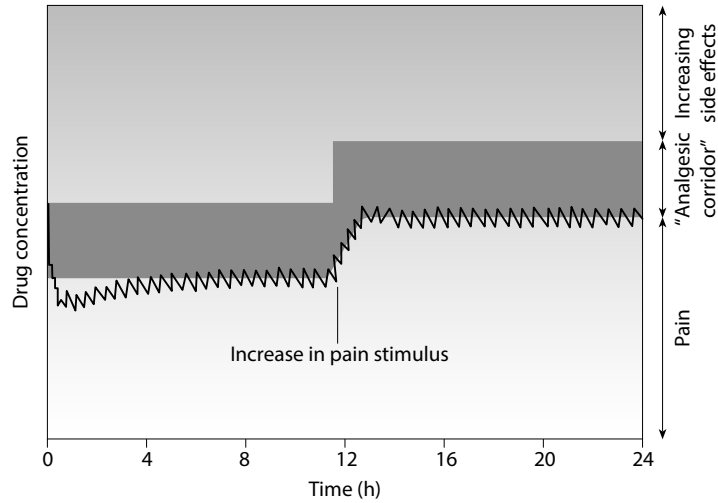

Figure 8.1 Patient-controlled analgesia. PCA is more likely to keep blood concentrations of opioid within the "analgesic corridor" and allows rapid titration if there is an increase in pain stimulus, requiring higher blood levels of opioid in order to maintain analgesia.

Most PCA machines can operate in three modes:

- PCA demand mode only
- Continuous (background) infusion only
- A combination of PCA demand mode with a continuous infusion

Within preset limits, PCA pumps deliver a bolus dose of drug when the patient presses a demand button connected to the pump. Certain variables are prescribed and programmed into the PCA machine (see below) and control how much opioid the patient can receive.

Patients using PCA (PCA mode) are instructed to push the demand button whenever they are uncomfortable. Some machines will also operate with an alternative demand mechanism such as a pressure-sensitive pad or foot pedal. These may be particularly useful for patients who cannot use their hands to press the demand button—for example, those with bilateral upper limb fractures, burns, or severe rheumatoid arthritis.

The inherent safety of the PCA technique lies in the fact that, as long as the machine is in PCA mode only (i.e., no background infusion), further doses of opioid will not be delivered should the patient become excessively sedated (an indicator of opioid-induced ventilatory impairment [OIVI]—see Chapter 3), because no further demands will be made.

This assumes that the patient is the only one pressing the button. In some settings (e.g., pediatric or intensive care), use by someone other than the patient ("PCA by proxy"—e.g., nurse or parent) may be allowed in selected circumstances. However, such use may reduce the inherent safety of PCA and must be accompanied by appropriate instructions and monitoring.

Some newer PCA machines use a handset with a light that shows whenever the machine is ready to respond to another demand. While this may be preferred by patients (Patak et al., 2013) there is a risk that some may then initiate a demand

whenever possible. A light that is on at all times, however, may make the handset easier to find.

The major advantages of electronic PCA systems are their flexibility, as adjustments can easily be made to parameters such as the bolus dose and rate of the background infusion; their security, as access to the syringe or other drug reservoir and the microprocessor program are only possible using a key or access code; and the ability to make accurate assessments of the total dose of drug delivered and the amount remaining in the drug reservoir.

8.1.1.1 "Smart pumps"

The so-called "smart pumps" have been developed in attempts to reduce programming errors—a leading cause of complications associated with the use of PCA (see Section 8.6.2.2). Drug "libraries" with preset "standard" dosing protocols (standardized drug concentrations and doses) and dose error reduction systems are now common inclusions, and some machines also have integrated bar code verification of the drug and drug concentration in the drug reservoir (ECRI, 2011).

8.1.1.2 Consumables

All electronic PCA pumps require disposable items to be used for each patient, including the drug reservoir (syringe or infusion bag) and tubing as well as antireflux and antisiphon valves.

Antireflux valves should be placed in the primary line delivering IV fluids unless the PCA is connected to the patient via a dedicated line. These one-way valves prevent backflow of the opioid into the primary IV line should the IV cannula become occluded, so that infusion of any doses delivered during the occlusion does not occur if the occlusion is cleared.

Antisiphon valves are recommended for use with PCA pumps and whenever a pump is used to deliver other drugs such as ketamine or epidural local anesthetic/opioid solutions. Placed between the drug reservoir and the patient, they will prevent siphoning (emptying by gravity) of the drug if the reservoir is above the level of the patient and not fixed in the PCA machine or leaking.

8.1.2 Disposable PCA devices

A number of disposable PCA devices have been developed. Their advantages are that they are small in size and weight, free from the need for an external power source, may not require IV access, and are simple to use thus eliminating program errors. Disadvantages include an inability to alter the size of the bolus dose (which limits dosing flexibility), add a background infusion, or accurately determine the amount of drug the patient has received. Other potential problems include possible ease of access to the opioid reservoir and higher long-term costs.

8.2 Analgesic drugs used with PCA

8.2.1 Opioids

Many opioids, including morphine, fentanyl, hydromorphone, oxycodone, tramadol, and pethidine (meperidine), have been used with PCA. There is no good evidence to suggest any major differences in either efficacy or the incidence of

side effects, although pruritus may be more common with morphine (Hudcova et al., 2006; ANZCA and FPM, 2010). However, if drug-related side effects fail to respond to specific treatment, some patients may benefit if a change to another opioid is made (Woodhouse et al., 1999). Many comparisons between different opioids used via PCA are often invalid as comparable (equianalgesic) bolus doses were not used in the studies.

Opioids having very short (e.g., alfentanil, remifentanil) or very long (e.g., methadone) durations of action are not usually recommended for use in PCA, at least for general ward use. It is probably best to avoid pethidine because of the risk or norpethidine (normeperidine) toxicity, which can occur with the use of higher doses even in the absence of renal impairment and within 24 hours of starting therapy (Simopoulos et al., 2002). Partial agonist or agonist–antagonist opioids are used far less commonly than pure opioid agonists. Remifentanil PCA has been used for pain relief in labor, but may be associated with a high risk of apnea (Stocki et al., 2014).

In patients with renal impairment, use of an opioid with no active metabolites (fentanyl) or clinically insignificant active metabolites (e.g., oxycodone) is preferred. In older patients PCA fentanyl may result in less depression of postoperative cognitive function compared with morphine (Herrick et al., 1996).

8.2.2 Other drugs

This chapter focuses on the use of a single opioid with PCA. Much less often, combinations of an opioid with another drug are used. Examples include the addition of ketamine, clonidine, tramadol, ketorolac, and lidocaine in attempts to improve pain relief, and droperidol or ondansetron in efforts to reduce the incidence of nausea and vomiting (ANZCA and FPM, 2010).

While some but not all of these additives may have a beneficial effect (Macintyre and Coldrey, 2009), large interpatient variations in PCA opioid requirements mean that patients are likely to receive very widely varying doses of the added drug. This could lead to an inadequate effect of the added drug in some patients and an excessive effect in others. In addition, the cost–benefit and risk–benefit of the routine addition of other medications to PCA must be considered because all patients receive the drug when not all will need it.

8.3 The PCA "prescription"

There are many different models of microprocessor-controlled PCA machines now available. Although the variables that can be programmed might differ slightly between devices, a number of features are common to most. Commonly used settings for IV PCA variables are listed in Table 8.1.

8.3.1 Loading dose

PCA is a maintenance therapy: it is a good way to maintain patient comfort but an ineffective way of achieving that comfort in the first place. To make the patient comfortable before PCA is started, a loading dose of opioid is needed. Most if not all electronic PCA machines have a "loading dose" facility that allows automatic administration of a dose of opioids before patient self-administration

Table 8.1 Commonly prescribed initial variables for IV PCA in opioid-naive patients

Variable	Value	Comments
Loading dose	0 mg (i.e., zero)	Patients should be comfortable before PCA is started and therefore it is best to titrate opioid analgesia for each patient individually before starting PCA
Bolus dose	Morphine: 1 mg Fentanyl: 20 μg Hydromorphone: 200 μg Oxycodone: 1 mg Tramadol: 10–20 mg	In patients ≥70 years, consider reducing bolus dose by 50% It may be helpful to have an order that allows an increase in the size of the bolus dose if needed Bolus dose may need to be increased if analgesia is inadequate and should be decreased if patient becomes sedated
Concentration		Best if standardized for each drug
Dose duration	May not be adjustable in some PCA machines	
Lockout interval	5–10 min	Not worth altering (no evidence to show any benefit)
Background (continuous) infusion	0 mg or μg/h (i.e., zero)	Not used routinely in opioid-naive patients If prescribed, it may be appropriate to use a rate of infusion per hour that is no greater than the size of the bolus dose
1-h or 4-h dose limits		Omit (no evidence to show any benefit)

commences. However, there is an enormous interpatient variation in the amount of opioid required to obtain good initial pain relief. It is therefore better to individualize the loading dose for each patient prior to starting PCA (e.g., by using the IV opioid protocol in Chapter 7) rather than program a single loading dose via the PCA machine.

8.3.2 Bolus dose

The bolus dose is the amount of opioid that the PCA machine will deliver when the demand button is pressed. The size of the dose can influence the success or otherwise of PCA. If the dose is too small, patients will not be able to obtain adequate analgesia and they may then question the efficacy of the drug or technique. A dose that is too large may result in adverse effects.

An early study aiming to identify the "optimal" size of a PCA bolus dose compared 0.5, 1, and 2 mg doses of morphine (Owen et al., 1989). Six of the seven patients prescribed the 0.5 mg dose were unable to obtain good pain relief, whereas OIVI was seen in four of the seven patients given 2 mg doses. It was concluded that 1 mg was the optimal dose for PCA morphine.

If the prescribed dose is not "optimal" and pain relief is inadequate, patients should be able to compensate to some degree by increasing their demand rate. However, this is probably only true if the bolus dose is not too small. Of interest in the study above (Owen et al., 1989) was that the eight patients in total with poor pain relief still made an average of only four demands an hour, even

though the lockout interval was 5 minutes. This is commonly seen in clinical practice. It may be best to aim, in most patients, for a dose size that means the patient requires only two to three bolus doses each hour on average. Some patients, for example, those who are very anxious, may have a high demand rate and increasing the size of the bolus dose may not be appropriate unless pain relief is inadequate.

Commonly used initial dose sizes (in opioid-naive patients) are given in Table 8.1. The optimal bolus dose for each patient is one that results in good pain relief with minimal side effects. Therefore, adjustments to the size of the initial dose may be required, so that PCA can be better tailored to the individual patient. It is not a "one size fits all" or "set and forget" therapy (Etches, 1999).

As with conventional intermittent opioid regimens, the dose of opioid prescribed should be reduced as the age of the patient increases—a reduction of 50% is suggested for patients older than 70 years. Patients who are opioid-tolerant may require much larger bolus doses to achieve adequate analgesia (see Chapter 14).

8.3.3 Dose duration

The rate at which the PCA machine delivers the bolus dose—the dose duration—can be altered in some machines, allowing the dose to be delivered as a short infusion (e.g., over 5 minutes). If subcutaneous (SC) PCA is used (see later in this chapter), rapid delivery of a dose may cause some stinging and a slower rate of delivery may be more comfortable.

8.3.4 Lockout interval

The time from the end of the delivery of one dose until the machine will respond to another demand is called the lockout interval. This interval aims to increase the safety of PCA by allowing the patient to feel the effect of one dose before another dose is delivered. There is no good evidence for an "optimal" lockout interval and, in practice, intervals of 5–10 minutes are commonly prescribed (for IV PCA) regardless of the opioid used, even though it may take up to 20 minutes or longer for the peak effect of an IV dose of morphine to be seen (see Chapter 7).

When patients are told about the lockout interval, it is important to ensure that they realize it only means that another dose can be delivered if they need one, and not that they should press every 5–10 minutes.

A lockout interval of 5 minutes means that, allowing for time for the dose to be delivered, a patient could demand and receive around 10 doses of opioid each hour. In reality, if patients feel that a particular incremental dose is not effective, they will not continue to press the demand button. As noted above, many patients will not sustain a demand rate of more than four doses per hour even if pain relief is inadequate. For these reasons a reduction in the lockout interval or instructing the patient to press the button more often than this is unlikely to lead to any improvement in analgesia.

8.3.5 Continuous (background) infusion

Most PCA machines can deliver a continuous (background) infusion. Used at a low rate (aiming for subanalgesic blood concentrations) in addition to PCA demand mode, it was hoped that a background infusion would enable the patient to make fewer demands, sleep for longer periods, and wake in less pain.

Unfortunately, the routine addition of a continuous infusion does not have the beneficial effects that were anticipated for the average opioid-naive patient. Instead, it does not always reduce the number of demands made by the patient, or result in better analgesia and improved sleep patterns; however, it may increase the total amount of opioid delivered and significantly increases the risk of OIVI (Schug and Torrie, 1993; Macintyre and Coldrey, 2009).

It should be remembered that regular administration of immediate-release (IR) or slow-release (SR) opioids in addition to PCA is essentially the same as adding a background infusion, and the same care must be taken as the same risks exist.

While the routine use of a continuous infusion is therefore not recommended, it may be required in some opioid-naive patients and, more commonly, in those who are opioid tolerant (see Chapter 14).

There may be some benefit from using a continuous infusion in opioid-naive patients who have high opioid requirements or who complain of waking repeatedly in severe pain at night but cannot take oral opioids. While routine initial use of an infusion is not safe, its relative safety may be increased once a patient's PCA opioid requirements are known. One approach is to order a continuous infusion at an hourly rate that provides no more than 50% of a patient's known hourly opioid dose. So that PCA is still operating primarily in demand mode, it is also recommended that the dose delivered per hour does not exceed the size of the bolus dose. As daily opioid requirements often decrease rapidly, the need for the infusion, as well as the rate of infusion prescribed, should be reassessed frequently.

In patients who are opioid-tolerant, background infusions may sometimes be used in place of the patient's normal (preadmission) maintenance opioids (see Chapter 14).

8.3.6 Concentration

For consistency and safety, each institution should standardize the concentrations of drugs administered by PCA where possible. If the IV line becomes occluded and then the occlusion is relieved, it is recommended that the volume of fluid that collects in the tubing should not exceed 0.5 mL (ECRI, 2011). That is, the occlusion alarm should be activated after no more than 0.5 mL has been delivered from the PCA machine after the occlusion. Therefore, the drug concentration used should mean that the volume delivered following each demand should not be less than 0.5 mL. The smaller the volume of the bolus dose, the greater number of doses required to trigger the occlusion alarm if IV access becomes obstructed.

8.3.7 Dose limits

The ability to set dose limits (commonly 1 hour or 4 hours) is a feature of most electronic PCA pumps. The aim is to prevent the patient receiving more than a designated amount of opioid within a set time. However, large interpatient variations in opioid requirements make it impossible to predict the "safe" limit for each patient. In general, patients have not received an excessive dose if they remain unsedated.

There is no evidence of any benefit that can be attributed to the use of such dose limits (Macintyre and Coldrey, 2009). On the contrary, a limit could give

staff a false sense of security, as they may believe that the patient cannot receive an excessive dose of the drug. As with other features designed to increase patient safety with PCA, the setting of a dose limit cannot compensate for any shortcomings in monitoring.

8.4 Requirements for the safe management of PCA

In addition to the use of appropriate PCA pumps and prescriptions, patient safety with PCA depends on appropriate patient selection and education, adequate and ongoing training of nursing and medical staff, and suitable standard orders and nursing procedure protocols.

8.4.1 Suitable patient and patient education

The "suitable" patient is one who is happy to take some control of their pain relief, wants to use PCA, and can understand how it is to be used. The majority of patients appreciate the control that PCA gives them, the ability to rapidly titrate their own analgesia and balance acceptable pain relief with the severity of any side effects that may occur, and not having to wait for analgesic medications or bother nursing staff. However, some patients may not want this control and would prefer others to manage their pain relief.

Safety and efficacy of PCA require the patient to have an adequate understanding of the technique. Although very young and very old patients may be less likely to manage PCA successfully, PCA should not be withheld simply on these grounds. Similarly, patients should not automatically be excluded from consideration if there is mild cognitive impairment or a language barrier. Relatives, caretakers, or translators can be asked to assist and patient education leaflets can be written in many languages. If, despite these measures, staff feel that the patient still does not understand PCA, alternative methods of pain relief will be needed. The patients who have preoperative evidence of dementia are often not suitable for PCA and those who become confused may need to have PCA discontinued.

Some patients and/or their relatives may be concerned about the risk of overdose or addiction, or do not trust the PCA machine. Appropriate education, both prior to and during PCA use, will usually help overcome these fears. This education needs to include warnings about those other than the patient using the button.

For examples of patient education related to PCA, see Chapter 2.

8.4.2 Nursing and medical staff education

Effective and safe use of PCA requires medical and nursing staff with the appropriate training as operator error remains a common cause of complications (see Section 8.6.2.2). An inadequate understanding of PCA, the drugs and doses used, the monitoring requirements, and the management of common problems can, at worst, increase the risk of complications. At best, it can prove to be a very expensive way of providing suboptimal analgesia.

Nursing education and accreditation programs that have to be completed by each nurse before they can take responsibility for a patient with PCA are recommended. For more detail, see Chapter 2.

In many institutions the use of PCA is supervised by an acute pain service (APS).

8.4.3 Standard orders and nursing procedure protocols

To maximize the effectiveness of PCA, minimize the risk of complications and improve recognition and treatment of adverse effects, standard orders, and nursing procedure protocols are recommended. The aim is to try and improve the quality of clinical decision making rather than to dictate clinical practice.

8.4.3.1 Standard orders

To standardize orders throughout the institution, preprinted forms are suggested. An example of a preprinted PCA standard order form is given in Appendix 8.1. Common components of PCA standard orders are listed in Table 8.2 and include:

- Values to be set for all prescribed initial PCA variables as well as the opioid to be used
- Nondrug treatment orders and any monitoring and documentation requirements, which allows a regular assessment of the progress of each patient and for rational changes to be made to PCA orders so that treatment is individualized

Table 8.2 Key components of PCA standard orders

- The opioid to be used
- The values to be set for all prescribed initial PCA variables
  - See Table 8.1 for more detail
- Nondrug treatment orders including:
  - A statement to prevent the concurrent ordering of CNS depressants or other opioids by unauthorized medical staff
  - Orders for supplemental oxygen
  - The need for a one-way antireflux and antisiphon valves
  - Contact instructions if analgesia is inadequate or there are other problems related to PCA
  - The need to cease PCA should the patient become confused
- Monitoring and documentation requirements including:
  - Regular assessment of pain scores, functional activity scale (FAS) scores, sedation score, and respiratory rate at appropriate intervals
  - A record of the amount of PCA opioid delivered
  - Dose of any medication administered for the treatment of side effects
  - Any changes that have been made to the PCA program
  - The need to check the PCA program at regular intervals (e.g., at change of shift as well as when the drug reservoir is replaced)
- Guidelines for the management of inadequate analgesia
- Guidelines for the management of adverse effects
- The name and signature of the prescribing doctor
  - In many institutions, the authority to prescribe PCA is limited to designated staff

- Instructions for the management of inadequate analgesia as well as adverse effects
- Which doctors have the authority to prescribe PCA in a particular institution

8.4.3.2 Nursing procedure protocols

The format of nursing procedure protocols for PCA will vary with each institution, but key elements include:

- The institution's policy on accreditation (credentialing) of nursing staff
- The mechanisms for checking and discarding PCA opioids
- Monitoring and documentation requirements
- Instructions relating to operation of the PCA machine:
  - Checking the PCA settings against the prescription (e.g., each time the drug reservoir is changed and at the change of each shift)
  - Checking the amount of drug delivered (from the infusion pump display) against the amount remaining in the drug reservoir
  - The setting up and programming of PCA pumps
  - The use of antireflux and antisiphon valves
  - Management of equipment faults and alarms

8.5 Management of inadequate analgesia

Inadequate analgesia may occur for a number of reasons including inadequate loading dose, inappropriate patient use, presence of opioid-related side effects, and ineffective PCA prescriptions.

However, increasing pain, increasing analgesic requirements, or pain out of proportion to the procedure or number of days elapsed postinjury or postoperatively, requires a reassessment of the patient before any changes are made to the PCA program. There may be another cause for the pain, for example, the development of a complication (e.g., a compartment syndrome following limb injury or a leaking anastomosis following bowel surgery). Other analgesic medications might not have been ordered or given, or the pain may not be completely responsive to opioids, such as acute neuropathic pain (see Chapter 12). Preoperative anxiety, catastrophizing, neuroticism, and depression have also been shown to be associated with high pain scores (ANZCA and FPM, 2010).

Suggestions for the management of inadequate analgesia are summarized in Table 8.3.

8.5.1 Inadequate loading dose

Patients must be given an adequate loading dose before PCA is started. This is essential as trying to establish analgesia or to catch-up with inadequate analgesia is difficult or often impossible with PCA alone. If a patient is noted to have inadequate analgesia at any time during PCA treatment, "reloading" may be needed.

8.5.2 Inadequate bolus dose

Standard orders are designed for the "average" patient, and in some patients the usual incremental bolus dose may be suboptimal. If PCA does not seem to

Table 8.3 Management of inadequate analgesia

- Reassess the patient
  - Consider another cause for new or increased pain such as development of postsurgical or postinjury complication, which might require treatment
  - If the pain is poorly responsive to opioids (e.g., neuropathic pain) other treatment options may be required
  - Treat opioid-related side effects as needed
  - Ensure that the patient understands the principles of PCA
- Check that other components of multimodal analgesia (e.g., paracetamol, NSAIDs, gabapentinoids, or ketamine) have been given as indicated
- Give additional opioid to "reload" the patient if needed
- If the patient is receiving ≤2–3 bolus doses/h (average), reeducate the patient and encourage more frequent use of the demand button
- If the patient is receiving ≥3 bolus doses/h (average), the size of the bolus dose may need to be increased
- If the patient cannot use the hand-held demand button alternative demand mechanisms can be used if available—for example, pressure sensitive pad or foot pedal activated

Note: These strategies are suggestions only and may not be needed in, or be suitable for, the treatment of all patients.

be providing satisfactory analgesia it is worth looking at the number of doses the patient has received over the preceding few hours. If it is fewer than two or three doses per hour (on average), further instruction is probably needed and the patient should be encouraged to use PCA more often. On the other hand, a patient who is already receiving three or more doses each hour cannot always be expected to maintain or increase that demand rate and it may be reasonable to increase the size of the bolus dose by 50–100%.

8.5.2.1 "Successful" and "unsuccessful" demands

Many PCA machines are able to record the numbers of both "successful" (when a dose was delivered) and "unsuccessful" (when the button was pressed during the lockout interval) demands. Unfortunately, a high number of "unsuccessful" demands does not always reflect the need for more opioid and it should not be used as a guide to adjusting the size of the PCA bolus dose. Some patients, like some people waiting at elevators or traffic lights, will always press the button a number of times in rapid succession although they only want the result of a single press.

Anxiety and depression have also been shown to correlate with more demands, including more "unsuccessful" demands (Macintyre and Coldrey, 2009). High demand rates may also result from inappropriate patient or nonpatient use (see Section 8.6.2.3) as well as the onset of confusion; other explanations may be the use of a bolus dose that is too small or poor opioid responsiveness of the pain.

8.5.2.2 Side effects

Patients who are experiencing nausea or vomiting, or other side effects they perceive to be due to the opioid, may be reluctant to continue with PCA. Staff should

ensure that appropriate therapy for the treatment of side effects is given. If side effects persist, a change to another opioid (an opioid rotation) may be effective.

8.6 Complications of PCA

Complications of PCA are a significant source of preventable harm to the patient and may be related to the side effects of the drugs used, the equipment involved, or management by staff or patients.

8.6.1 Side effects related to the opioid

Opioid-related side effects may develop regardless of the route of administration of the drug (see Chapter 2) and there is no good evidence to suggest any major differences between the opioids commonly used with PCA (Hudcova et al., 2006; ANZCA and FPM, 2010).

Suggested options for the management of these side effects are the same as for opioid administration in general, outlined in Chapter 4 and summarized in Table 8.4. However, there are some additional points that are specifically relevant to PCA.

8.6.1.1 Opioid-induced ventilatory impairment

The best clinical indicator of early OIVI is increasing sedation (see Chapter 3). If a patient with PCA has a sedation score of 2 (easy to rouse but cannot stay awake) a reduction in the size of the PCA bolus dose (e.g., by 50%) is usually indicated. If the patient has a sedation score of 2 and a respiratory rate below 8 breaths per minute, the size of the bolus dose should also be reduced. Whether or not a small dose of naloxone (40–100 μg IV) is considered necessary in this instance may depend on factors such as staffing levels. If no nurse is available to keep a continued close watch on the patient (e.g., in an intensive care or post-anesthesia recovery unit), it may be safer to administer naloxone. Monitoring should revert to more frequent intervals for a period—for example, until the sedation score has been less than 2 for at least 2 hours.

If a patient develops severe OIVI with a sedation score of 3 (difficult to rouse or unrousable), naloxone should be given regardless of the patient's respiratory rate. Remember that naloxone has a shorter half-life than commonly used opioid agonists and repeated doses or an infusion may be needed.

8.6.1.2 Confusion

Opioids will not usually be the cause, or the sole cause, of confusion. Other possible causes include hypoxemia, sepsis, other drugs (particularly those with anticholinergic side effects), and alcohol or drug withdrawal (see Chapter 14). Nevertheless, PCA may need to be discontinued as the patient may press the demand button inappropriately. Alternative methods of pain relief should be organized.

8.6.1.3 Nausea and vomiting

If nausea or vomiting occurs, an appropriate antiemetic should be given or, if that antiemetic appears to be ineffective, an alternative given. Patients who

Table 8.4 Management of side effects of PCA opioids

Nausea/vomiting	Administer antiemetics and add additional antiemetics if ineffective
	If nausea seems related to the PCA demand, try decreasing size of the bolus dose (if requirements are low) or increasing the "dose duration"
	Consider other possible causes (e.g., ileus)
	Change to another opioid
Pruritus	Check that pruritus is likely to be opioid-related
	Consider a change to another opioid
	While naloxone may relieve the pruritus, it may also reverse analgesia, especially if given in repeated doses
	Antihistamines may not be effective as the pruritus is thought to result from an action on opioid receptors rather than histamine release (see Chapter 4) and may increase the risk of sedation; if an antihistamine is thought to be indicated, the least sedating preparation available should be chosen
Sedation/opioid-induced ventilatory impairment	Check no other reason for sedation (e.g., administration of a sedative)
	Sedation score = 2, halve the bolus dose, cease any background infusion
	Sedation score = 2, respiratory rate ≤7/min, halve the bolus dose, cease any background infusion; close supervision of the patient, consider naloxone
	Sedation score = 3 (regardless of respiratory rate), attempt to wake patient with both verbal and/or physical stimulation, provide close observation, give naloxone 40–100 μg IV and repeat 2 minutely prn, cease PCA until patient is more awake, restart at half the dose
	In all cases, revert to more frequent monitoring of sedation scores
Urinary retention	Catheterize
Confusion	Probably not related to the PCA opioid; look for other possible causes (e.g., hypoxia, sepsis, alcohol, or benzodiazepine withdrawal)
	Consider a change to another opioid
	PCA may need to be stopped and alternative analgesia organized
Decreased bowel motility/ colicky pain	Anticipatory treatment where possible
	Discourage use of PCA to cover discomfort resulting from resumption of peristalsis; if pain becomes severe, consider bowel obstruction
Hypotension	Look for hypovolemia and other causes of hypotension

Note: These strategies are suggestions only and may not be needed in, or be suitable for, the treatment of all patients.

complain of a wave of nausea or dizziness a few minutes after pressing the demand button may benefit from a smaller bolus dose (especially if their opioid requirements are small) or a slower rate of infusion of the bolus dose (i.e., an increase in the "dose duration"). If these actions fail, a transition to another opioid can be tried.

8.6.1.4 Masking of postoperative or postinjury complications

Concerns have been expressed about the risk of PCA "masking" signs of a postsurgical or postinjury complication (e.g., urinary retention, compartment syndrome, myocardial infarction, and pulmonary embolus) and that patients will simply increase their PCA use to treat any "new" pain without informing nursing or medical staff, resulting in a delay in diagnosis (ANZCA and FPM, 2010).

If the patient is monitored carefully and proper attention paid to changes in pain scores and analgesic consumption, the risk of this occurring should be very low. Any unexpected increase in analgesic use or pain scores, or the site, severity or character of the pain being treated, warrants careful assessment and investigation, as it may signal the development of a new surgical or medical diagnosis. Any adjustment to the PCA program should be made bearing the potential underlying problem in mind.

8.6.2 Complications related to equipment or human factors

Complications related to PCA can also arise as a result of equipment and human (staff/operator or patient) factors.

8.6.2.1 Equipment malfunction

In general, modern PCA pumps are very reliable and if there is a machine malfunction, it will usually "fail-safe." Equipment malfunctions that have been reported in the past include spontaneous triggering, cracks in drug cartridges and syringes and malfunctions of the device hardware or software (Schein et al., 2009).

8.6.2.2 Operator-related errors

Operator error remains a leading cause of complications associated with PCA. Examples include (Macintyre and Coldrey, 2009; Schein et al., 2009):

- Mistakes in programming the PCA pump (e.g., incorrect bolus dose, concentration, or background infusion); these form the majority of operator-related errors
- Loading the wrong drug or wrong concentration of a drug
- Incorrect use of (or failure to use) antireflux or antisiphon one-way valves
- Administration of sedative medications, or supplementary opioids by other routes
- Errors in PCA prescriptions including incorrect dose, poor medication choice (e.g., morphine in patients with renal impairment, known patient allergy to the drug).

8.6.2.3 Patient-related errors

Patient-related errors leading to OIVI can result from a failure to adequately comprehend the PCA technique. Examples include pushing the demand button every time the lockout interval ends, or mistaking the button for a nurse-call button. Complications have also been reported following unauthorized activation of PCA by someone other than the patient ("PCA by proxy") including

well-meaning relatives or friends of the patient and hospital staff (ANZCA and FPM, 2010). If a patient using PCA is sedated but there is evidence of ongoing PCA demands, "PCA by proxy" should be excluded.

The ability for patients to tamper with and access the PCA opioid is less with the modern devices. However, care must be taken with pumps that require an access code as it might be easy for some patients to witness the code being entered.

8.7 "Step-down" analgesia

The importance of appropriate "step-down" analgesia (i.e., analgesia that a patient is prescribed after PCA has been stopped) needs to be acknowledged. There is little point in trying to maximize patient comfort with PCA and then leaving them in significant discomfort when PCA is stopped, simply because adequate attention has not been paid to the subsequent pain relief regimen.

Opioid requirements during PCA can be used as a guide to the appropriate "step-down" opioid regimen. In general, PCA is usually continued at least until oral opioids can be used and once the patient is tolerating oral fluids, oral opioids can be ordered.

There should be some overlap of pain therapies so that the subsequent regimen has time to have an effect before PCA is stopped. If there is to be a change in clinician responsibility for the pain management of the patient, then this change needs to be clearly documented and understood by all staff.

8.7.1 Oral opioids

Any of the oral opioids suitable for the management of acute pain may be used following PCA (see Chapter 4). The oral dose can be based on the amount of IV opioid used in the 24 hours prior to stopping PCA and the equianalgesic doses of PCA and oral opioids.

As intensity of acute pain usually decreases daily, it is likely that the patient will require less opioid than would be expected based solely on equianalgesic doses. The oral regimen therefore needs to accommodate this expected decrease in dose requirement.

8.8 Alternative systemic routes of PCA administration

Although not as common, SC PCA can be used as an alternative to IV PCA. Devices have been developed or adapted in order to allow oral, intranasal (IN), sublingual, and transdermal opioid PCA.

8.8.1 Subcutaneous PCA

A number of opioids have been administered by SC PCA. Evidence comparing pain relief achieved and side effects with IV and SC PCA are conflicting (ANZCA and FPM, 2010). However, while onset of analgesia will be slower with SC PCA, it may be a useful route of administration if another drug that is incompatible with the opioid is running in the primary IV line or if there is no IV access (even temporarily).

The same drug and same drug concentration as for IV-PCA can be used, but the following changes to the PCA program are suggested:

- Double the bolus dose
- Double the lockout period to 10 minutes
- Where possible, increase the dose duration to 5 minutes

8.8.2 Transmucosal PCA

A number of different IN opioids have been administered in metered (fixed) doses which can be "patient-controlled," the most common being fentanyl. Each dose should be less than 200 μL in volume (see Chapter 7). IN PCA may be as effective as IV PCA in some circumstances (ANZCA and FPM, 2010). Issues around easy and unauthorized access to the opioid reservoir remain.

Sublingual sufentanil administration using a portable electronic dispenser is being investigated for the treatment of postoperative pain as an alternate to IV PCA (Minkowitz et al., 2013).

It is possible that, as with other fixed-dose systems, adequate analgesia in patients with high opioid requirements may be more difficult to achieve.

8.8.3 Transdermal PCA

An iontophoretic patient-controlled transdermal delivery systems for fentanyl was introduced into practice but later withdrawn following reports of technical problems (ANZCA and FPM, 2010). It has undergone further work and may be remarketed. As with all disposable PCA devices, the size of the bolus dose of fentanyl will be fixed. Safe use and disposal of the patch will be important.

8.8.4 Epidural and other regional PCA

Epidural and other regional analgesia route can also be used with PCA. For further details see Chapters 9 and 10.

Key points

1. IV PCA provides better analgesia than conventional parenteral opioid regimens and is preferred by patients.
2. There is little difference between the different opioids used with PCA in terms of analgesic or adverse effects but some patients may tolerate one opioid better than another.
3. Initial orders for PCA bolus doses should take into account individual patient factors such as a history of prior opioid use and patient age but they should then be adjusted to suit each patient as required.
4. The routine use of a background infusion with IV PCA in opioid-naive patients does not improve pain relief or sleep but does increase the risk of OIVI.
5. Patients should be comfortable before PCA is commenced; this may require individualized loading doses.

6. Patient safety with PCA depends on appropriate patient selection and education, adequate and ongoing training of nursing and medical staff, and suitable standard orders and nursing procedure protocols.
7. Complications related to PCA can arise as a result of equipment and human (operator or patient) factors as well as the drugs used; operator error remains a leading cause of complications.

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Appendix 8.1: Example of a "standard order" form for PCA

CALHN
RAH ☐ TQEH ☐

ACUTE PAIN SERVICE

PATIENT-CONTROLLED ANALGESIA (PCA)

PATIENT LABEL

Unit Record No.: _____

Surname: _____

Given Names: _____

Date of Birth: _____ Sex: _____

PCA PROGRAM ORDERS:

1. **DRUG:** .....

Place appropriate drug label here

2. **CONCENTRATION:** ...../mL
3. **LOADING DOSE:** 0 (zero)
4. **PCA BOLUS DOSE:** (Order as mg or microgram)

Initial bolus dose:

.....

If pain not controlled bolus dose may increase to:

.....

Subsequent bolus doses: (must be signed and dated)

.....

.....

.....

5. **DOSE DURATION:** 'stat'
6. **LOCKOUT PERIOD:** 5 minutes
7. **CONTINUOUS (BACKGROUND) INFUSION:**

..... hr (..... mL/hr)

ROUTE (if other than IV): .....

The patient's regular long-acting opioids should be continued: YES NO

Signature ..... Date .....

GENERAL ORDERS:

1. Oxygen at *2 to 4 L/min via nasal specs or 6 L/min via mask* while orders are in effect.
2. No systemic opioids or sedatives (including antihistamines) to be given except as ordered or approved by the APS.
3. Naloxone to be immediately available.
4. One-way anti-reflux valve to be used in IV line and an anti-syphon valve must be in-line between patient and PCA machine at all times.
5. *Monitoring requirements:* see overleaf.
6. Cease PCA if the patient becomes confused. Maintain oxygen therapy and notify the APS.
7. For inadequate analgesia or other problems related to the analgesia, contact the APS. The APS should be notified if the patient has two consecutive pain scores >7 at rest and/or FAS = C.
8. If respiratory rate is 8-10/min, no action is required as long as sedation score is < 2. If respiratory rate is ≤ 7/min and sedation score is < 2, notify the APS. If sedation score is 2 or 3, follow instructions below.

TREATMENT OF SIDE EFFECTS:

RESPIRATORY DEPRESSION (EXCESSIVE SEDATION):

1. If sedation score = 2, reduce size of the bolus dose by half and cease any background infusion. Notify the APS. Revert to hourly sedation scores until sedation score < 2 for at least 2 hours.
2. If sedation score = 3 (irrespective of respiratory rate) OR sedation score = 2 and respiratory rate ≤ 7/min, initiate a MER call and give 100 microgram NALOXONE IV stat. Repeat 2 minutely PRN up to a total of 400 microgram. Cease PCA and call the APS anaesthetist. Revert to hourly sedation scores until sedation score < 2 for at least 2 hours.

NAUSEA AND VOMITING: (Note: check for duplicate antiemetic orders on the NIMC)

1. Give a 5-HT3 antagonist antiemetic: Drug: .....
   Dose: ..... Route: IV Frequency: ..... PRN
2. If ineffective after 15 minutes, add DROPERIDOL 500 microgram IV 4 hourly PRN (250 microgram if > 70 years).
3. If patient not responding to antiemetics contact the APS.

ITCHING:

1. If severe, or patient complains or requests treatment, contact the APS.

SIGNATURE OF ANAESTHETIST: ..... Date: .....

(Print name .....)

Cease above orders:

Signature of anaesthetist: ..... Date: ..... Time: .....

APS-PATIENT CONTROLLED ANALGESIA **MR 98.2**

CALHN

PATIENT-CONTROLLED ANALGESIA (PCA)

Observations and Record of Drug Administration

PATIENT LABEL

Unit Record No.: _____

Surname: _____

Given Names: _____

Date of Birth: _____ Sex: _____

MONITORING REQUIREMENTS: **Record items 1 to 4 EACH HOUR for 8 hours and then 2 HOURLY**

1. PAIN SCORES AND FAS **2. SEDATION SCORE** **3. RESPIRATORY RATE** **4. CURRENT TOTAL DOSE**

Pain Score:	**Sedation Score:**	**Functional Activity Score (FAS):**
0 = no pain 10 = worst pain imaginable *NB: record pain scores at rest and with movement eg. coughing*	0 = wide awake 1 = easy to rouse 2 = easy to rouse but cannot stay awake 3 = difficult to rouse (severe respiratory depression)	A = no limitation of relevant activity due to pain (relative to baseline) B = mild limitation of activity due to pain C = unable to complete activity due to pain

Current total dose: Record in mg or microgram as appropriate and not in mL. Reset total dose to zero when syringe is changed and document the volume discarded.

DRUG: .....

Date	Time	Dose	Pain Scores ..... X 0 2 4 6 8 10	FAS	Sed'n Score	Resp Rate	Comments	Signature RN or MO
			0 2 4 6 8 10					

ADVERSE DRUG REACTIONS			
Drug	Date	Details	Signature

DRUG:.....

Date	Time	Dose	Pain Scores ..... X 0 2 4 6 8 10	FAS	Sed'n Score	Resp Rate	Comments	Signature RN or MO
			0 2 4 6 8 10					

CHAPTER 9

Epidural and intrathecal analgesia

Epidural analgesia is one of the most effective methods available for the management of acute pain after major surgery, and has consistently been shown to provide better pain relief than parenteral opioid administration (ANZCA and FPM, 2010).

When local anesthetics are used, with or without opioid, this technique is of particular benefit for the treatment of pain associated with activity, such as coughing or walking, and in improving patient outcomes (Manion and Brennan, 2011). Epidural analgesia provided by local anesthetics, with or without the addition of a small amount of opioid, may lead to a reduction in postoperative complications (particularly respiratory, cardiac, and gastrointestinal) and possibly mortality (Popping et al., 2014). The technique is also commonly part of "fast-track" or "enhanced recovery after surgery" (ERAS) protocols for colorectal surgery, where good pain relief combined with early mobilization, enteral feeding, and an aggressive rehabilitation program, have been shown to reduce duration of hospital stay and the incidence of complications (Lv et al., 2012). This combined analgesia–rehabilitation approach is also used in ERAS protocols for a number of different operations. Excellent guidelines and resources for this approach are offered by the ERAS Society at http://www.erassociety.org.

However, epidural analgesia is also associated with a number of uncommon but significant complications (discussed later), so potential risks must always be weighed against possible advantages for each patient.

Epidural analgesia will commonly be initiated and managed by an anesthesiologist. If it is to be used after spinal surgery, the surgeon may place the epidural catheter at the end of the operation. To reduce the risk of possible complications, all medical and nursing staff involved must have a good understanding of this form of pain relief.

Patients with epidural and intrathecal analgesia do not need to be nursed in a high-dependency or intensive care setting unless this is indicated for other reasons such as the type of surgery or patient comorbidities. They can be safely managed on general hospital wards if certain prerequisites are fulfilled (ANZCA and FPM, 2010). These include:

- Appropriate patient selection criteria
- Appropriate standard orders and procedure protocols for doctors and nurses
- Nursing education and accreditation programs specific to epidural and intrathecal analgesia
- Regular review of the patient by an anesthesiologist
- Availability of an anesthesiologist at all times for consultation or management of complications or inadequate pain relief
- Agreement to delegate all responsibility for pain relief to one group of specialist medical staff (anesthesiologists) with consultation of this group by other medical personnel as required

9.1 Anatomy

The spinal cord and brain are covered by three membranes, the meninges. The outer membrane is called the dura mater. The middle layer, the arachnoid, lies directly below the dura and both jointly form the dural sac. The inner layer, the pia mater, adheres to the surface of the spinal cord and brain. The *epidural space* lies outside the dura mater and is limited by the bones and ligaments of the spinal canal (Figure 9.1). It is a potential space filled primarily with fat and connective tissue, but it also contains blood vessels and is traversed by nerve roots. Inside the dural sac, which extends down to S2 beyond the arachnoid membrane, is the subarachnoid or *intrathecal space* containing cerebrospinal fluid (CSF). It contains the spinal cord above the level of L1–2 and the cauda equina, comprising lumbar and sacral nerve roots, below L1–2.

To obtain *epidural analgesia*, analgesic drugs are administered directly into the epidural space. This can be done through a needle ("single shot") or, more commonly, an epidural catheter is placed to enable repeated doses or an infusion. Epidural local anesthetics gain access primarily to nerve roots, but also the spinal cord, by crossing the dura and subarachnoid membranes (Schug et al., 2006). This results in segmental anesthesia or analgesia (i.e., a band-like distribution of variable width depending on the volume given). Opioids and other adjuvant analgesic drugs administered into the epidural space produce analgesia only via effects on the spinal cord (Bujedo et al., 2012). However, a proportion of all the drugs is also absorbed into the epidural blood vessels and thereby enters the circulation, where it may cause systemic effects.

The doses of drugs administered directly into the CSF and used for *intrathecal analgesia* are much smaller than those required for epidural analgesia. Intrathecal analgesia for the management of acute pain more commonly involves

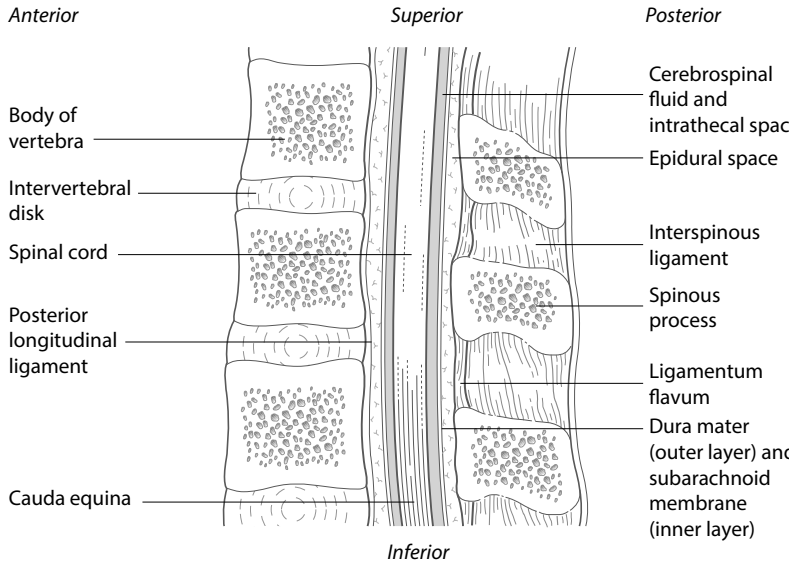

Figure 9.1 Anatomy of the spinal cord.

administration of opioids alone, usually given as a single dose through a spinal needle at the time of spinal anesthesia (Bujedo et al., 2012). The opioid is delivered directly into the CSF, avoiding absorption by epidural fat and blood vessels. However, rostral (upwards) migration in the CSF will occur, particularly with less lipid-soluble opioids such as morphine. This may result in effects at higher levels of the spinal cord and even the brain.

9.2 Contraindications

The contraindications to epidural and intrathecal analgesia are summarized in Table 9.1.

9.2.1 Untrained nursing and medical staff

Epidural and intrathecal analgesia carry specific risks and should only be used in hospital wards where staff have received appropriate training in these methods of pain relief (ANZCA and FPM, 2010). Staff need to have a good understanding of the principles of the techniques, the monitoring requirements and adverse effects, and be able to recognize and treat (according to written orders) these and inadequate analgesia. Many institutions require some form of accreditation before nurses are allowed to take responsibility for patients with epidural or intrathecal analgesia. In addition, these methods of pain relief require at least daily review by and on-site availability of an anesthesiologist.

9.2.2 Patient rejection

For many reasons patients may refuse epidural analgesia. For example, they may have heard of possible complications, either from friends or relatives, or from the media including the Internet. A full explanation needs to be given to each patient and the risks and possible benefits explained, but this cannot always overcome rejection of the technique.

Table 9.1 Absolute or relative contraindications to epidural and intrathecal analgesia

Untrained staff

Patient rejection

Contraindications to catheter or needle placement

- Local or generalized sepsis
- Large infected soft-tissue injuries
- Some central or spinal neurological diseases
- Hypovolemia
- Coagulation disorders
- Concurrent treatment with anticoagulant medications

Presence of a dural puncture

9.2.3 Contraindications to the placement of an epidural needle or catheter

There are a number of reasons why placement of an epidural needle or catheter might be contraindicated, or at least relatively contraindicated (i.e., potential benefits of placement may outweigh the risk).

9.2.3.1 Local and systemic infection

Epidural needles and catheters should never be placed at the site of a local infection. Generalized sepsis and large infected soft-tissue injuries (which could result in bacteremia) may increase the risk of an epidural space infection, and placement of an epidural catheter in such patients remains controversial (Horlocker and Wedel, 2008). If the patient is receiving appropriate antibiotic cover and if the risk–benefit ratio has been considered, it may be appropriate in selected patients. The risk of performing epidural blockade in patients with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS) is unknown, as is the risk of blood patch for the treatment of postdural puncture headache in these patients.

9.2.3.2 Central nervous system disease

The decision to proceed with epidural analgesia in patients with diseases such as multiple sclerosis should be made on a case-by-case basis after an assessment of risks and benefits. One of the potential issues is that any exacerbation of the disease is likely to be blamed on the analgesic technique, whereas disease progression may have been coincidental. However, there is no good evidence that use of epidural techniques in these patients carries a specific risk.

9.2.3.3 Hypovolemia

Epidural local anesthetics block the sympathetic nervous system. The resultant vasodilatation may unmask hypovolemia (a low blood volume), leading to or at least contributing to hypotension, as the normal response to hypovolemia is peripheral vasoconstriction. This can be partially avoided by slow titration of local anesthetics. The more dilute local anesthetic solutions commonly used to provide analgesia may be less likely to contribute to hypotension. Treatment of hypovolemia with intravenous fluids is recommended as well as appropriate use of vasoconstrictors to maintain blood pressure.

9.2.3.4 Coagulation disorders or concurrent treatment with anticoagulant or antiplatelet medications

The risk of epidural hematoma must be always considered along with the potential benefits of epidural analgesia for each patient. In general, insertion of epidural or intrathecal needles and catheters should be avoided in patients with coagulation disorders or in those who are fully anticoagulated (Horlocker, 2011). However, when necessary, thromboprophylaxis (drugs given to prevent deep-vein thrombosis) can be instituted after the epidural catheter has been inserted and fixed in place.

More details about epidural analgesia and the concurrent use of anticoagulant medications are given later in Section 9.9 of this chapter.

9.2.3.5 Presence of a dural puncture

If the dura has been punctured, either inadvertently during insertion of an epidural needle or catheter, or during spinal surgery, part of any drug injected into the epidural space may theoretically gain direct access to the CSF. The patient must be observed more closely than usual if a decision is made to proceed with epidural analgesia, although the incidence of complications arising from this appears to be rare.

9.3 Drugs used with epidural analgesia

Opioids and local anesthetics are the two classes of drugs most frequently used for epidural analgesia, most often in combination. They can be given as single or repeated bolus doses or, more commonly, by continuous infusion. The doses and infusion rates suggested later are guidelines only and may vary according to patient age, medical condition, site of injection, and other factors.

To improve both the quality and duration of analgesia, clonidine (an α_2-adrenergic agonist) or epinephrine (adrenaline) are sometimes added to local anesthetic or opioid solutions. The epidural use of other drugs for acute pain management (e.g., neostigmine and ketamine) still requires further investigation before they can be introduced into routine clinical practice. This is particularly important as epidural administration carries the risk of neurotoxicity. Therefore, all drugs administered in the epidural space should have been tested appropriately for neurotoxicity and should be preservative-free (Hodgson et al., 1999). Furthermore, regulatory approval for the epidural administration of drugs varies between countries and depends on the neurotoxicity studies required, commercial interests of the pharmaceutical industry and varying availability of different drug preparations.

9.3.1 Local anesthetic drugs

9.3.1.1 Site of action

Local anesthetics given epidurally act mainly on nerve roots crossing the epidural space, by diffusion through the dura and subarachnoid membranes which cover them (Schug et al., 2006). Part of any given dose will also act on the spinal cord and be absorbed into epidural blood vessels and thereby the systemic circulation. As with all other local anesthetic use, high doses can carry the risk of systemic toxicity.

The effect on nerve roots in the vicinity of the orifice of the epidural catheter explains the band-like distribution of the block. Therefore, the level of insertion of the epidural catheter—near the middle of the dermatomal segments to be covered—is of particular importance when local anesthetics are used.

9.3.1.2 Doses

Local anesthetics used to provide epidural *analgesia* (e.g., 0.0625–0.25% bupivacaine or levobupivacaine; 0.1–0.2% ropivacaine) are administered in lower concentrations than those commonly used for epidural *anesthesia* (e.g., 0.25–0.5% bupivacaine or levobupivacaine; 0.5–0.75% ropivacaine). In acute pain management, combinations of local anesthetic and opioid are more commonly used than infusions of local anesthetic alone. The suggested infusion rates are similar for both local anesthetics and for local anesthetic–opioid combinations (see Table 9.2).

Table 9.2 Suggestions for initial infusion rates and bolus doses using 0.0625–0.125% bupivacaine/levobupivacaine or 0.1–0.2% ropivacaine with or without 2–5 μg/mL fentanyl

	Younger patients older patients (up to 40 years)	To	Older patients (>70 years)
Infusion rate (mL/h)	8–15	To	4–10
PRN bolus doses (mL)	4–8	To	2–4

- These doses may also vary according to other factors such as site of catheter placement and height of patient
- Thoracic epidural infusions may require slightly smaller volumes than lumbar epidural infusions
- Lower infusion rates are needed if higher concentrations of local anesthetic drugs are used
- Lower infusion rates (e.g., upper limit of 8 mL/h or less) are suggested in the older patient if the higher concentrations of opioid are used (e.g., 5 μg/mL fentanyl)

Smaller bolus doses and lower infusion rates are suggested in older patients because the volume of the epidural space decreases as people age—see Chapter 14. However, optimization of epidural analgesia requires individual titration of infusion rate to effect and adverse effects in all patients.

9.3.1.3 Side effects

Systemic local anesthetic toxicity may follow epidural administration of local anesthetics if accidental intravascular injection occurs or an inadvertent overdose is given (for details refer to Chapter 5).

Blockade of autonomic and motor fibers as well as sensory nerves may result in the other side effects discussed below. An even more extreme side effect is the so-called "total spinal anesthesia," which is due to inadvertent intrathecal administration of much larger doses that were intended for injection into the epidural space. Unconsciousness and cardiovascular collapse will occur rapidly and require immediate and appropriate resuscitation.

9.3.1.3.1 Respiratory system

The diaphragm is the most important respiratory muscle. As it is innervated by the cervical nerve roots 3–5 (C3–5), it is unlikely that the usual volumes and concentrations of local anesthetics used for epidural anesthesia and analgesia will achieve such a high block. However, even a dense motor block of the intercostal muscles can reduce a patient's ability to take a deep breath and cough. This is unlikely to have clinical relevance in the setting of epidural *analgesia*, as the low concentrations of local anesthetic normally used for the management of acute pain will only result in a minimal degree of motor block, if any.

Improved respiratory function is an important advantage of epidural analgesia (Popping et al., 2008).

9.3.1.3.2 Cardiovascular system

Sympathetic block can lead to hypotension—even more so if the patient is hypovolemic as outlined above. Higher total doses (high volumes and/or high concentrations of local anesthetic) lead to a more dense block and/or greater number of segments blocked and therefore a greater chance of hypotension.

In the low concentrations normally used for pain relief on general wards, significant hypotension due only to the local anesthetic is unlikely (Freise and Van Aken, 2011). However, even partial sympathetic blockade prevents compensatory mechanisms from being fully effective and may therefore unmask hypovolemia. For this reason, postural or orthostatic hypotension may also occur.

If hypotension occurs in the presence of hypovolemia, it will normally respond to and is best treated with intravenous fluid administration. However, vasopressors (such as ephedrine or metaraminol) may be required in some patients. Therefore, appropriate vasopressors should be available in all wards where epidural local anesthetics are used. In some situations, in particular to avoid giving large amounts of intravenous fluids to a patient who is hypotensive but normovolemic, a low-dose infusion of such a vasopressor may be necessary. As most hospitals have no protocols for the use of these infusions in a general ward setting, transfer to a monitored environment is preferred.

If a relatively dense epidural block extends above T4 (nipple line), the sympathetic fibers to the heart may be blocked, resulting in relative bradycardia. This can be beneficial, particularly in patients with coronary artery disease, and is one reason that a high thoracic block may reduce the incidence of perioperative myocardial infarction. If the bradycardia has hemodynamic consequences requiring treatment, it may respond to atropine. In more severe bradycardia combined with hypotension, titration of low doses of epinephrine may be required.

9.3.1.3.3 Sedation

One of the big advantages of epidural analgesia using local anesthetics only is pain relief without sedation. Sedation will only be seen if the local anesthetic doses given are so excessive that systemic toxicity develops (see Chapter 5).

9.3.1.3.4 Nausea, vomiting, and pruritus

Lower rates of nausea, vomiting, and pruritus compared with epidural or parenteral opioids are another advantage of epidural local anesthetics.

9.3.1.3.5 Motor/sensory block

As early and comfortable mobilization is a desirable outcome of postoperative analgesia, low concentrations of a local anesthetic drug are used in an attempt to preferentially block smaller sensory fibers (i.e., providing analgesia) while avoiding a block of the larger motor fibers (*differential block*: see Chapter 5). Motor blockade leading to difficulties with walking is much less likely to occur with thoracic epidural blockade (e.g., after thoracic or abdominal surgery) compared with lumbar placement of the catheter (e.g., after orthopedic surgery) (Freise and Van Aken, 2011).

Commonly, infusions of low concentrations of local anesthetics with an opioid are used. This permits effective analgesia with minimum motor or sensory block. If a patient complains of numbness or weakness, the infusion can be stopped for a short while and then restarted at a lower rate. If the problem persists, the concentration of the local anesthetic drug may need to be reduced. It should be noted that numbness and weakness may be the first signs of catheter migration into the intrathecal space, epidural abscess, or epidural hematoma (see later) and these causes need to be excluded immediately.

Patients receiving epidural infusions of a local anesthetic (or local anesthetic and opioid) should be able to sit out of bed and even walk, in particular with

thoracic catheter placement. Mobilization should be approached slowly and with assistance given to the patient because of the potential issues of leg weakness, loss of position sense, and/or postural hypotension.

Pressure areas have been reported rarely following epidural analgesia, presumably due to a combination of decreased mobility combined with decreased sensation. As with all patients, appropriate pressure area care should minimize this risk.

There is an ongoing debate about the risk of epidural analgesia (and other good analgesic techniques such as patient-controlled analgesia [PCA]) potentially masking the early signs and symptoms of surgical complications such as compartment syndrome after orthopedic surgery (Mar et al., 2009). However, the pain that results from compartment syndrome is usually so severe that it will "break through" the analgesia provided by low doses of local anesthetics. The literature reveals no convincing evidence that good analgesic techniques delay the diagnosis of compartment syndrome or other postoperative complications. Nevertheless, patients at risk require regular and adequate monitoring. Any unexplained increase in pain must be treated with a high index of clinical suspicion until compartment syndrome or other complications have been excluded, preferably in consultation with the surgical team.

9.3.1.3.6 Urinary retention

Urinary retention can occur, but is not inevitable with low concentrations of local anesthetics, and patients do not require routine prophylactic catheterization.

9.3.1.3.7 Gastrointestinal system

The sympathetic blockade that results from epidural administration of local anesthetics improves bowel motility. The quicker recovery of gastrointestinal function after abdominal surgery and the reduction of nausea and vomiting permit earlier enteral feeding. The benefit is seen in patients with thoracic epidural catheters placed for analgesia, rather than those with lumbar catheters (Freise and Van Aken, 2011).

Initial concerns about an increased risk of anastomotic breakdown due to increased intestinal motility appear to be unfounded. Thoracic epidural analgesia using local anesthetic drugs does not increase the risk of an anastomotic leak in patients who have had a bowel resection (Lai et al., 2013). Earlier recovery of bowel motility is also seen when very low doses of opioids are added to the local anesthetic solution, but not with epidural opioids alone.

9.3.2 Opioids

Epidural opioids can provide good analgesia (Bujedo et al., 2012). However, most of the outcome improvements attributed to epidural analgesia are the result of the sympathetic blockade caused by local anesthetics and cannot be achieved by opioids alone. Nevertheless, combining low doses of opioids with low doses of local anesthetics maintains the benefits of the local anesthetic use and improves analgesia. This approach has become the standard technique worldwide.

9.3.2.1 Site of action

The analgesic effect of epidural and intrathecal opioids is primarily mediated by their binding to opioid receptors in the dorsal horn of the spinal cord after they

cross the dura and arachnoid membranes (Bujedo et al., 2012). However, binding at other sites also contributes to this effect, as a portion of the epidural opioid circulates with the CSF and can reach higher centers by rostral (toward the head) spread. Some is absorbed into epidural blood vessels, enters the systemic circulation and reaches opioid receptors in the brain, contributing to both analgesia and the development of opioid-related side effects.

From the CSF a proportion of drug is taken up into the spinal cord. However, flow of CSF in a rostral direction means that any drug remaining in the CSF will be carried to opioid receptors some distance from the site of injection, including in the brain stem. This implies that opioids can reach the respiratory center; therefore, depression of this center may occur as well as other side effects of opioids such as nausea, vomiting, and pruritus.

Lipid solubility explains the major differences that are seen between the opioids used in epidural analgesia (Schug et al., 2006). This physicochemical property of the opioid influences the time to onset of effect, duration of effect, and side-effect profile.

Less lipid-soluble drugs (e.g., morphine, hydromorphone) take longer to cross from the epidural space to the CSF and have a slower onset of action. However, they are also cleared more slowly from the CSF and therefore have a longer duration of action and are more likely to spread rostrally, with an increased risk of respiratory center depression.

The more lipid-soluble drugs (e.g., fentanyl) cross the dura quickly and have a more rapid onset but also a much shorter duration of action. Their analgesic effect is more segmental (i.e., confined within a dermatomal band around the level of the injection) because they are cleared more rapidly from the CSF to the spinal cord, and so a smaller proportion of the dose is available to spread to higher levels. The positioning of the epidural catheter is therefore as important for lipid-soluble opioids as it is for local anesthetics. Lipid-soluble opioids (e.g., fentanyl, sufentanil) are subject to greater vascular uptake from the epidural space, resulting in higher plasma levels of the drug and more pronounced systemic effects compared with opioids like morphine.

9.3.2.2 Doses

In general, the analgesic efficacy of opioids is greater when given epidurally compared with parenteral administration and a smaller dose is needed in order to achieve the same or better degree of pain relief. However, this depends again on the lipid solubility of the individual drug. Morphine, being the least lipid-soluble opioid used in epidural analgesia, shows the greatest difference in dose required by these and other routes to produce a similar analgesic effect (Table 9.3). With highly lipid-soluble drugs such as fentanyl, these differences become nearly irrelevant, except with very low doses.

Table 9.3 Approximate equianalgesic doses of morphine according to route of administration

Oral	30 mg
Intramuscular	10 mg
Epidural	2–3 mg
Intrathecal	0.2–0.3 mg

Longer-acting opioids may be administered by intermittent bolus doses as well as by infusion. Highly lipid-soluble opioids (e.g., fentanyl and sufentanil) require a continuous infusion because of their short duration of action. The use of bolus doses of lipid-soluble opioids can be useful in the event of breakthrough pain in a patient receiving epidural morphine due to their faster onset of action.

The total dose of opioid administered into the epidural space is the primary determinant of analgesic activity, but the volume in which the dose is given influences the spread of the dose (Bujedo et al., 2012). This is particularly so for more lipid-soluble opioids.

As with any opioid administered by any route, older patients are more sensitive to the CNS effects of epidural opioids (see Chapter 14) and so the initial dose should be based on the age of the patient and subsequent doses titrated to effect.

Morphine is the most commonly used opioid when administered alone for epidural analgesia. Suggested initial doses via lumbar catheters for nonthoracic surgery or via thoracic catheters for thoracic surgery range from 4 mg in patients less than 45 years of age to 1 mg in patients over 75 years.

An extended-release formulation of morphine for epidural use is also available. It has a higher risk of opioid-induced ventilatory impairment (OIVI) than the conventional morphine used for epidural or systemic analgesia (Sumida et al., 2009; ANZCA and FPM, 2010). While a single dose can provide analgesia for up to 48 hours, it cannot be given in conjunction with local anesthetics (other than a small test dose of local anesthetic given at least 15 minutes earlier) as this can cause early release of the morphine (Atkinson Ralls et al., 2011).

9.3.2.3 Side effects

9.3.2.3.1 Respiratory system

Opioid-induced ventilatory impairment is a potential complication of epidural opioids (Bujedo et al., 2012). The lipid solubility of the opioid determines the time to onset of OIVI should it occur.

- *Early OIVI* usually occurs within 2 hours of an injection (or later with an infusion) and results from high blood levels of opioid following absorption from the epidural space into the systemic circulation. The relatively high blood concentrations of the lipid-soluble drugs are more likely to cause early OIVI.
- *Delayed OIVI* is most commonly seen between 6 and 24 hours after the opioid was given and results from rostral migration of drug in the CSF to the brain stem and respiratory center. The onset is usually gradual with the patient becoming progressively more sedated. Delayed OIVI can persist for many hours and if naloxone is necessary it may have to be given by infusion. The risk of delayed OIVI is much higher with poorly lipid-soluble agents (e.g., morphine). This is because the more lipid-soluble drugs (e.g., fentanyl) are subject to rapid absorption into the spinal cord and blood vessels, and there is less risk of significant concentrations remaining in the CSF and reaching the respiratory center.

There is an increased risk of OIVI associated with

- Increasing patient age
- High doses of epidural (or intrathecal) opioid

- Use in the opioid-naive patient
- Concurrent use of sedatives or systemic opioids (including long-acting sedatives or large doses of parenteral opioid given before or during an operation)

As with other methods of opioid administration, a decrease in respiratory rate can be a late and unreliable sign of OIVI (see Chapter 3). Therefore, frequent assessments of a patient's level of sedation should be made. If a patient becomes excessively sedated, subsequent bolus doses should be reduced and infusions stopped or decreased. Naloxone may be required (see later in this chapter).

9.3.2.3.2 Cardiovascular system

Hypotension is unlikely following epidural administration of opioids unless the patient is already hypovolemic. It has, however, been reported (rarely) following the use of pethidine (meperidine). This may be in part due to the fact that pethidine has some intrinsic local anesthetic activity.

9.3.2.3.3 Nausea and vomiting

The cause of postoperative nausea and vomiting is often multifactorial and conditions or drugs other than opioids may be responsible. Antiemetics should be administered and consideration given to a reduction in opioid dose. Severe and intractable nausea and vomiting may respond to opioid antagonists or agonist–antagonists (see Chapter 4).

9.3.2.3.4 Pruritus

Pruritus, particularly over the face and trunk, is more likely to follow epidural and intrathecal administration of opioids, especially morphine, than any other route (Kumar and Singh, 2013). It can be rated as very unpleasant by patients and appears to be less common in the older patient. Although the exact mechanism is unknown, it is presumed to be centrally mediated via an "itch center" in the medulla as well as a consequence of disinhibition of itch neurons in the dorsal horn of the spinal cord. Many therapies have been tried, but good evidence supports only the use of opioid antagonists (low-dose naloxone infusion at 0.25–1 μg/kg/h), mixed opioid agonist–antagonists (e.g., nalbuphine), 5-HT_3 receptor antagonists (e.g., ondansetron) and droperidol. Small doses of the anesthetic induction agent, propofol, have also been shown to relieve pruritus following epidural morphine.

Other causes of itching in a hospital setting should always be considered. For example, the plastic covering of a mattress may result in sweating and itching of the back, and itching may occur under dressings or plaster casts or as an allergic reaction to antibiotics, detergents, and disinfectants.

9.3.2.3.5 Motor/sensory block

Epidural opioids will not affect motor or sensory function.

9.3.2.3.6 Urinary retention

Urinary retention is another potential complication of epidural opioids and is again more likely with morphine. It is due to inhibition of the micturition reflex evoked by increases in bladder volume and transient dysfunction of the detrusor muscle. However, it is not inevitable and does not require routine prophylactic catheterization of all patients. Small doses of an opioid antagonist or agonist–antagonist may be given if required. If this is unsuccessful, a urinary catheter will be needed, but it can be "in-out" and does not have to remain in situ.

9.3.2.3.7 Gastrointestinal system

Epidural opioids decrease bowel motility, but to a lesser degree than equianalgesic doses of opioid given by systemic routes.

9.3.3 Combinations of local anesthetics and opioids

The side effects of opioid and local anesthetic agents used in epidural analgesia are compared in Table 9.4.

The most commonly used solutions for epidural infusion are combinations of low concentrations of local anesthetics and opioids (colloquially called an "epidural cocktail"). The effects appear to be synergistic and permit a reduction in the concentration of each class of drug, while providing better analgesia and lower risk of adverse effects than could be obtained with either agent alone, and retaining the major outcome benefits of epidural local anesthetics. It is essential that the concentration of opioid used is kept low in order to avoid significant opioid-related adverse effects, which would reduce the benefits of the combination.

Evidence for the "optimal" concentration of each is limited and research into identifying such a solution has been discontinued. Commonly used mixtures contain bupivacaine or levobupivacaine 0.0625%–0.125%, or ropivacaine 0.1%–0.2% with 2–5 μg/mL fentanyl, 1 μg/mL sufentanil, or 20–40 μg/mL morphine.

Other opioids that are used in combination with these local anesthetics include pethidine, diamorphine, hydromorphone, and sufentanil. It is the total dose of drugs given that is important; the higher the concentration, the lower the volume infused.

9.3.3.1 Dose regimens

Infusion rates will vary according to the concentration of drugs in the solutions, the site of injury or surgery relative to the site of epidural catheter placement, and the age of the patient. In institutions where nursing staff are allowed to administer

Table 9.4 Comparison of the possible side effects of epidural opioids and local anesthetic drugs

	Opioid	Local anesthetic
Respiratory	Delayed opioid-induced ventilatory impairment (OIVI)	Usually unimpaired
	Early OIVI	
Cardiovascular	Usually no reduction in blood pressure	Overt or postural hypotension
		Reduced heart rate with high block
Nausea/vomiting	Yes	Less common
Pruritus	Yes	No
Motor	No effect	Block
Sensation	No effect	Block
Urinary retention	Yes	Yes
Gastrointestinal	Decreased motility	Increased motility

"top-up" doses as well as alter infusion rates, orders should include bolus doses of the solution for breakthrough pain. Suggested bolus doses and infusion rates for some of the combinations of local anesthetics with fentanyl that may be used are listed in Table 9.2. The use of smaller local anesthetic/opioid bolus doses and lower infusion rates are suggested in older patients for the reasons outlined earlier.

9.3.4 Alpha-2 receptor agonists

As α_2-receptors are a component of the descending inhibitory system of pain control within the spinal cord, administration of an α_2-adrenergic agonist has an analgesic effect. The most commonly used drugs are clonidine and epinephrine (Schug et al., 2006). There is increasing interest in the use of dexmedetomidine, but data on neurotoxicity are inconsistent and limited.

9.3.4.1 Clonidine

Neuraxial (epidural or spinal) administration of clonidine has been widely investigated and regarded as safe with regard to neurotoxicity. It is approved for use by this route in the treatment of cancer pain by the US Food and Drug Administration.

Epidural clonidine is used mainly as an adjunct to opioids and local anesthetics. It reduces the dose of local anesthetic required for pain relief, improves duration of analgesia, and extends motor blockade. The evidence of any benefit from coadministration with opioids is weak and inconsistent.

Given in bolus doses of 25–150 μg, epidural clonidine leads to both dose-dependent analgesia and dose-dependent side effects, especially sedation, hypotension, and bradycardia. Sedation may follow systemic drug absorption of the drug (the lipid solubility of clonidine is similar to fentanyl) and hypotension occurs commonly with doses that exceed 75 μg.

9.3.4.2 Epinephrine

Epidural epinephrine has α_2-agonist effects that lead to pain relief and also to vasoconstriction. The latter effect reduces the clearance of some epidurally administered drugs increasing their duration of action. Therefore, the addition of low concentrations of epinephrine to local anesthetic or local anesthetic–opioid solutions results in improved analgesia. The most commonly used concentrations are in the range of 1.5–2 μg/mL. Concerns about the risk of reducing spinal cord blood flow are unfounded.

9.3.5 Other adjuvant drugs

A number of other agents such as ketamine and neostigmine have been administered epidurally, primarily in experimental settings (Schug et al., 2006). Given with epidural opioids and/or local anesthetics, they may improve pain relief without an increase in adverse effects. However, preservative-free solutions, which should be used to avoid neurotoxicity, are not available in all countries, and the risk of neurotoxicity needs to be considered carefully with the use of any agent introduced into the epidural space.

While these results are encouraging, further evaluation is needed before these and other adjuvants (e.g., midazolam and magnesium are under investigation) becomes part of routine clinical practice.

9.4 Requirements for the safe management of epidural analgesia

The safety and effectiveness of epidural analgesia can be achieved best by well-trained staff, the consideration of contraindications to insertion of an epidural catheter (discussed earlier) and the implementation of standard orders and nursing procedure protocols.

To reduce the risk of drugs or fluids intended for intravenous (IV) administration being inadvertently given via an epidural catheter with potentially catastrophic consequences, all pumps and lines utilized for epidural drug administration and all epidural catheters should carry a clearly visible label. Yellow is the recommended identification color for this route of administration in many countries (Beckers et al., 2012). Ideally, dedicated infusion pumps should also be used. These pumps should be rate limited (e.g., to 20 mL/h) so infusion rates that are too high cannot be inadvertently programmed and delivered. Work is continuing on the development of an international standard for a fitting that would not allow an IV line to be connected to an epidural catheter.

9.4.1 Standard orders and nursing procedure protocols

To maximize the effectiveness of epidural analgesia, minimize the risk of complications, and improve recognition and treatment of adverse effects, standard orders, and nursing procedure protocols are recommended. The aim is to try and improve the quality of clinical decision making rather than to dictate clinical practice.

9.4.1.1 Standard orders

To standardize orders throughout the institution, preprinted forms are recommended. An example of a preprinted standard order form for epidural and intrathecal analgesia is given in Appendix 9.1. Common components of these standard orders are listed in Table 9.5 and include:

- Orders for the local anesthetic and/or opioid infusion and/or bolus doses that can be given
- Nondrug treatment orders and any monitoring and documentation requirements, which allows a regular assessment of the progress of each patient and for rational changes to be made to epidural infusion orders so that treatment is individualized
- Instructions for the management of inadequate analgesia as well as adverse effects

The forms need to be completed, signed, and dated by the treating anesthesiologist or other member of a pain service.

It should be noted that while standard orders are used for the initial prescription of epidural analgesia, these orders may not remain effective for all patients. At least daily evaluation of the patient by an anesthesiologist (or more often if required) will allow appropriate alterations to be made to the prescription or analgesic technique and early identification of complications.

Table 9.5 Key components of epidural standard orders

- *Orders for the epidural analgesic agent(s) including*:
  - Drug(s) name and concentration
  - Infusion rate (usually a range)
  - Size of bolus doses permitted
- *The infusion rates and/or bolus doses that can be given*
- *Nondrug treatment orders including*:
  - A statement to prevent the concurrent ordering of CNS depressants, other opioids, or antiplatelet or anticoagulant drugs by unauthorized medical staff
  - Orders for supplemental oxygen
  - The need to maintain IV access for the duration of epidural analgesia
  - Contact instructions if analgesia is inadequate or there are other problems related to the epidural catheter or drugs used
- *Monitoring and documentation requirements including*:
  - Regular assessment of pain scores, functional activity scale (FAS) scores, sedation score, respiratory rate, blood pressure, heart rate, temperature, and motor and sensory function, at appropriate intervals
  - A record of the amount of epidural analgesic agent(s) delivered
  - Dose of any medication administered for the treatment of side effects
  - Any changes that have been made to the epidural infusion rate or bolus dose size
  - The need to check the infusion pump program at regular intervals (e.g., at change of shift as well as when the drug reservoir is replaced)
  - The monitoring of motor and sensory function for a period after removal of the epidural catheter
- *Guidelines for the management of inadequate analgesia*
- *Guidelines for the management of adverse effects*
- *The name and signature of the prescribing doctor*

9.4.1.1.1 Monitoring and documentation requirements

The following should be monitored at regular intervals:

- Pain score, functional activity score, sedation score, and respiratory rate
- Blood pressure and heart rate
- Sensory block—Block height may be measured by testing the level at which the patient reports a loss of sensation to cold, for example, when ice or alcohol is applied to the skin. However, sensory block may be minimal or not easily demonstrable when low concentrations of local anesthetic drugs are used, despite good analgesia. Routine monitoring of sensory block height is not required and may not be helpful in these circumstances. Any increasing sensory deficit should, however, be noted as it may reflect development of a complication.
- Motor block—The ability of a patient to raise a straight leg or lift and bend their knee toward their chest will provide evidence that lower extremity motor block resulting from the local anesthetic is not excessive. It will also enable early identification of spinal cord compression resulting from an epidural hematoma or abscess.

Initial monitoring intervals of hourly for up to 8–24 hours are suggested. These can be increased to 2- to 4-hourly the longer epidural analgesia continues and the more stable the patient is. Shorter intervals may be needed if changes in the prescription, infusion rates, or bolus doses are required.

9.4.1.2 Nursing procedure protocols

The format of nursing procedure protocols for epidural analgesia will vary with each institution, but key elements include:

- The institution's policy on accreditation (credentialing) of nursing staff
- Mechanisms for checking and discarding of opioids
- Monitoring and documentation requirements
- Instructions for:
  - Administration of bolus doses
  - Checking the amount of drug delivered (from the infusion pump display) against the amount remaining in the syringe/infusion bag
  - Checking the infusion pump settings against the prescription (e.g., at the change of each shift)
  - Checking the epidural insertion site and dressing
  - Checking and documenting that the catheter is complete after removal
  - The setting up and programming of infusion pumps
  - The management of equipment faults and alarms
  - Mobilization of the patient

9.5 Patient-controlled epidural analgesia

Patient-controlled epidural analgesia (PCEA) using either opioids alone or, more commonly, combinations of opioid and local anesthetic drugs, combines the benefits of more effective analgesia with the advantages of patient control and greater patient satisfaction (Momeni et al., 2006). Besides increased patient satisfaction, there may be a reduced need for staff interventions (e.g., administration of bolus doses).

A loading dose to establish an initial block, often with a higher concentration of local anesthetic than that of the infusion solution, should be given before PCEA is commenced. Unlike IV-PCA, a continuous (background) infusion is commonly ordered, as maintenance of a block by continuous infusion improves analgesia (ANZCA and FPM, 2010).

Commonly used parameters for PCEA are bolus doses of 2–4 mL with background infusions of 6–12 mL/h with a lockout interval of 10–20 minutes.

9.6 Management of inadequate analgesia

In general, it is best to establish epidural anesthesia using stronger concentrations of a local anesthetic agent before the lower-concentration local anesthetic/opioid solutions used for analgesia is commenced. This is usually done in the operating room when epidural anesthesia is initiated before surgery. The analgesic infusion should be started before the initial block has regressed completely. For safety reasons, reduction in intensity of motor and sensory block should be

evident before the patient is transferred to a general ward. The continued resolution of motor and sensory blockade will usually proceed despite the infusion of a lower-concentration solution.

If a patient receiving epidural analgesia complains of inadequate pain relief or pain out of proportion to the procedure or number of days elapsed postinjury or postoperatively, initial assessment must always consider causes of the pain, as it may not be the same pain for which epidural analgesia was first commenced. Examples include new pain resulting from a postoperative complication (such as developing peritonitis or compartment syndrome) that is severe enough to "break through" the epidural analgesia, or pain at sites distant to the incision not covered by epidural analgesia (e.g., shoulder tip pain following laparoscopic or thoracic surgery, arthritis pain after positioning on an operation table). Another example would be a trauma patient with a thoracic epidural catheter placed to manage pain from fractured ribs, but who has additional injuries at other more peripheral sites.

In some of these situations, additional analgesia may be required. If other opioids are needed to supplement epidural analgesia (e.g., by PCA), it may be appropriate to use local anesthetic drugs only in the epidural infusion in order to minimize the risk of OIVI.

If pain appears to be related to the reason for which epidural analgesia was commenced and better pain relief is required, the procedures outlined in Table 9.6 can be tried.

Table 9.6 Management of inadequate analgesia

Reassess the patient

- Consider another cause for new or increased pain such as development of postsurgical or postinjury complication, for example, bowel perforation and/or peritonitis after abdominal surgery, compartment syndrome after orthopedic surgery or limb injury, or other pain not covered by epidural analgesia
- Test for the level of the block using ice or alcohol

Bilateral block but inadequate spread (e.g., "too low")

- Give a bolus dose of opioid or opioid/local anesthetic solution and increase the rate of an infusion

Unilateral block

- Suggests that catheter tip may have exited the epidural space through an intervertebral foramen or that there is an anatomical reason for asymmetrical spread
- Try a larger bolus dose (anesthesiologist only) and/or
- Withdraw catheter a little (allow adequate time after any heparin administration)

No block or generally poor pain relief

- Exclude intravascular catheter migration by aspiration test (anesthesiologist only)
- Check position of catheter using a "test dose" of 3–8 mL of local anesthetic solution (e.g., 1% lidocaine or 0.25% bupivacaine) and test for level of sensory block ("test dose" to be administered by an anesthesiologist only)
- If "test dose" shows no block the catheter is displaced; order alternative analgesia or reinsert catheter (allow adequate time after any heparin administration)

Note: These strategies are suggestions only and may not be needed in, or be suitable for, the treatment of all patients.

9.7 "Step-down" analgesia

Epidural analgesia should be provided for a limited time only to reduce the risk of catheter-related infections. Patients and staff need to be aware that in view of the excellent pain relief commonly provided by this technique, discontinuation may be accompanied by an initial, and often surprisingly significant increase in pain intensity. Appropriate "step-down" analgesia needs to be titrated to accommodate for this change in pain control. In particular, there should be some overlap of pain therapies so that the "step-down" regimen has time to have an effect before epidural analgesia is withdrawn. Many pain services discontinue the epidural infusion, but leave the epidural catheter *in situ* for a while. This allows for the option to reestablish epidural analgesia for another day or so should the change to systemic analgesia fail.

Unlike systemic opioids, epidural doses cannot be used as a guide for the prescription of subsequent systemic analgesic regimens. If patients are still "nil by mouth" at the termination of epidural analgesia, IV PCA is an ideal step-down technique. If the step down is to oral opioids, appropriate age-based doses are suggested (see Chapters 4 and 7). Implementation of other components of multimodal analgesia such as nonsteroidal antiinflammatory drugs (NSAIDs) prior to discontinuation of epidural analgesia will facilitate weaning.

If the discontinuation of epidural analgesia is accompanied by change in clinical responsibility for the pain management of the patient (i.e., from APS to surgical team), then this change needs to be documented and clearly understood by all staff.

9.8 Complications and side effects of epidural analgesia

Complications of epidural analgesia may be related to the epidural needle or catheter, the equipment, or side effects of the drugs. Management of these complications is summarized in Tables 9.7 through 9.9.

9.8.1 Postdural puncture headache

Whenever the dura is punctured, intentionally or unintentionally, leakage of CSF can occur. This can lead to a decrease in CSF pressure and tension on meningeal vessels and nerves, which can result in headache (Gaiser, 2013). The risk of dural puncture is estimated to be about 0.16–1.3%, with the subsequent risk of headache

Table 9.7 Possible complications of epidural analgesia

Related to the insertion of an epidural needle or catheter:

- Postdural puncture headache
- Nerve or spinal cord injury
- Epidural hematoma
- Epidural abscess/meningitis
- Catheter migration

Related to the equipment:

- Catheter/filter: leakage/disconnection
- Infusion pumps: malfunction, incorrect program, gravity flow

Related to the use of opioid and/or local anesthetic drugs

Table 9.8 Management of complications related to epidural needles or catheters

Dural puncture headache

- History and examination to exclude other cause of headache
- Bed rest as required for patient comfort only
- Analgesia (nonopioids often better than opioids) +/– caffeine
- Hydrate (oral or IV)
- Blood patch as definitive treatment if required

Nerve or spinal cord injury

- Immediate neurological assessment
- A thorough history and examination will help to determine the site and extent of injury as well as the time of onset of signs and symptoms (the injury may be unrelated to the epidural needle or catheter)

Epidural space infection or hematoma

- Perform a history and examination (NB: a patient with an epidural abscess may be afebrile)
- Immediate neurosurgical assessment
- MRI scan (contrast CT if no MRI)
- Urgent surgical decompression will usually be required if neurological changes develop due to nerve or spinal cord compression and if there are no contraindications to surgery
- Antibiotic therapy alone may be appropriate in the absence of significant neurological deficit

Epidural catheter migration

- Treat as for complications of excessive opioid and/or local anesthetic doses

Epidural catheter/filter disconnection

- If the disconnection is witnessed, it may be reasonable to clean a section of catheter with an alcohol wipe (allowing to dry completely), then cut with sterile scissors and attach a new filter

Leaking at the epidural insertion site

- If some leaking is noted at the epidural insertion site, the catheter may be left *in situ* if still providing adequate analgesia

Note: These strategies are suggestions only and may not be needed in, or suitable for, the treatment of all patients.

ranging from 0.4% to 80%. It is less with smaller needles, certain types of needles, and in older patients.

The signs and symptoms are fairly typical and usually occur within 1–2 days after the puncture. The headache is usually bifrontal and/or occipital, positional (worse if the patient stands, sits, or strains), and has accompanying features such as neck stiffness, nausea and vomiting, photophobia, and tinnitus. Severe cases may be associated with diplopia or other cranial nerve palsies, resulting from traction on these nerves. Very rarely, intracranial bleeding has resulted.

Initial treatment consists of bed rest, hydration, and analgesia (simple or opioid); in some centers caffeine has been used. However, the evidence base for all these treatments is poor. The definitive treatment is the epidural "blood patch" which can be performed if these conservative measures are not effective within a reasonable time (this may vary according to patient and their circumstances). This requires insertion of an epidural needle and, in a sterile manner, injection of the patient's own blood (usually 20 mL) into the epidural space at the level of the previous puncture (Gaiser, 2013). The resulting epidural blood clot effectively seals the hole through which the CSF is leaking. Relief from the headache is almost immediate in 80–90% of cases; in case of failure it can be repeated. Blood patches may occasionally cause minor backache or headache.

Table 9.9 Management of side effects of epidural analgesia

Nausea/vomiting	Administer antiemetics and add additional antiemetics if ineffective
	Consider other possible causes (e.g., ileus)
	If nausea seems related to epidural analgesia, consider omitting the opioid (if used in combination with a local anesthetic) or changing to another opioid
Pruritus	Check that pruritus is likely to be related to the epidural analgesia
	Administer small doses of IV naloxone or an opioid agonist–antagonist (e.g., nalbuphine)
	Use other proven treatments: 5-HT_3 receptor antagonists (e.g., ondansetron) or droperidol
	If pruritus seems related to epidural analgesia, consider omitting the opioid (if used in combination with a local anesthetic) or changing to another opioid
Sedation/respiratory depression	Check no other reason for sedation (e.g., administration of a sedative)
	Sedation score = 2: reduce the size of bolus doses and/or the rate of infusion
	Sedation score = 2, respiratory rate ≤7/min: reduce the bolus dose and/or infusion rate, consider naloxone
	Sedation score 3 (regardless of respiratory rate): attempt to wake the patient with both verbal and/or physical stimulation, provide close observation, give naloxone 40–100 μg IV and repeat 2 minutely PRN, cease infusion until the patient is more awake
	A decrease in opioid concentration may be required or the opioid can be omitted if being used in combination with a local anesthetic
Urinary retention	Try small doses of IV naloxone (if opioid only being used)
	Catheterize – "in-out" or indwelling
Hypotension	Look for hypovolemia and other causes of hypotension
	Administer IV fluids +/– vasopressors as appropriate
	Cease/reduce (often only temporarily) infusion if needed (often not required)
Numbness/weakness	Check for catheter migration (into CSF)
	Cease infusion for a short while, restart at a lower rate once there is evidence of resolution of sensory and motor deficit
	Consider reducing local anesthetic concentration if above fails
	Consider urgent exclusion of spinal cord compression by hematoma/infection if there is no resolution of sensory and motor deficit within a reasonable time

Note: These strategies are suggestions only and may not be needed in, or be suitable for, the treatment of all patients.

9.8.2 Nerve or spinal cord injury

Injuries to nerves or spinal cord from needle or catheter placement are very uncommon and it is therefore difficult to obtain an exact estimate of the risk. Results from a large survey of nearly 100,000 adults with perioperative epidural catheters suggest an incidence of permanent harm (including nerve or spinal cord injury and death) of between 8.2 and 17.4 per 100,000 patients (Cook et al., 2009). The incidence of paraplegia or death was said to be between 1 and 6.1 cases per 100,000.

It needs to be acknowledged, that in a considerable number of instances, neurological problems have occurred in a temporal but not causal relationship with epidural analgesia. For example, paraplegia can result from a decrease in spinal cord blood flow leading to spinal cord infarction. While this may occur after an epidural catheter has been inserted, it may be caused by problems that are unrelated to the epidural blockade, such as hypotension due to bleeding, increased intraabdominal pressure leading to raised epidural venous pressure, surgical injury to an anterior spinal artery or cross-clamping of the aorta, or preexisting arteriovascular disease. Similarly, damage to lumbosacral nerve roots may occur during labor and delivery due to pressure of the presenting fetal part. Any signs and symptoms of spinal cord or nerve root injury, irrespective of assumed cause, require immediate neurological assessment.

Local anesthetics, opioids and adjuvants assessed for neurotoxicity and administered in commonly used concentrations and doses epidurally do not cause nerve damage (Schug et al., 2006). However, rare neurological complications have been reported after intrathecal administration of local anesthetic drugs as outlined in Chapter 5.

9.8.3 Epidural hematoma

The exact incidence of epidural hematoma following epidural anesthesia or analgesia is difficult to quantify, but surveys estimate it to be in the range of 0.5 to 1 in 100,000 in general, with incidences as high as 1 in 3000 in at-risk populations (Horlocker, 2011). Risk factors include multiple attempts at needle insertion, coagulation disorders, concurrent administration of anticoagulants (see below), female gender, and older age. Again, epidural hematomas have also been reported to occur spontaneously in patients, in particular those with bleeding disorders or taking anticoagulant medications.

9.8.3.1 Diagnosis and treatment

The onset of signs and symptoms after placement or removal of an epidural catheter may be sudden (Horlocker, 2011). In many patients a neurological deficit (especially muscle weakness) may be the first indication of a hematoma. Increasing neurological dysfunction (motor, sensory, bladder, or bowel) develops as the hematoma increases in size and compresses nerve roots and the spinal cord. The patient may also complain of sharp back or nerve root pain. Immediately after epidural or spinal anesthesia, a hematoma may present as an unusually dense or patchy block, or one that is unusually slow to resolve.

The first step in the diagnosis is immediate discontinuation of the epidural infusion without removing the epidural catheter. No resolution of the neurological symptoms in response to this should trigger immediate magnetic resonance

imaging (MRI) and urgent neurosurgical consultation, as potential recovery depends on time-contingent diagnosis and treatment.

9.8.3.2 Treatment

A neurosurgical decision on observation versus decompression is urgently required. There have been cases with spontaneous resolution of neurological symptoms, but this requires neurosurgical assessment. Surgical decompression within 8 hours after the onset of neurological symptoms offers the best chance of full recovery (Horlocker, 2011).

9.8.3.3 Prevention

While it may not be possible to prevent the development of a hematoma, attempts should be made to minimize the risk. This requires an assessment of the risks versus benefits of epidural analgesia for each patient. In particular, as outlined below, antithrombotic and antiplatelet therapy, and/or coagulation disorders must be considered. Standard protocols and procedures should be in place with regard to the timing of insertion and removal of an epidural catheter in relation to anticoagulation and antiplatelet therapies.

The chances of early detection of a hematoma need to be maximized, thus allowing early and thereby more successful treatment. A high index of suspicion is required when clinical features that might suggest a hematoma are seen, as well as the use of epidural analgesia in a way that does not mask the onset of neurological signs and symptoms.

Ideally, postoperative epidural analgesia should provide good pain relief with little or no motor or sensory block. This is more easily achieved with the use of combinations of local anesthetics and opioids and via thoracic catheters. Nursing staff need to be aware of the early signs and symptoms of a hematoma as described above and should regularly monitor and record the patient's motor and sensory function. Any new neurological deficit should be reported immediately to the anesthesiologist or pain service concerned. Immediate cessation of the infusion should result in some resolution of the deficit within an hour or two, as most motor or sensory deficits are due to the local anesthetic agent in the epidural infusion solution (Horlocker, 2011).

Any new neurological find is presumed to indicate epidural hematoma (or abscess—see below) until proven otherwise. It is also important for the patient to be aware of the need to report any motor or sensory changes as well as alterations in bladder or bowel function.

9.8.4 Epidural space infection

Infections of the epidural space (epidural abscess or meningitis) are also rare complications of epidural analgesia. The reported incidence is in the range of 1–5 in 10,000 (Hebl and Niesen, 2011). The risk of infection is increased in patients with a malignancy, diabetes or those who are immunocompromised or IV drug users. It may result from infusion of contaminated solutions, breaches of aseptic technique during insertion and maintenance of epidural catheters (including catheter and hub disconnections), hematogenous spread during episodes of bacteremia, or by migration of skin bacteria through insertion sites. The last is probably the most common source as the majority of infections are caused by

various *Staphylococcus* bacteria, usually *Staphylococcus aureus* (Hebl and Niesen, 2011). If an abscess develops, nerve root or spinal cord compression may result. Meningitis has also been reported.

As with epidural hematomas, epidural space infections often occur spontaneously and unrelated to epidural analgesia, usually as the result of hematogenous spread of bacteria, in particular in IV drug users. In a review of 915 published cases of epidural abscess, only 5.5% were related to epidural catheterization (Reihsaus et al., 2000).

9.8.4.1 Diagnosis

The signs and symptoms of an epidural abscess may be similar to those of an epidural hematoma, except that onset is often later and commonly much slower. Presentation of an epidural abscess may be delayed until days or even weeks after the patient has been discharged from hospital. The most frequent presenting symptoms are increasing and persistent back pain, back tenderness, and signs of infection (Hebl and Niesen, 2011). Importantly, the patient may not be febrile. Patients with severe increasing back pain after epidural catheter placement should be investigated promptly, even in the absence of a fever (ANZCA and FPM, 2010).

If neurological signs develop they may be delayed until some days later, although this is not always the case. Patients with meningitis may present with typical symptoms such as fever, severe headache, photophobia, neck stiffness, and altered levels of consciousness, without motor or sensory loss.

The MRI scan is superior to other methods of imaging and should be the diagnostic test of choice if available (with or without contrast enhancement). CT scans have given false or inconclusive findings, although reliability may be improved if contrast enhancement is used. CT scans may be utilized if rapid access to an MRI scan is not possible.

9.8.4.2 Treatment

An urgent neurosurgical consultation should be requested if an epidural abscess is suspected. In the absence of neurological signs and symptoms, epidural space infections have been successfully treated with antibiotics without surgical decompression (ANZCA and FPM, 2010). However, the development of any neurological changes indicates the need for an urgent neurosurgical consultation, as immediate surgical decompression may be required. Again, decompression within 8 hours of the onset of neurological loss will maximize the chance of a full recovery.

9.8.4.3 Prevention

As with an epidural hematoma, it may not be possible to prevent the development of an epidural space infection, but every attempt should be made to minimize the risk (Hebl and Niesen, 2011). For example, the catheter should always be inserted using an aseptic technique (including gown, face mask, and gloves), skin preparation should be done with chlorhexidine in alcohol following standard procedures, and epidural infusion solutions should be prepared under sterile conditions, ideally by a pharmaceutical company or a hospital pharmacy. If epidural analgesia is to be used in patients at increased risk of an abscess, an assessment of risk versus benefit should, as always, be made. Duration of

catheterization is a major predictor of risk. While epidural infections have been reported as soon as one day after insertion of an epidural catheter, most infections occur after more than 48 hours.

As with epidural hematomas, it is possible to maximize the chance of early detection of an abscess if epidural analgesia is used in a way that does not mask the onset of neurological changes, and if staff maintains a high index of suspicion. The epidural catheter insertion site should be inspected daily and note made of the patient's temperature. The catheter should usually be removed if inflammation or tenderness at the insertion site is present. Significant local infection should be treated with the appropriate antibiotics and surgical drainage may be required. If the patient develops a fever that is higher than would be expected in the immediate postoperative period, consideration may be given to removal of the catheter, unless the perceived benefit of continuing outweighs possible risks.

There appears to be little benefit from routine culture of epidural catheter tips after removal, as positive cultures may be as high as 30% (ANZCA and FPM, 2010). The results are therefore not reliable predictors of epidural space infection.

Patient education and involvement are again important. Patients must be instructed to report to the hospital or their anesthesiologist immediately if any problems are noted after discharge. An information card to be taken home may serve as a reminder. (See Appendix 2.1.)

9.8.5 Catheter migration

Rarely, a catheter placed in the epidural space will migrate into the intrathecal space or an epidural blood vessel. If migration is not recognized, large doses of drugs (opioids and/or local anesthetics) intended for epidural administration will be delivered into the CSF or systemic circulation. Migration into the intrathecal space will usually result in rapidly increasing block height, while migration into a blood vessel leads to a loss of block and increasing pain.

Complications due to catheter migration will be more obvious and of greater magnitude if bolus doses of epidural opioid and/or local anesthetics are given.

9.8.6 Problems related to equipment

9.8.6.1 Epidural catheter or filter

Disconnection of the catheter from the epidural filter can result in contamination of the end of the catheter and migration of bacteria in the epidural infusion solution. If this disconnection is witnessed and it is important for epidural analgesia to continue, it may be reasonable to reconnect the catheter after the outside of the catheter has been thoroughly cleaned with an antiseptic solution, 10–20 cm trimmed from its end with sterile scissors and a new filter attached. This should not be done without consulting the anesthesiologist or pain service responsible for the epidural analgesia.

Kinking of the catheter can occur, making infusion or administration of a bolus dose difficult or impossible. The length of the catheter should be checked for obvious kinks; if none are visible it may be worth pulling the catheter back by 1–2 cm (time of any heparin administration allowing). Slight flexion of the patient's back may also overcome the problem.

Leakage at the connection of the filter and the infusion line or catheter should be addressed, as this carries a risk of contamination of the epidural solution. If the catheter appears to be leaking at the insertion site but analgesia appears to be adequate, the leakage might be due to backtracking of infusion solution along the catheter and the epidural infusion can be continued. If analgesia is inadequate, it may be that the tip of the catheter has migrated and is no longer in the epidural space but lying in subcutaneous tissue.

The catheter should be inspected upon removal to ensure that the tip is complete. If it is not, the patient should be told and details entered in the patient's record. However, the catheter material is inert and surgical removal of the tip is usually unnecessary.

9.8.6.2 Infusion pumps

Fatal or near-fatal doses of epidural analgesic drugs have been given when infusion pumps delivering the epidural solution have been mistakenly programmed to the rate prescribed for the infusion of intravenous fluids (Beckers et al., 2012). Furthermore, a wide variety of drugs intended for intravenous administration has also been injected or infused into the epidural space; common reasons are swapped syringes, errors in ampoule selection, and confusion between epidural and intravenous access. Clear labeling of all epidural catheters and infusion devices used for epidural analgesia is therefore strongly recommended. Color coded (yellow) infusion lines and dedicated epidural pumps may help to prevent such errors as will electronic safeguards against incorrect programming (e.g., internal upper limits for infusion rates). Non-luer-lock epidural ports and syringes are currently under discussion, but a widely accepted standard has not yet been developed.

Operator error can lead to misprogramming of infusion pumps, infusion pumps may malfunction, or patients may attempt to interfere with the running of the pumps. Excessive doses of epidural infusion solutions have also been administered when the contents of a syringe or infusion bag have accidentally been allowed to empty by gravity. Therefore, antisiphon valves should be placed in the infusion line between the drug syringe/bag and the patient.

9.8.7 Side effects related to drugs

Possible side effects of epidural and intrathecal opioids and local anesthetic agents were outlined earlier in this chapter (see Table 9.4). Side effects will be exaggerated if doses intended for epidural administration are inadvertently given directly into the CSF. Suggestions for the management of these complications are listed in Table 9.9. Drug-related problems may also occur if there are errors in prescription—either by mistake or due to inadequate knowledge.

9.9 Concurrent antithrombotic or antiplatelet therapy

The following recommendations are not evidence based, as the incidence of epidural hematomas is very small and therefore controlled studies are not possible. They are primarily based on expert opinion and, in particular, on consensus statements published in the United States (Horlocker et al., 2010; Horlocker, 2011),

United Kingdom (Harrop-Griffiths et al., 2013), and Europe (Gogarten et al., 2010). They are not intended to provide a specific "standard of care," but to offer reasonable options for patient management. They cannot replace an individual risk–benefit analysis for every patient.

9.9.1 Warfarin

There is little information about the risks of epidural hematoma in association with the use of warfarin. A major difficulty in making recommendations is the wide interindividual variability in response to this drug. In patients on long-term warfarin therapy, hemostasis may require 3–5 days to normalize once the drug is stopped. Coagulation status (prothrombin time [PT] and international normalized ratio [INR]) should be checked before insertion of an epidural needle or catheter. An INR <1.5 is regarded as relatively safe in this setting.

Some patients are prescribed low-dose warfarin for postoperative thromboprophylaxis (e.g., after major orthopedic surgery). The best time for removal of an epidural catheter in these patients is not known. Relying on an average time to effect of 48 hours (peak effect will be seen at 3–5 days) may be dangerous in individual patients, as there will be an effect on the INR after a single dose of warfarin in some. If the epidural catheter is left in for longer than 24 hours after first dose, monitoring of coagulation status is suggested. Again the INR should ideally be <1.5 at time of removal.

9.9.2 Heparins

9.9.2.1 Standard unfractionated heparin (intravenous)

Epidural catheterization appears to be relatively safe in patients who receive intravenous heparin, either during or after surgery. However, consideration must be given to the timing of both catheter placement and catheter removal *before* heparin is given and *after* heparin is commenced. The current guidelines suggest that after placement of epidural needles and catheters, administration of IV heparin should be delayed for at least 1 hour.

If a postoperative heparin infusion is required, the epidural catheter should be removed only after the infusion has been suspended for 2–4 hours and after the patient's coagulation status has normalized, as indicated by measurement of the activated partial thromboplastin time (APTT).

9.9.2.2 Standard unfractionated heparin (subcutaneous)

Low-dose standard heparin is commonly administered for thromboprophylaxis, although regarded as insufficient after orthopedic surgery, and is generally considered safe to use in patients with concurrent epidural analgesia at doses under 10,000 units daily. However, appropriate precautions should be taken regarding the timing of epidural catheter insertion and removal, as the peak effect of a dose of standard heparin is likely to be seen at 1–2 hours and the duration of effect may be 4–6 hours or more.

Therefore, some guidelines recommend that epidural catheters can be inserted or removed 1–2 hours before the next dose in a twice-daily (BD) regimen (commonly 5000 units BD). There are currently no recommendations for thrice daily regimens, although commonly one dose is omitted.

Longer therapy with heparin can result in heparin-induced thrombocytopenia. Guidelines recommend a platelet count prior to insertion or removal of an epidural catheter after more than 5 days of heparin therapy.

9.9.2.3 Low molecular weight heparin

In December 1997, after reports of nearly 60 patients who developed an epidural hematoma, the US Food and Drug Administration issued a public health advisory alert regarding the risk of epidural hematoma in association with epidural and spinal anesthesia in patients receiving low molecular weight heparin (LMWH) for postoperative thromboprophylaxis (Horlocker, 2011). This high rate was probably the result of the higher doses and a twice-daily dosing schedule used in the United States, as a trough in anticoagulant activity between doses (which may allow for safer catheter removal) is less likely to occur with this regimen.

The time-to-peak effect of a dose of LMWH is about 3–5 hours and normal hemostasis may not return until more than 12 hours after that dose. The effect and its duration are increased in patients with severe renal insufficiency, when the half-life may be prolonged from 4 to 6 hours to as long as 16 hours. Therefore, the timing of epidural catheter insertion and removal must be carefully considered.

Current guidelines suggest that epidural catheters should only be placed at least 10–12 hours after a standard prophylactic dose of LMWH and 24 hours after a high therapeutic dose (the latter is usually given twice a day). Therefore, it is recommended that epidural catheters should not be left *in situ* if a patient requires the higher treatment doses of LMWH.

In patients prescribed standard prophylactic LMWH doses (once a day), the first postoperative dose should not be given earlier than 6–12 hours after surgery (and catheter placement). The epidural catheter should not be removed until at least 12 hours after the last dose of prophylactic LMWH and the next dose should not be given until at least 4 hours after removal (Food and Drug Administration, 2013).

One system that might reduce risk is to introduce a hospital-wide policy requiring LMWH injections be given in the evening, as removal the next morning (at least 12 hours after the last dose) allows easier monitoring of neurological function throughout the day. Another way, if LMWH is given in the mornings, is to still remove the catheter the next morning (22–24 hours after the last dose), and ask for the next dose of LMWH to be given 4 hours later.

9.9.3 Newer anticoagulants

9.9.3.1 Fondaparinux

Fondaparinux has been used as an alternative to heparin. It has a half-life of 21 hours and is recommended for once-daily dosing after orthopedic surgery. Concerns about epidural needle insertion relate to the long half-life of the drug (further increased in patients with renal impairment), its prolonged antithrombotic effect and its "irreversibility." Current guidelines are therefore extremely cautious and recommend that epidural catheters not be used in patients receiving fondaparinux unless the drug has been ceased for at least 36 hours. If "single-shot" epidural or spinal anesthesia can be achieved with a single atraumatic needle pass, fondaparinux can be administered no sooner than 6 hours later.

9.9.3.2 Dabigatran

Dabigatran is an oral anticoagulant used primarily in patients with atrial fibrillation. As with fondaparinux, there are significant concerns about the safety of epidural techniques. Again difficulties in reversal and prolonged duration of effect (which is even longer in patients with renal impairment) create uncertainty about its safe use. Dabigatran should be discontinued 7 days before epidural or spinal blocks are performed and epidural catheters should be removed 6 hours before the drug is restarted.

9.9.3.3 Rivaroxaban

Rivaroxaban is an oral antithrombotic agent recommended for thromboprophylaxis after total hip and knee joint replacement. It also has a long half-life (9 hours), which increases with declining renal function, but its effect can be monitored by measuring PT and APTT levels. Guidelines recommend about a 24-hour interval between the last dose of rivaroxaban and neuraxial blockade in patients with normal renal function, with this interval to be extended in patients with renal impairment. Administration to patients with an epidural catheter *in situ* is not recommended.

9.9.4 Nonsteroidal antiinflammatory drugs and other antiplatelet agents

9.9.4.1 Nonsteroidal antiinflammatory drugs

The use of NSAIDs including aspirin (given alone) has not been identified as an independent risk factor for epidural hematoma. However, concurrent use with other medications that affect coagulation status (such as heparin or LMWH) may increase the risk. Therefore, if required in combination with other anticoagulants, coxibs (selective COX-2 inhibitors) should be used in preference to nonselective NSAIDs.

9.9.4.2 Other antiplatelet drugs

For all other antiplatelet agents it is recommended that time is allowed for platelet function to recover before performing a neuraxial block. The recommended time intervals for these antiplatelet agents are therefore dependent on their duration of effect. Suggested acceptable intervals between cessation of the drug and block performance are for clopidogrel and prasugrel 7 days, ticlopidine 10–14 days, eptifibatide and tirofiban 8 hours, and abciximab 48 hours.

9.9.5 Thrombolytic and fibrinolytic therapy

There are no data to guide the time frames for performance of epidural needle and catheter insertion in relation to initiation or discontinuation of these therapies. Guidelines suggest assessment of fibrinogen levels to guide decisions. Epidural catheters should be removed before the use of such agents.

9.10 Intrathecal analgesia

The contraindications, complications, and the management of complications of intrathecal analgesia are similar to epidural analgesia. Standard orders and nursing procedure protocols are also recommended.

9.10.1 Drugs used for intrathecal analgesia

Opioids alone are commonly used for intrathecal analgesia in acute pain management—the one most commonly given for postoperative pain relief is morphine (Bujedo et al., 2012). The opioid is delivered directly into the CSF, avoiding absorption by epidural fat and blood vessels. Rostral migration in the CSF will occur, particularly with the less lipid-soluble morphine.

Much less often, infusion of local anesthetics (sometimes combined with opioids) via intrathecal catheters at very low infusion rates (in the range of 1 mL/h of the dilute solutions used for epidural infusion) have been used to provide effective postoperative analgesia (Bevacqua, 2003).

There is also increasing interest in the use of adjuvant drugs such as clonidine, dexmedetomidine (a more selective α_2-receptor agonist than clonidine), and neostigmine, although their use in the management of acute pain remains uncommon. The latter two are not licensed for intrathecal administration because of insufficient data on neurotoxicity (Schug et al., 2006).

9.10.2 Opioid doses

The doses of opioids administered intrathecally are much smaller than doses required for epidural analgesia. As with epidural opioid analgesia, the more lipid soluble the drug, the more rapid the onset and the shorter the duration of action (Bujedo et al., 2012).

The drugs listed in Table 9.10 have all been used for intrathecal analgesia. Because pethidine (meperidine) has local anesthetic as well as opioid properties, it has been used as the sole spinal anesthetic agent (in larger doses of 30–50 mg) for a variety of lower limb operations.

Although most intrathecal opioids are given as a "once only" dose at the time of spinal anesthesia, a catheter may occasionally be left in place. All spinal catheters must be clearly labeled to distinguish them from epidural catheters.

9.10.3 Possible side effects

Side effects are similar to those that occur with epidural opioids. Although some believe that the incidence is higher with intrathecal opioids, this is, to a large extent, dose dependent (Gehling and Tryba, 2009).

If OIVI occurs following administration of intrathecal morphine, the time-of-peak risk is about 8–10 hours after injection, although it can be much later. The time-of-peak risk of OIVI following intrathecal administration of highly lipid-soluble drugs is around 5–20 minutes.

Table 9.10 Intrathecal opioids: examples of doses used

Opioid	Dose (mg)	Onset (min)	Duration (h)
Morphine	0.1–0.5	15–30	8–24
Pethidine	10–25	5–10	6–12
Fentanyl	0.006–0.05	<10	1–4
Sufentanil	0.005–0.02	<10	2–6

Increasing patient age, high doses of intrathecal opioid, an opioid-naive patient and concurrent use of sedatives or systemic opioids are associated with an increased risk of OIVI.

9.10.4 Management of inadequate analgesia

Usually, intrathecal opioids are administered as a single dose so that if analgesia is inadequate, supplementation with oral or parenteral opioids will be required. As this may increase the risk of OIVI, smaller than average doses (e.g., half the normal size bolus doses for PCA) should be administered initially and increased only if they prove to be inadequate.

Key points

1. All techniques of epidural analgesia for all types of surgery provide better postoperative analgesia than parenteral opioid administration.
2. Thoracic epidural analgesia in particular reduces perioperative morbidity and possibly mortality; pulmonary complications and infections are specifically reduced. It also improves bowel recovery without increasing risk of anastomotic leakage and may be an important component of the so-called "fast-track" or "enhanced recovery after surgery" (ERAS) protocols.
3. Epidural infusion of combinations of low-dose local anesthetics and opioids are the most commonly used technique; patient-controlled epidural analgesia techniques (PCEA) increase efficacy and patient satisfaction.
4. The provision of epidural analgesia by continuous infusion or patient-controlled administration of local anesthetic–opioid mixtures is safe on general hospital wards, as long as supervised by an anesthesiology-based pain service with 24-h medical staff cover and monitored by well-trained nursing staff.
5. Anticoagulation is the most important risk factor for the development of epidural hematoma after neuraxial blockade; guidelines governing time intervals and specific rules with regard to anticoagulation and neuraxial blockade should be strictly followed.
6. 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 hematoma or abscess. Immediate decompression (within 8 h of the onset of neurological signs) increases the likelihood of good neurological recovery from an epidural hematoma or abscess.
7. Intrathecal morphine at doses of 100–200 μg offers effective analgesia with a low risk of adverse effects.

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Appendix 9.1: Example of a "standard order" form for epidural and intrathecal analgesia

CALHN
RAH ☐ TQEH ☐

ACUTE PAIN SERVICE

EPIDURAL/INTRATHECAL ANALGESIA

PATIENT LABEL

Unit Record No.: _____

Surname: _____

Given Names: _____

Date of Birth: _____ Sex: _____

EPIDURAL ORDERS:
(sign and date any changes)

1. **DRUG:** .....

Place appropriate drug label here

2. **CONCENTRATION:** .....
3. **BOLUS DOSE:**

..... to ..... mL 1 hourly PRN

4. **INFUSION RATE:**
*** = sign and date any changes*

..... to ..... mL/hr

..... to ..... mL/hr**

INTRATHECAL MORPHINE DETAILS (as needed)

Dose ..... microgram

Time given .....

The patient's regular long-acting opioids should be continued: YES NO

Signature ..... Date .....

GENERAL ORDERS:

1. Oxygen at *2 to 4 L/min via nasal specs or 6 L/min via mask* while orders are in effect.
2. No systemic opioids or sedatives (including antihistamines) to be given except as ordered or approved by the APS.
3. No anticoagulant or antiplatelet medications, including NSAIDS, to be given (other than heparin for the prevention of DVTs or low-dose aspirin) before consulting with the APS.
4. Naloxone to be immediately available.
5. A yellow minimum volume extension set with an anti-syphon valve must be in-line between patient and any epidural syringe or infusion bag at all times.
6. Maintain IV access while orders are in effect.
7. *Monitoring requirements:* see overleaf.
8. For inadequate analgesia or other problems related to the analgesia, contact the APS. The APS should be notified if the patient has two consecutive pain scores >7 at rest and/or FAS = C, or if temperature > 38.5°C, or if unexpected or new back pain during or after epidural analgesia.
9. Mobilise patients (if leg strength normal) according to parent clinic instructions but accompanied by 2 staff members initially in case of postural hypotension or problems with gait and/or balance.

   YES NO Signature .....
10. If respiratory rate is 8-10/min, no action is required as long as sedation score is < 2. If respiratory rate is ≤ 7/min and sedation score is < 2, notify the APS. If sedation score is 2 or 3, follow instructions below.

TREATMENT OF SIDE EFFECTS:

RESPIRATORY DEPRESSION (EXCESSIVE SEDATION):

1. If sedation score = 2, reduce rate of infusion by one quarter to one third. Notify the APS. Revert to hourly sedation scores until sedation score < 2 for at least 2 hours.
2. If sedation score = 3 (irrespective of respiratory rate) OR sedation score = 2 and respiratory rate ≤ 7/min, initiate a MER call, and give 100 microgram NALOXONE IV stat. Repeat 2 minutely PRN up to a total of 400 microgram. Cease infusion and call the APS anaesthetist. Revert to hourly sedation scores until sedation score < 2 for at least 2 hours.

NAUSEA AND VOMITING: (Note: check for duplicate antiemetic orders on the NIMC)

1. Give a 5-HT3 antagonist antiemetic: Drug: .....
   Dose: ..... Route: IV Frequency: ..... PRN
2. If ineffective after 15 minutes, add DROPERIDOL 500 microgram IV 4 hourly PRN (250 microgram if > 70 years).
3. If patient not responding to antiemetics contact the APS.

SEVERE ITCHING:

Give 40 microgram NALOXONE IV stat. Repeat 10 minutely PRN up to a total of 120 microgram. If patient not responding to treatment contact the APS.

HYPOTENSION:

The most likely cause of hypotension is hypovolaemia so do not cease or reduce the rate of the epidural infusion without discussing with the APS. Lie patient on flat bed (not head down) and elevate legs if possible. Call the medical officer responsible for the patient. If the patient meets the criteria, initiate a MER call. Do not give any epidural bolus doses.

SIGNATURE OF ANAESTHETIST: ..... Date: .....

(Print name .....)

Cease infusion: Date: ..... Time: ..... **Remove analgesia catheter:** Date: ..... Time: .....

Give next dose of heparin at: Date: ..... Time: .....

Signature of Anaesthetist: .....

Catheter removed and complete: Signature of RN: ..... Date: ..... Time: .....

APS-EPIDURAL/INTRATHECAL ANALGESIA MR 98.0

CALHN

EPIDURAL/INTRATHECAL/ ANALGESIA

Observations and Record of Drug Administration

PATIENT LABEL

Unit Record No.: _____

Surname: _____

Given Names: _____

Date of Birth: _____ Sex: _____

MONITORING REQUIREMENTS: For epidural analgesia, record items 1 to 6 EACH HOUR for 8 hours and then 2 HOURLY. For intrathecal morphine, record items 1 to 6 EACH HOUR for 24 hours.

1. **PAIN SCORES AND FAS**
2. **SEDATION SCORE**
3. **RESPIRATORY RATE**
4. **BP AND HEART RATE**
5. **MOVEMENT AND SENSATION**
6. **CURRENT TOTAL DOSE**
7. **EPIDURAL INSERTION SITE:** At each handover of shift, check epidural insertion site and record and notify the APS if any new or increasing inflammation, tenderness, swelling or leakage. Reinforce dressing if needed but do not remove or replace.

After administration of a bolus dose:
Record Items 1 to 5 every 5 minutes for 20 minutes.

After removal of an epidural catheter:
Record movement and sensation every 4 HOURS for 24 HOURS.

Pain Score:

0 = no pain

10 = worst pain imaginable

NB: record pain scores at rest and with movement eg. coughing

Sedation Score:

0 = wide awake

1 = easy to rouse

2 = easy to rouse but cannot stay awake

3 = difficult to rouse (severe respiratory depression)

Functional Activity Score (FAS):

A = no limitation of relevant activity due to pain (relative to baseline)

B = mild limitation of activity due to pain

C = unable to complete activity due to pain

Current total dose:

Record in mL. Reset total dose to zero when syringe is changed and document the volume discarded.

Movement and Sensation:

- Ask the patient if they have any numbness/weakness. Unless injured, get the patient to flex their hips and knees (ie, draw their knees up to their chest).
- IF ALL IS NORMAL, record M✓ S✓ in the M/S column; otherwise document and call the APS immediately.

DRUG: .....

Date	Time	Dose (total mL)	Pain Scores ..... X 0 2 4 6 8 10	FAS	Sed'n Score	Resp Rate	PR	BP	M/S	Comments	Signature RN or MO
			0 2 4 6 8 10								

ADVERSE DRUG REACTIONS

Drug	Date	Details	Signature

DRUG: .....

Date	Time	Dose (total mL)	Pain Scores ..... X 0 2 4 6 8 10	FAS	Sed'n Score	Resp Rate	PR	BP	M/S	Comments	Signature RN or MO
			0 2 4 6 8 10								

CHAPTER 10

Other regional and local analgesia

The use of regional and local anesthetic techniques other than neuraxial blockade to provide postoperative and postinjury analgesia has gained in popularity. The reasons are multiple and include the excellent pain relief provided by many of these techniques, in particular with mobilization, which will facilitate rehabilitation and early recovery. Other reasons include the availability of ultrasound guidance for nerve location, aiming to improve reliability and success rates for nerve blocks; concerns about the risks of epidural analgesia, in particular in patients taking antithrombotic or antiplatelet medications; the ability to provide selective analgesia with minimal systemic adverse effects, which may be an advantage in some patients in particular (e.g., the older patient); and the option of early discharge from hospital, with some of these techniques able to be continued at home.

One particularly successful development in the field of regional analgesia has been the extension of the effect of "single shot" regional techniques long into the postoperative or postinjury period by the use of catheters and infusions—continuous peripheral nerve blockade (CPNB).

10.1 Continuous peripheral nerve blockade

A "single-shot" peripheral nerve block (one-time nerve or nerve plexus block) with injection of a local anesthetic agent is common practice in anesthesia and continues to be widely used. While this may provide many hours (often 8–16 hours but rarely 24 hours) of analgesia, an alternative technique will be required if pain relief is to be continued for a longer period.

The benefits of "single-shot" blockade can be sustained for a number of days if a catheter is placed at the time of nerve or nerve plexus block. This allows local anesthetics to be given by repeated bolus doses or more commonly by continuous infusion. The technique provides extended regional analgesia with minimal systemic adverse effects, facilitating recovery and ongoing physiotherapy and rehabilitation.

CPNB can often be used without the need for supplemental systemic analgesia. In general, compared with systemic opioid analgesia including patient-controlled analgesia (PCA), CPNB leads to better pain relief and fewer opioid-related side effects (Ilfeld, 2011). In some circumstances, CPNB may even be as effective as epidural analgesia (e.g., after thoracotomy and total knee joint replacement), again with a lower incidence of side effects and fewer concerns about potential serious complications of epidural analgesia, in particular when patients have been given anticoagulation or antiplatelet medications.

There is an ongoing and unresolved debate about the best way to locate a nerve prior to injecting a local anesthetic drug to block the nerve or nerve plexus. The classic technique is to use an insulated needle and nerve stimulator to locate the nerve prior to insertion of the catheter for CPNB. However, this

may result in the so-called "secondary block failure," as the catheter tip may be misplaced after successful needle insertion. The development of stimulating catheters permitting stimulation at the catheter tip were supposed to enable better catheter placement, but their clinical usefulness has not yet been confirmed. The alternative is ultrasound-guided needle and catheter insertion with the theoretical advantage of visualization of the needle tip. This may result in a slightly higher success rate of the block and a lower incidence of accidental vascular puncture, but no difference in pain relief with movement; the results may also vary according to the nerve or nerve plexus blocked (Schnabel et al., 2013). Currently available data do not support either technique as the optimal technique in all circumstances (Ilfeld, 2011).

Another issue under debate is the depth of catheter insertion past the tip of the needle, when a compromise needs to be achieved between the risks of dislodgement if only a short length of catheter is inserted, or coiling and secondary failure with too deep insertion. It is suggested that the catheter is inserted to a maximum of 5 cm only (Ilfeld, 2011).

10.1.1 Upper limb

A catheter placed near the brachial plexus (by any of the usual approaches such as interscalene, supraclavicular, infraclavicular, and axillary) can be used to provide pain relief after most types of upper limb surgery or injury (including traumatic amputation and replantation).

For shoulder surgery, interscalene blocks are preferred and catheter techniques consistently outperform single shot blocks with regard to analgesia, sleep, and patient satisfaction (Cowlishaw et al., 2012). For surgery at the elbow and below, the infraclavicular approach may provide better pain relief than that achieved by supraclavicular or axillary catheters (Ilfeld, 2011). It also allows easier and more reliable fixation of catheters to the chest wall.

In addition to analgesia, the sympathetic blockade that results from the use of upper limb CPNB may be beneficial in situations where peripheral vasodilatation is an advantage (e.g., after microvascular surgery, digit replantation, limb salvage or if the patient has an ischemic arm or hand) (Ilfeld, 2011).

10.1.2 Lower limb

Continuous regional blockade of the femoral nerve (including "three-in-one" blocks of the femoral, obturator, and lateral femoral cutaneous nerves), the sciatic or posterior tibial nerves, or the lumbar plexus can provide excellent analgesia following surgery or injury to the lower limb.

The use of femoral nerve catheters after knee surgery, in particular, knee replacement, has consistently been shown to be superior to systemic opioid analgesia and local infiltration analgesia (LIA), and comparable with epidural analgesia, with fewer adverse effects (Cowlishaw et al., 2012). Continuous lumbar plexus blockade (with increased risk of complications) is also effective (Chelly et al., 2010). Femoral nerve or lumbar plexus catheters can also be used after hip replacement (Ilfeld, 2011), although continuous blockade via the latter provides better pain relief (Chelly et al., 2010).

Sciatic nerve catheters placed via the popliteal approach also provide excellent analgesia after ankle and foot surgery (Ilfeld, 2011).

Catheters placed adjacent to, or directly into, the sheath of a transected nerve following limb amputation (e.g., the sciatic nerve following lower limb amputation) are often called nerve sheath or "stump" catheters. They are probably better used in patients having an above knee amputation, as below the knee the sciatic nerve has already divided into the tibial and common peroneal nerves, and a catheter placed into just one of these nerves (which is usually the case) may not provide adequate pain relief.

10.1.3 Thoracic

Paravertebral blockade has become the technique of choice for thoracic and chest wall surgery in some centers (Greengrass and Duclas, 2012). Compared with thoracic epidural analgesia, this technique provides the same benefits in terms of pain relief and pulmonary function after unilateral thoracotomy, but with fewer adverse effects and a reduced risk of serious complications. The same results have been shown when used in patients with multiple unilateral rib fractures.

Paravertebral blockade is also an ideal technique for breast surgery, although CPNB is not necessary and a single shot block seems sufficient. It may also reduce the risk of chronic pain development after breast cancer surgery (Andreae and Andreae, 2012).

Continuous intercostal or interpleural blockade has also been used for the management of thoracic pain, although good evidence for such use is lacking (Ilfeld, 2011).

10.1.4 Abdominal

The transversus abdominis plane (TAP) block has become a popular method of providing pain relief after a wide range of abdominal surgical procedures (Taylor et al., 2013). The block is ideally suited for ultrasound guidance and this might explain the increased interest reflected in the large number of clinical trials published (Cowlishaw et al., 2012).

While single-shot blocks seem sufficient for the pain of minor abdominal surgery (such as appendectomy), benefits after abdominal surgery have mainly been reported when TAPs catheters have been used. These allow local anesthetic infusions or repeated bolus doses to be administered. There has been discussion about this technique being an alternative to epidural analgesia, however, data are limited and the benefits of epidural analgesia other than pain relief are not achievable. Overall, the technique is too new to be able to assess its value in the management of postoperative pain and better comparative data are needed (Taylor et al., 2013).

10.1.5 Drugs used with CPNB analgesia

10.1.5.1 Local anesthetics

As with local anesthetics used for epidural analgesia, the aim of CPNB is usually to provide good pain relief (and, possibly sympathetic blockade) without significant motor or sensory block. The most commonly used local anesthetics are levobupivacaine and ropivacaine because of their better sensory/motor block separation. Bupivacaine is best avoided if large doses of local anesthetic are needed, because of its higher cardiotoxicity and poor responsiveness to

resuscitation (see Chapter 5). Repeated large doses of bupivacaine have also been reported to cause myotoxicity at the site of infusion (Ilfeld, 2011).

There remains uncertainty about what dose or concentration and/or volume of local anesthetic used in CPNB infusions will provide the best analgesia, and so no evidence-based recommendations can be given for ideal infusion rates and concentrations. However, most services use 0.1–0.125% bupivacaine or levobupivacaine, or 0.1–0.2% ropivacaine (Ilfeld, 2011).

The use of these concentrations allows motor function to be monitored and often maintained. This is particularly important if the patient is needed to actively participate in physiotherapy. Maintenance of analgesia with minimal sensory block will also reduce the risk of pressure areas and improve patient satisfaction (Cowlishaw et al., 2012).

10.1.5.2 Opioids

There are no good data to support the use of opioids in infusions used for CPNB (Ilfeld, 2011).

10.1.5.3 Clonidine and epinephrine

Clonidine and epinephrine (adrenaline) are two α_2-adrenergic agonists that are often added to local anesthetic drugs to increase the duration of "single-shot" nerve blocks (e.g., sciatic nerve). However, there are no clinical benefits from adding either clonidine or epinephrine to solutions used for CPNB; epinephrine may even carry an increased risk of reduced blood flow to nerves due to prolonged vasoconstriction (Ilfeld, 2011).

10.1.5.4 Dexamethasone

Dexamethasone added to the local anesthetic drug in "single-shot" blocks also prolongs the duration of effect (Choi et al., 2014), but it is not used in the infusion solutions for CPNB.

10.1.6 Requirements for the safe management of CPNB

10.1.6.1 Equipment

All CPNB catheters and pumps delivering the local anesthetics should be identified with a clearly visible label; the recommended color coding is yellow.

The pumps that are used to deliver CPNB infusions fall into two main categories—electronic and nonelectronic. If electronic, the use of dedicated pumps (e.g., either color coded or a brand of pump that is different from those used for PCA and sometimes even epidural analgesia) for CPNB is a recommended practice in many services. These pumps should be rate limited (e.g., to 20 mL/h) so infusion rates that are too high cannot inadvertently be programmed and delivered, with the risk of systemic local anesthetic toxicity and major complications including death, especially if inadvertently infused by the intravenous route.

The most common form of nonelectronic pump is the elastomeric device. Most deliver a fixed infusion rate (some allow more flexibility) and the reservoir, once empty, should not be refilled. These devices commonly deliver a higher-than-expected infusion rate (up to 30% higher) and the rate may also be affected by ambient temperature, although this may not be clinically significant (Ilfeld, 2011).

10.1.6.2 Standard orders

Continuous regional nerve blockade will normally be initiated and managed by anesthesiologists. Standard orders and nursing policies and procedures are recommended and are often similar to those used for epidural analgesia.

As with other techniques, preprinted forms are recommended to standardize orders throughout the institution. The forms need to be completed, signed, and dated by the treating anesthesiologist or other member of the pain service. An example of a preprinted CPNB standard order form is given in Appendix 10.1.

At least daily evaluation of the patient by an anesthesiologist or other member of the pain team will allow appropriate alterations to be made to the CPNB regimen and early identification of complications.

Standard orders for CPNB should cover the following requirements.

10.1.6.3 Monitoring and documentation requirements

The following should be monitored at regular intervals:

- Pain score, functional activity score, sedation score, and respiratory rate.
- Blood pressure and heart rate.
- Sensory block—routine monitoring of sensory block is not required and may not be helpful with CPNB. Any increasing sensory deficit should, however, be noted as it may reflect development of a complication.
- Motor block—motor function should be assessed and any decreasing motor function should also be noted.

All observations should be documented at regular intervals, along with the total amount of drug delivered, dose of any drug administered for the treatment of side effects and any changes that have been made to the infusion rates.

10.1.6.4 Drug orders

Orders for drug doses, drug concentrations, dose intervals or infusion rates, and instructions for the treatment of inadequate analgesia are required.

Reported infusion and bolus dose regimens vary considerably, often according to anatomical location, and there is no good information on which to base any firm recommendations. However, in general, infusion rates between 6 and 10 mL/h of a local anesthetic such as 0.2% ropivacaine or 0.125% bupivacaine or levobupivacaine are commonly used. Some forms of CPNB (e.g., femoral) may require the higher infusion rates and bolus doses, while lower rates and bolus doses may be effective in others (e.g., interscalene). Lower infusion rates (e.g., 4–6 mL/h) of a stronger concentration of local anesthetic may also be preferred for use with nerve stump catheters placed after limb amputation, as there is a better chance of the stump dressing remaining relatively dry. In addition, better pain relief may be obtained with a higher concentration in a situation such as this where any concerns about motor blockade are irrelevant.

Bolus doses can also be prescribed—as they are for epidural analgesia, and the size of the dose will also vary according to the form of CNPB used. If bolus doses of local anesthetic only are prescribed, for example, for repeated administration via TAP catheters, larger volumes may be needed.

Increasing motor or sensory deficit should trigger a review of the infusion rate prescribed. In the first instance, a reduction in the rate should be tried, possibly followed by a reduction in concentration if needed.

10.1.6.5 Nursing procedure protocols

The format of nursing procedure protocols for CPNB will vary with each institution, but key elements are similar to those used for epidural analgesia and should include:

- The institution's policy on accreditation (credentialing) of nursing staff
- Monitoring and documentation requirements
- Instructions for
  - Administration of bolus doses
  - Checking the amount of drug delivered (from the infusion pump display when an electronic pump is used) against the amount remaining in the syringe/infusion bag
  - Checking the infusion pump settings against the prescription (e.g., at the change of each shift)
  - Checking the catheter insertion site and dressing
  - Checking and documenting that the catheter is complete after removal
  - The setting up and programming of infusion pumps
  - The management of equipment faults and alarms
  - Recommendations with regard to the positioning of the blocked limb in order to avoid pressure areas and nerve compression
  - Information to be given to patients warning about the risk of decreased sensation, for example, when using sharp tools or touching hot items, and about mobilization.

10.1.7 Patient-controlled CPNB

As multiple factors including catheter site and type influence required infusion regimens and ideal bolus dose, current literature does not support one best approach. However, patient-controlled CPNB, using patient-controlled bolus doses with a continuous background infusion, seems to consistently reduce total consumption of local anesthetic and often supplemental systemic analgesic requirements (Ilfeld, 2011). The approach should thereby decrease motor block, minimize sensory block and enable better control of breakthrough pain, for example, with dressing changes or physiotherapy.

Overall, a low basal infusion rate of 4–6 mL/h for lower and 6–10 mL/h for upper extremity catheters with small bolus doses of 2–10 mL and 20–60 minutes lockout intervals are commonly used (Ilfeld, 2011).

10.1.8 Ambulatory CPNB

Increasingly, a number of forms of CPNB (e.g., interscalene, infraclavicular, axillary, and popliteal sciatic) have been used in patients for ambulatory (day-stay) surgery or after early discharge from inpatient surgery (Ilfeld, 2011). Multiple studies and widespread clinical use confirm the efficacy and safety of ambulatory CPNB. However, successful and safe practice requires careful patient selection, use of reliable infusion devices (reusable or disposable), good patient and carer education (including verbal and written information and 24-hours contact numbers), appropriate patient follow-up (home visit vs. phone calls) and catheter removal protocols.

10.1.9 Complications of CPNB

The risks of complications following CPNB, in particular severe ones, are much lower than the risks associated with epidural analgesia. This is reinforced by the increasing use of CPNB in patients discharged home after surgery (Ilfeld, 2011).

10.1.9.1 Complications arising from the drugs used

Rarely, local anesthetic toxicity (see Chapter 5), either due to inadvertent intravascular injection or excessive dose of the drug, has been reported in association with CPNB (Ilfeld, 2011).

Local anesthetic blockade other than the intended nerves may also lead to complications—for example, brachial plexus blockade may be followed by a block of the phrenic nerve and subsequent diaphragmatic paralysis on the same side.

A specific problem with CPNB of the lumbar plexus (including the femoral nerve) is the increased risk of falls in patients after hip and knee surgery because of impaired motor and/or sensory function including proprioception (Johnson et al., 2013). This requires patient and staff education as well as hospital fall prevention policies for patients with CPNB.

10.1.9.2 Neurological injury

Neurological injury with transient or permanent nerve deficit is the most widely feared complication of all regional anesthetic techniques. Again, as with epidural analgesia, not all neurological deficits after surgery are caused by these techniques, as many orthopedic operations (e.g., hip joint replacement) have an intrinsic risk of surgical nerve damage.

Available data suggest that the risk of a transient neurologic deficit due to CPNB is in the range of 0.2% (0.1%–1.4%) and most of these resolve within 3 months; the risk of longer lasting (>9 months) and potentially permanent neurologic injury is in the range of 0.07% (Ilfeld, 2011).

10.1.9.3 Complications arising from infection

The indwelling catheters used for CPNB carry an inherent risk of clinically relevant infection in the range of <1%, although the incidence of bacterial colonization of the infusion catheter is much higher (Ilfeld, 2011). The risk rises with admission to an intensive care unit, lack of perioperative antibiotic cover, male gender, and increasing duration of use. However, long-lasting use of CPNB has been used without problems in a considerable number of patients. Initially, catheters inserted via the axillary and femoral route were seen as carrying an increased risk, but the interscalene catheter has been added to this list.

10.1.9.4 Complications arising from anticoagulation

Significant blood loss and hematoma formation (rarely requiring surgical drainage) rather than neurological deficit seems to be the main risk when CPNB is used in patients taking antithrombotic medications, although nerve damage from bleeding has been reported. It has been suggested that the guidelines for the use of anticoagulant and antiplatelet drugs in patients for epidural analgesia (see Chapter 9) also be used in patients with deep plexus and deep peripheral CPNB (Horlocker, 2011). However, it is also recognized that these guidelines may be too conservative for superficial and compressible CPNB sites.

10.1.9.5 Other complications

Multiple other complications can occur in the setting of CPNB. These include those related to the needle insertion (e.g., pneumothorax following brachial plexus blockade), pump malfunction, catheter dislodgement, migration or leakage, catheter knotting, and catheter retention after breakage.

10.2 Intraarticular analgesia

Intraarticular morphine was commonly used after arthroscopic surgery on the knee. While it was thought to provide reasonable pain relief for up to 24 hours, there is now clear evidence that the effect is no better than placebo (ANZCA and FPM, 2010).

Less commonly, intraarticular administration of local anesthetics, either as a bolus dose or by continuous infusion, has been tried after knee and shoulder surgery. However, good evidence for reliable analgesia is currently lacking. There is evidence from a case series (35 cases), and supportive evidence from animal studies, of chondrolysis (necrosis and destruction of cartilage) after intraarticular infusion of local anesthetics, in particular with bupivacaine. With the exception of ropivacaine, the FDA warns against such local anesthetic infusions (Kamath et al., 2008).

10.3 Wound infiltration

Infiltration of a wound with a local anesthetic at the end of surgery can provide pain relief for a short while. It may be of particular benefit for pain after minor surgery such as inguinal hernia surgery. However, after more major surgery, a longer duration of analgesia is preferred.

The efficacy of continuous wound infiltration with local anesthetics appears to vary with the type of surgery. For example, improved pain scores and reduced opioid consumption have been reported in patients after obstetric and gynecological surgery, but are much less likely to be seen after major abdominal and urological procedures (Gupta et al., 2011). Patient-controlled wound infusion techniques have also been used.

Since the initial description from Australia in 2008 (Kerr and Kohan, 2008), high-volume LIA techniques have become popular for the treatment of pain, primarily after hip and knee joint replacement, although there remains limited information about comparisons with peripheral nerve blockade (Fowler and Christelis, 2013). The injection techniques described vary widely, both single-shot and continuous infusions have been used. However, the benefit of some of the drugs that have been added to the local anesthetic (commonly ketorolac, morphine, epinephrine) remains under investigation.

10.4 Topical analgesia

Topical use of local anesthetics is often forgotten in acute pain settings. As long as recommended maximum doses of the drugs are not exceeded, it can be a very simple and safe way of providing pain relief (ANZCA and FPM, 2010).

One example is during dressing changes in patients with leg ulcers. The top layers of the dressing can be removed and then the remaining layers soaked with local anesthetic and left for 10–15 minutes. Additional local anesthetic can then be added in increments as the last layers of the dressing are slowly removed. Topical EMLA® cream (eutectic mixture of lidocaine and prilocaine) has also been used for venous ulcer debridement (Briggs et al., 2012).

Key points

1. The use of CPNB can lead to excellent analgesia with minimal adverse effects and improvement of recovery with a number of techniques after a wide range of operations; they can replace systemic analgesia and even epidural analgesia in defined circumstances.
2. CPNB techniques for upper and lower limb surgery as well as thoracic surgery (paravertebral catheters) and abdominal surgery (TAP catheters) have been found to provide excellent pain relief and when they can be used as an alternative to epidural analgesia they have a lower risk of complications.
3. CPNB can be optimized by use of patient-controlled techniques and has been used successfully in patients who have been discharged home.
4. Complications of CPNB are rare and can be prevented in part with appropriate monitoring.
5. Intraarticular analgesia is ineffective with morphine; intraarticular administration of local anesthetists may cause damage to cartilage within the joint and should be avoided.
6. Wound infiltration of local anesthetics and the infusion of local anesthetics through catheter places in the wound are effective analgesic techniques in some circumstances.
7. High-volume LIA is a potentially useful technique in particular after knee joint replacement, but requires further investigations.
8. Topical analgesia with local anesthetics is simple and effective, but often a neglected technique and in particular is useful for dressing changes and debridement in leg ulcers.

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Appendix 10.1: Example of a "standard order" form for continuous regional analgesia

CALHN
RAH ☐ TQEH ☐

ACUTE PAIN SERVICE
OTHER CONTINUOUS REGIONAL ANALGESIA

PATIENT LABEL

Unit Record No.: _____

Surname: _____

Given Names: _____

Date of Birth: _____ Sex: _____

LOCAL ANAESTHETIC ORDERS: *(* = sign and date any changes)*

1. **DRUG:** .....

Place appropriate drug label here

2. **CONCENTRATION:** .....

3. **BOLUS DOSES AND INFUSION RATES**

If continuous regional analgesia catheter (CRA) is not labelled please call the anaesthetist who signed these orders or the APS.

CRA CATHETER 1	**CRA CATHETER 2**
Location:	**Location:**
Bolus Dose: *	**Bolus Dose: ***
..... to .....mL	..... to .....mL
..... hourly PRN or	..... hourly PRN or
at..... hrs, ...hrs,.....hrs	at..... hrs, ...hrs,.....hrs
Infusion rate: *	**Infusion rate: ***
..... to .....mL/hr	..... to .....mL/hr
Requested duration of infusion ..... days	**Requested duration of infusion** ..... days

GENERAL ORDERS:

1. Oxygen at *2 to 4 L/min via nasal specs or 6 L/min via mask* while orders are in effect.
2. Systemic opioids (including intermittent PRN oral or subcutaneous opioids, or PCA opioid, or any long-acting opiod that the patient takes on a regular basis) may be continued.
3. No anticoagulant or antiplatelet medications, including NSAIDS, to be given (other than heparin for the prevention of DVTs or low-dose aspirin) before consulting with the APS. *Anaesthetist to delete if not applicable (please sign and date).*

   Signature .....

   Date .....
4. An anti-syphon valve must be in-line between patient and any CRA syringe or infusion bag at all times.
5. Maintain IV access while orders are in effect.
6. *Monitoring requirements:* see overleaf.
7. For inadequate analgesia or other problems related to the analgesia, contact the APS. The APS should be notified if the patient has two consecutive pain scores >7 at rest and/or FAS = C.
8. Mobilise patients according to parent clinic instructions but accompanied by 2 staff members initially in case of problems with gait and/or balance.

   YES NO Signature .....

SIGNATURE OF ANAESTHETIST: ..... Date: .....

(Print name .....)

CATHETER 1	**CATHETER 2**
Cease infusion and remove catheter: Date:..... Time:	**Cease infusion and remove catheter:** Date:..... Time: .....
Give next dose of heparin: Date:..... Time:	**Give next dose of heparin:** Date:..... Time: .....
Signature of anaesthetist:	Signature of anaesthetist: .....
Catheter 1 removed and complete:	**Catheter 2 removed and complete:**
Signature of RN:.....	Signature of RN:.....
Date:.....	Date:.....

APS-OTHER REGIONAL ANALGESIA **MR 98.1**

CALHN

OTHER CONTINUOUS REGIONAL ANALGESIA

Observations and Record of Drug Administration

PATIENT LABEL

Unit Record No.: _____

Surname: _____

Given Names: _____

Date of Birth: _____ Sex: _____

MONITORING REQUIREMENTS: **Record Items 1 to 5 EACH HOUR for 8 hours and then 2 HOURLY**

If the patient also has PCA, record pain scores and FAS, sedation scores and respiratory rate on the PCA order form only. Movement, sensation and cumulative total local anaesthetic doses must be charted on this form.

1. **PAIN SCORES AND FAS**
2. **SEDATION SCORE**
3. **RESPIRATORY RATE**
4. **MOVEMENT AND SENSATION**
5. **CURRENT TOTAL DOSE**

After administration of a bolus dose:
Record Items 1 to 4 every 5 minutes for 20 minutes.

Pain Score:

0 = no pain

10 = worst pain imaginable

NB: record pain scores at rest and with movement eg. coughing

Sedation Score:

If the patient is also requiring systemic opioid analgesia, sedation scores should be recorded according to the guidelines for that technique of opioid administration.

If sedation score ≥ 2, notify the APS. If sedation score = 3 also initiate a MER call. Cease CRA infusion and/or administration of a bolus dose. Revert to hourly observations until sedation score < 2 for at least 2 hours. Do not give any opioid.

Functional Activity Score (FAS):

A = no limitation of relevant activity due to pain (relative to baseline)

B = mild limitation of activity due to pain

C = unable to complete activity due to pain

Current total dose of infusion (if running):

Record in mL. Reset total dose to zero when syringe is changed and document the volume discarded.

Movement and Sensation:

- Ask the patient if they have any numbness/weakness.
- IF ALL IS NORMAL, record M✓ S✓ in the M/S column; otherwise document and call the APS.

CRA insertion site:

At each handover of shift, check CRA catheter insertion site and record and report any new or increasing inflammation, tenderness, swelling or leakage. Reinforce dressing if needed but do not remove or replace.

DRUG: ..... **Location of Catheter 1:** ..... **Location of Catheter 2:** .....

Date	Time	**Catheter 1** Dose (total mL)	**Catheter 2** Dose (total mL)	Pain Scores ..... X 0 2 4 6 8 10	FAS	Sed'n Score	Resp Rate	M/S	Comments	Signature RN or MO
				0 2 4 6 8 10						

ADVERSE DRUG REACTIONS

Drug	Date	Details	Signature

LOCAL ANAESTHETIC TOXICITY

Signs and symptoms include: metallic taste, tingling around mouth, visual disturbances, tinnitus, muscle twitching, convulsions, loss of consciousness.

If patient shows symptoms, cease CRA infusion and/or administration of a bolus dose. Give oxygen by mask, notify APS. Initiate a MER call if patient meets criteria.

DRUG: ..... **Location of Catheter 1:** ..... **Location of Catheter 2:** .....

Date	Time	**Catheter 1** Dose (total mL)	**Catheter 2** Dose (total mL)	Pain Scores ..... X 0 2 4 6 8 10	FAS	Sed'n Score	Resp Rate	M/S	Comments	Signature RN or MO
				0 2 4 6 8 10						

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CHAPTER 11

Nonpharmacological therapies

Nonpharmacological therapies can also be used in the treatment of acute pain and may be beneficial for some patients in some settings. However, when used alone, these strategies will usually not be effective for the treatment of moderate-to-severe acute pain. They should therefore be considered as supplementary to the analgesic techniques described in earlier chapters.

A number of the techniques described below require time and specialized training and will not be suitable for routine use in the management of acute pain.

11.1 Psychological interventions

Psychological therapies aim to alter the psychological processes that may contribute to pain. They include provision of information, stress, and tension reduction (relaxation and hypnosis), attentional techniques, and cognitive behavioral interventions (ANZCA and FPM, 2010).

As a group, psychological interventions may reduce pain, disability, and mood in adults with chronic non-headache pain, and children and adolescents with chronic and recurrent pain (Eccleston et al., 2014a,b), although evidence for the benefit of each type of therapy may vary.

In general, in the acute pain setting, most information related to psychological strategies comes from their use in the treatment of procedural pain.

11.1.1 Information

Information given to patients can be procedural (summarizing what will happen during treatment), sensory (describing the sensory experiences the patient may expect during treatment) or a combination of the two.

Appropriate education and information (see Chapter 2) about the details of all procedures and expected levels of discomfort and ways to decrease pain may, in some patients, decrease distress and analgesic use and improve pain relief, although evidence of benefit remains inconsistent (ANZCA and FPM, 2010; Louw et al., 2013). For other patients, however, especially those with an avoidant coping style (e.g., a tendency to use denial or avoidance to deal with problems), excessive information and the need to make decisions can exacerbate anxiety and pain. As much as possible, the information given should therefore be tailored to each patient.

11.1.2 Relaxation and attentional strategies

Relaxation strategies (e.g., controlled breathing, muscle relaxation, and the use of imagery) teach patients various ways to reduce their feelings of stress and tension. In the acute pain setting, some studies have suggested some benefit, however good-quality evidence is lacking (ANZCA and FPM, 2010).

Attentional techniques include distraction (e.g., listening to music) and imagery (e.g., imagining pleasant events or scenes). Immersive virtual reality (VR) distraction systems aim to allow patients to "escape" into a computer-generated world during painful procedures. Most work has been done in patients (both children and, to a lesser extent, adults) undergoing burns dressing changes, where VR has been shown to significantly reduce the pain experienced (Hoffman et al., 2011). Less immersive VR systems may be adequate for less severe pain.

11.1.3 Cognitive behavioral interventions

Some patients respond to pain in a way which is helpful, while others may become overly alarmist and catastrophize, which can lead to more pain (ANZCA and FPM, 2010). Cognitive behavioral therapies (CBT) are derived from the study of learning and behavior change and are usually aimed at identifying unhelpful responses and reducing the distress or threat. They can be used to alter the way in which patients perceive, interpret, and cope with pain. In patients with chronic pain, CBT may improve pain and mood, and reduce disability and catastrophizing (Williams et al., 2012).

11.1.4 Hypnosis

Hypnosis may be effective in some patients with chronic pain (Jensen and Patterson, 2014).

In the acute setting, it has usually been used for the management of pain associated with medical procedures (e.g., burns wound care, bone marrow aspiration) and childbirth. In these settings it may also provide some pain relief (Stoelb et al., 2009).

11.2 Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is simple, safe, noninvasive, and free from systemic side effects, and allows patients some control over their own therapy. The battery-powered TENS unit generates a small electric current which is transmitted to electrodes placed on the skin. In human experimental pain studies, high-frequency TENS has been shown to have analgesic properties that can be blocked by the administration of naloxone (Leonard et al., 2010).

It has been suggested that benefit from TENS may differ according to whether high or low current intensities are used—high rather than low intensity being thought to be effective (ANZCA and FPM, 2010). However, most studies have used TENS in combination with other acute pain relief therapies and not as the sole means of treatment. Evidence of benefit for TENS as a treatment on its own in the management of acute pain is lacking (Walsh et al., 2009).

11.3 Acupuncture

Despite its popularity, there is little good evidence that acupuncture is of benefit in patients with pain in general (Ernst et al., 2011), but it may help with the management of pain in labor (Smith et al., 2011). There is limited evidence of benefit in the treatment of postoperative pain, although it may improve pain after some types of surgery, but not reduce opioid consumption (Cho et al., 2014).

11.4 Physical interventions

Applications of heat or cold, massage, exercise, and immobilization (e.g., of a limb) may help to relieve pain and muscle spasm, especially that associated with back and other musculoskeletal injuries.

Key points

1. Of the available psychological interventions used for the management of acute pain, immersion VR appears to be the most effective.
2. Hypnosis, TENS, and acupuncture may be effective in some patients in some acute pain settings, but evidence of benefit is limited.

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CHAPTER 12

Acute neuropathic and persistent postacute pain

Although neuropathic pain is common in many chronic pain states, its role in the acute pain setting is underestimated. There are a number of patients in whom neuropathic pain contributes to or even predominates the acute pain they are experiencing. However, acute neuropathic pain often goes undiagnosed and is therefore undertreated. It may develop immediately after the initial injury or quite some time later, but often still in the phase of acute pain treatment. Therefore, it is important for those who look after patients with acute pain to be aware of the signs and symptoms of neuropathic pain and available treatment options. These patients may present with pain that is responding poorly to opioids. Such patients may be labeled as inappropriately sensitive to pain or even as "drug seeking," when they are simply seeking effective pain relief ("pseudoaddiction").

In addition, patients after surgery or recovering from injury are at risk of developing persistent (chronic) pain, which is also often neuropathic in origin (Schug and Pogatzki-Zahn, 2011). The incidence and severity of persistent postsurgical pain (PPSP) is also widely underestimated. Early recognition and aggressive management of pain in these patients (possibly including preventive measures—see later) may reduce the incidence and severity of subsequent persistent pain problems.

Provision of effective pain relief in patients with acute or later persistent neuropathic pain can be a difficult and a challenging task and one that may be ongoing for weeks, months, or even years. In such cases it is recommended that advice be obtained from a specialist pain medicine physician. Often these patients need appropriate referral to a chronic pain clinic for follow-up after treatment of the acute situation and after discharge from hospital. Losing these patients to follow-up can delay appropriate ongoing treatment and thereby impair functional recovery after otherwise successful surgery or treatment of injury.

12.1 Pathophysiology of neuropathic pain

Pain can be broadly classified into two main types—nociceptive and neuropathic—see Chapter 3.

Nociceptive pain is the most common type of pain seen in the acute clinical setting and its treatment is therefore the primary focus of this book. Neuropathic pain is defined as "pain caused by injury or disease of the somatosensory nervous system" (Jensen et al., 2011). It is also referred to as neurogenic pain, deafferentation pain, neuralgia, neuralgic pain, and nerve pain. It is the pathophysiological consequence of multiple changes in the peripheral and central nervous systems that occur after nerve injury (Cohen and Mao, 2014) (see Table 12.1).

In the periphery, such lesions lead to structural and functional changes in the damaged neuron. Increased expression of ion channels (in particular,

Table 12.1 Pathophysiological changes underlying neuropathic pain

Peripheral nervous system

- Increased expression of ion channels and receptors leading to increased discharge of action potentials (ectopic)
  - Spontaneous
  - Evoked
- Microneuroanatomical changes
  - Collateral sprouting
  - Cross-connections
  - Sympathetic-sensory coupling
- Phenotypical changes
  - Touch fibers develop pain fiber behavior

Spinal cord

- "Central sensitization"
- Overexpression of voltage-gated calcium channels
- Loss of large fiber inhibition
- Deafferentiation hyperactivity
- Anatomical reorganization
- Microglia activation

Brain

- "Central sensitization"
- Reorganization of somatosensory cortex

Source: Modified from multiple sources including Baron R, Binder A, Wasner G. 2010. *Lancet Neurology* **9**(8): 807–19; Zhuo M, Wu G, Wu LJ. 2011. *Molecular Brain* **4**: 31; Saab CY. 2012. *Trends in Neurosciences* **35**(10): 629–37; Cohen SP, Mao J. 2014. *British Medical Journal* **348**: f7656.

voltage-gated sodium channels) and upregulated receptors reduce the threshold for inducing action potentials and lead to increased numbers of action potentials described as "ectopic discharges"—that is, spontaneous firing of nerve impulses (Baron et al., 2010). Other peripheral changes are related to alterations in the microneuroanatomy (e.g., touch fibers become pain fibers).

At a central level, central sensitization develops as a result of ectopic activity in the periphery. This results in increased release of excitatory amino acids (e.g., glutamate) and neuropeptides (e.g., substance P) in the dorsal horn of the spinal cord, where they lead to functional changes of second-order neurons. These changes are referred to as neuroplasticity and manifest as hyperexcitability leading to hyperalgesia and allodynia. Similar changes also occur at a supraspinal level (Baron et al., 2010). Nerve injury leads to loss of inhibitory interneurons and the resulting disinhibition contributes to the pain experienced. Furthermore, chemokine release as an inflammatory response to the nerve injury leads to microglial activation with release of immune modulators, thereby maintaining the neuropathic pain state (Zhuo et al., 2011).

There is also increasing recognition of the role of reorganization of the somatosensory cortex as a contributing factor to neuropathic pain, including phantom limb pain and complex regional pain syndrome (CRPS) (Saab, 2012).

12.2 Clinical features and diagnosis of neuropathic pain

The diagnosis of neuropathic pain can usually be made on the basis of a complete history and basic physical examination (see Chapter 3). Patients will typically describe their pain as "strange" and different from "normal" wound pain.

A common feature is the coexistence of negative (neurological deficit) and positive signs such as spontaneous (e.g., stabbing, shooting) or evoked pain and paresthesias. Evoked pain can be allodynia—the perception of pain in response to a non-nociceptive stimulus, or hyperalgesia—an exaggerated pain response to a nociceptive stimulus (Baron et al., 2010).

Neuropathic pain is most obvious when the pain occurs in an area of complete neurological deficit, for example, below the level of the lesion after spinal cord injury or in a flaccid arm after brachial plexus injury. However, neuropathic pain can also be the consequence of very minor nerve injury, which does not result in any or any major neurological signs or symptoms. These might even go undetected by diagnostic tests such as nerve conduction studies.

Features that suggest neuropathic pain are listed in Chapter 3 in Table 3.1. It is important to note that not all of these have to be present in order for a diagnosis of neuropathic pain to be made.

Screening tools such as the *Douleur Neuropathique en 4 questions* (DN4), the *Leeds Assessment of Neuropathic Symptoms and Signs* (LANSS), the *Neuropathic Pain Questionnaire* (NPQ), ID-Pain, and the *PainDetect* questionnaires can identify patients with neuropathic pain with relatively high specificity and sensitivity, but should not replace clinical assessment and diagnosis (Haanpaa et al., 2011).

There are published recommendations for the diagnosis of neuropathic pain in general (Haanpaa et al., 2011) and specifically after surgery (Searle et al., 2012). The items identified as predictive in the postsurgical setting were spontaneous, shooting or burning pain, dysaesthesia, allodynia and hyperalgesia, and pain that was difficult to manage, poorly responsive to opioids or showed a good response to antineuropathic agents.

12.3 Acute neuropathic pain syndromes

It makes sense to separate postoperative and posttraumatic neuropathic pain (i.e., the majority of cases presenting in an acute pain setting) from neuropathic pain caused by cancer or associated with medical illnesses. While the latter two are more commonly chronic pain states, they can present acutely—for example, rapidly increasing spinal cord compression by an epidural metastasis, acute herpes zoster (shingles), Guillain–Barré syndrome, or multiple sclerosis.

A few of the many possible clinical situations where acute neuropathic pain is common are listed in Table 12.2. Some specific acute neuropathic pain syndromes are discussed below—postamputation pain and CRPS, and pain after burns and spinal cord injury, and that associated with herpes zoster, HIV/AIDS, multiple sclerosis, and Guillain–Barré syndrome are discussed in Chapter 13.

12.3.1 Postamputation pain syndrome

Amputation of a limb by trauma or surgery is inevitably associated with nerve injury. This can lead to a number of phenomena—stump pain, phantom sensations, and phantom pain (Hsu and Cohen, 2013). The underlying mechanisms are a combination of peripheral, spinal, and supraspinal ones.

Table 12.2 Examples of neuropathic pain in the acute setting

Postoperative

- Postamputation
- Postthoracotomy
- Postmastectomy
- Posthernia repair

Postinjury

- Spinal cord injury
- Postamputation
- Burns injury
- Brachial plexus avulsion
- Sacral nerve root injury in association with a fractured pelvis
- Sciatica
- Major crush injuries of upper or lower limbs

Associated with cancer

- Pancreatic cancer (involvement of the celiac plexus)
- Compression or infiltration of the brachial plexus after spread of lung cancer to apical lymph nodes
- Involvement of sacral nerve roots by pelvic lymph node metastases
- Compression or infiltration of the spinal cord by epidural metastases (impending acute danger of paraplegia)

Associated with medical illnesses

- Viral infections, for example, acute herpes zoster (shingles), HIV/AIDS, CMV
- Poststroke pain
- Guillain–Barré syndrome
- Diabetic neuropathy
- Alcoholic neuropathy
- Demyelinating diseases such as multiple sclerosis

Stump pain (residual limp pain) refers to pain in the stump itself. It can be of nociceptive or neuropathic origin and has multiple etiologies (Clarke et al., 2013). It is most common in the early postoperative period—usually as nociceptive wound pain. If it becomes persistent, it is often neuropathic and can lead to severe disability and interfere with the wearing of a prosthesis.

Phantom sensation is defined as any sensation of the absent body part except pain and is experienced by almost all patients (80–100%), who have undergone amputation. The sensation can range from a vague awareness of the limb (possibly with associated paresthesia) to complete sensation including size, shape, position, temperature, and movement. While there is no treatment for phantom sensations, it is important to explain to patients that these usually diminish in intensity and size over time. "Telescoping" of the phantom limb is a common experience; the limb gradually shrinks to approach the stump.

Phantom limb pain is defined as any painful sensations that are referred to the absent body part and is estimated to occur in up to 85% of patients (ANZCA and FPM, 2010). The pain is independent of gender, cause (elective or traumatic

amputation), or side of amputation, but appears to have a lower incidence in children and congenital amputees. The pain usually occurs in the distal portion of the missing limb and may resemble any preamputation pain in character and localization. Often the limb is described as being in a hyperextended or otherwise unnatural position. Phantom pain can develop immediately following amputation or have a delayed onset; in 75% of patients it occurs within the first few days, often in connection with stump pain (Hsu and Cohen, 2013).

All three phenomena can occur in the same patient. The risk of phantom limb pain appears to be increased if severe pain existed prior to amputation. Other potential risk factors are severe postoperative stump pain and chemotherapy.

Phantom pain and sensations can also follow surgery for amputation other than limbs, for example, mastectomy, excision of tongue or rectum, or after removal of teeth.

12.3.2 Complex regional pain syndrome

Complex regional pain syndrome is not a straightforward manifestation of neuropathic pain, but excellently described as a "disease of neuronal systems" (Janig and Baron, 2003). There are currently at least eight major hypotheses on the pathophysiology, which illustrate the lack of understanding about the syndrome; these range from inflammatory processes via autoimmune disease to nerve damage (Marinus et al., 2011).

The diagnosis is currently made according to the Budapest criteria (Marinus et al., 2011). The patient has continuing pain disproportionate to an inciting event (often fracture, but can be a minor injury). The presentation includes sensory disturbances such as allodynia or hyperalgesia; vasomotor dysfunction leading to temperature or skin color changes/asymmetry, sudomotor dysfunction with changes in sweating or asymmetry or edema; and/or motor dysfunction (range, weakness, tremor, dystonia); or dystrophy (hair, skin, or nails). Signs in two or more, or symptoms in three or more of these four areas are required to make a diagnosis by exclusion of other causes.

The nomenclature differentiates between CRPS Type 1 and 2. Type 1 (previously referred to as "reflex sympathetic dystrophy" or RSD) shows the features listed above in the absence of detectable nerve injury. The term CRPS type 2 (previously referred to as "causalgia") is used when these features occur subsequent to nerve injury.

Early detection and immediate appropriate treatment are the key factors to success and require acute pain therapists to be aware of these syndromes. There is some evidence that intake of vitamin C has a preventive function on CRPS (Shibuya et al., 2013), but further studies are needed.

12.4 Treatment of acute neuropathic pain

Treatment of neuropathic pain may require a combination of pharmacological, physical, and behavioral therapy. In the acute stage, initial treatment usually begins with drug therapy and/or the use of regional neural (neuraxial or peripheral nerve) blockade. Most studies that look at the treatment of neuropathic pain investigate the management of chronic neuropathic pain (e.g., diabetic neuropathy, postherpetic neuralgia [PHN]). There is much less evidence for the treatment of acute neuropathic pain, so management strategies in the acute setting must be extrapolated from evidence-based treatment of the chronic pain state (Dworkin et al., 2010).

12.4.1 Pharmacological treatments

12.4.1.1 Specific treatment of acute neuropathic pain states

First-line treatments for acute neuropathic pain are identified in Table 12.3. Tramadol and opioids are recommended as first-line agents as their onset of effect is fast (Dworkin et al., 2010). While neuropathic pain has often been regarded as unresponsive to opioids, this is not correct. Multiple studies have shown opioid responsiveness in a number of neuropathic pain conditions (McNicol et al., 2013). However, neuropathic pain is typically less responsive to opioids than nociceptive pain. One of the early signs of development of neuropathic pain in the acute situation is ineffective pain relief despite increasing doses of opioid, and/or possibly the onset of sedation in a patient who still reports high pain scores.

Table 12.3 Commonly used pharmacological options ranked for the treatment of acute and chronic neuropathic pain

Drugs	Examples	Ranking for use in acute neuropathic pain	Ranking for use in chronic neuropathic pain
Gabapentinoids	Pregabalin, gabapentin	First-line	First-line
TCAs[a]	Amitriptyline, nortriptyline, desipramine, imipramine, dothiepin, doxepin	First-line	First-line
SNRIs[b]	Duloxetine, venlafaxine	First-line	First-line
Opioids and tramadol[c]	Tramadol, oxycodone, morphine, methadone	First-line	Second- to third-line
NMDA receptor antagonists	Ketamine	First-line	Fourth-line
Membrane stabilizers	Lidocaine (lignocaine)	Second-line	First- to second-line in topical neuropathic pain (patch)
Other anticonvulsants	Carbamazepine		First-line only in trigeminal neuralgia
Alpha-2-adrenergic agonists	Clonidine		Useful adjuvant

Source: Modified from multiple sources including O'Connor AB, Dworkin RH. 2009. *The American Journal of Medicine* **122**(10 Suppl): S22–32; Attal N, Cruccu G, Baron R et al. 2010. *European Journal of Neurology* **17**(9): 1113–e88; Dworkin RH, O'Connor AB, Audette J et al. 2010. *Mayo Clinic Proceedings. Mayo Clinic* **85**(3 Suppl): S3–14; and Western Australian Therapeutic Advisory Group (WATAG). 2013. *Guidelines for the Treatment of Neuropathic Pain*. http://www.watag.org.au/watag/docs/130717_Advisory%20Note_Neuropathic%20Pain%20Guidelines%20ver2.pdf. Accessed January 2014.

[a] TCAs, tricyclic antidepressant agents.

[b] SNRIs, serotonin noradrenaline reuptake inhibitors.

[c] Neuropathic pain is often only partially responsive to opioids.

Other drugs recommended for the first-line treatment of acute neuropathic pain are gabapentinoids and tricyclic antidepressants (TCAs) or serotonin norepinephrine (adrenaline) reuptake inhibitors (SNRIs) (Dworkin et al., 2010). Benefits with TCAs may be seen within a few days in some patients, but it may take longer in others. In view of this gabapentinoids are preferred by some in the acute setting.

In severe acute neuropathic pain that is not responsive to opioids, ketamine offers a unique opportunity to achieve control quickly with a drug that can be given parenterally. There are case-based data to support this approach in the acute phase of spinal cord injury pain (Kim et al., 2013). An alternative to ketamine is intravenous (IV) lidocaine (lignocaine), but the efficacy of lidocaine is lower and potential risks higher (Kvarnstrom et al., 2004). In contrast, ketamine is only a fourth-line treatment option for chronic neuropathic pain (WATAG, 2013).

12.4.1.2 Treatment approaches to neuropathic pain in general

Multiple evidence-based guidelines for the treatment of neuropathic pain are available (O'Connor and Dworkin, 2009; Attal et al., 2010; Dworkin et al., 2010; WATAG, 2013). In contrast with the recommendations given for the treatment of acute neuropathic pain, these agree that that gabapentinoids (gabapentin and pregabalin), TCAs, and SNRIs should be the first-line treatment options for chronic neuropathic pain and that tramadol and opioids be relegated to second- or third-line choices. Topical lidocaine patches should be reserved for localized pain (see below).

The sequence of treatments used will inevitably be altered in clinical practice due to factors such as clinical experience in the acute pain setting, interpatient variations and financial constraints.

Effective relief of neuropathic pain is often difficult to achieve and may require the use of a combination of different drugs, ideally with different mechanism of action (Vorobeychik et al., 2011). These are often added in a stepwise manner as needed at intervals of a few days to weeks, so that the effectiveness of each addition can be seen.

For more details on the various pharmacological options, see Chapter 6.

12.4.1.3 Topical treatments

Topical agents may be useful for localized neuropathic pain states such as PHN and nerve entrapment syndromes, in particular when allodynia is a prominent feature of the pain.

Lidocaine is now widely available as a patch for topical use. These 10×14 cm adhesive patches, which are very soft and contain 700 mg of lidocaine, are worn over the painful area. Due to the poor diffusion of lidocaine through the skin, they have no local anesthetic effect on the skin and no systemic effect (plasma concentrations are barely measurable) (Mick and Correa-Illanes, 2012). Where available, lidocaine patches are regarded as the first-line treatment of focal neuropathies including PHN, especially in the older patient (O'Connor and Dworkin, 2009).

Some patients with a localized neuropathy use EMLA® (eutectic mixture of local anesthetics—prilocaine and lidocaine) cream for similar purposes, but this mixture is easily absorbed systemically and the high prilocaine content can result in methemoglobinemia if used repeatedly in higher doses.

Capsaicin (the active ingredient of hot chili peppers) is another compound used topically in these situations. It is available as a low-concentration cream that is applied to the painful area several times a day, or as a high-concentration plaster. Its analgesic effect is believed to result from the depletion of substance P (a neurotransmitter) in unmyelinated sensory nerves, which then leads to a block of these nerves. When applied to the skin, capsaicin cream first induces a burning feeling and hyperalgesia, which is why patients sometimes like to use EMLA® cream before capsaicin is applied. There is no high-level evidence for the effectiveness of low-concentration capsaicin in neuropathic pain (Derry and Moore, 2012). The high-concentration (8%) patch registered in a number of countries needs to be administered under controlled conditions and with prior local anesthetic use, and has shown efficacy in some patients depending on diagnosis and duration of effect (Derry et al., 2013).

Topical applications of aspirin (better than other NSAIDs) in chloroform or ether suspension have also been reported to be of some benefit in patients with PHN (De Benedittis and Lorenzetti, 1996).

12.4.2 Regional neural blockade

A variety of regional and sympathetic blocks have been used in the treatment of neuropathic pain, however, most of these interventions are either ineffective or only of short-term efficacy.

Evidence-based recommendations show that the evidence for most interventions is inconclusive (Dworkin et al., 2013). A weak recommendation was made for epidural or paravertebral local anesthetic/steroid blocks for treatment of acute pain associated with herpes zoster, which may also have a preventive effect on PHN; however, sympathetic blocks to treat PHN are not recommended. Similarly there is a weak recommendation for epidural steroid injections to treat radiculopathy.

However, in the acute setting, even an effect of limited duration can be useful, similar to the palliative care setting. Therefore, regional nerve blockade, ideally using an infusion through a catheter, should be considered for the treatment of acute localized neuropathic pain after surgery or injury. Furthermore, as outlined below, regional neural blockade may have a preventive effect on development of persistent postsurgical pain including phantom limb pain after amputations (Gehling and Tryba, 2003).

12.4.3 Transcutaneous electrical nerve stimulation

The experience with transcutaneous electrical nerve stimulation (see Chapter 11) suggests a clinically useful effect of this simple, harmless, and noninvasive approach to pain relief. However, there are insufficient data to support this as an evidence-based treatment of neuropathic pain (Johnson and Bjordal, 2011).

12.4.4 Treatment of postamputation pain syndromes

In general, acute neuropathic pain resulting from most causes can be managed as described above. Some specific comments regarding neuropathic pain resulting from spinal cord injury, burns injury, and neurological disease are made in Chapter 13. However, as pain after amputation is common, more detail about the management of postamputation pain syndromes is given below.

The treatment of stump pain, which is often of a nociceptive and inflammatory origin, requires the use of multimodal analgesia. However, if it has more neuropathic qualities or does not respond to this approach, then treatment options for acute neuropathic pain in general should be tried.

Treatment options for phantom limb pain also include those mentioned above for the management of acute neuropathic pain in general. Although based on limited evidence, there is some support for the use of ketamine, opioids, tramadol, gabapentinoids, and amitriptyline (ANZCA and FPM, 2010). Acute phantom limb pain can also be treated more specifically by the use of repeated daily IV infusions, subcutaneous injections or intranasal administration of salmon calcitonin (100–200 IU) after prophylactic use of an antiemetic (ANZCA and FPM, 2010). Institution of preventive analgesia prior to amputation (see below) is also worthwhile.

12.5 Progression of acute to persistent pain

The progression of acute pain to persistent pain after surgery, trauma, or even acute medical disease (such as shingles to PHN) is an underestimated problem, which has significant long-term consequences for the patient as well as for healthcare costs and for society (Schug and Pogatzki-Zahn, 2011). Persistent postsurgical pain has been defined as pain that develops after surgery and lasts at least two months. It is a diagnosis made by exclusion of other causes of pain, in particular, pain from a condition preceding surgery. The epidemiological data on this condition are conflicting, but overall the estimated incidence of severe disabling PPSP is in the range of 2–10% and depending on the type of surgery (Kehlet et al., 2006).

Most of these pain states have an element of neuropathic pain (Kehlet et al., 2006). The risk of nerve injury appears to be higher after some operations than others and this may lead to PPSP (see Table 12.4). Two commonly quoted examples are thoracotomy and mastectomy, where an intercostal nerve or the

Table 12.4 Incidence of persistent postsurgical pain

Surgery	Incidence (%)[a]
Amputation	30–85
Thoracotomy	5–65
Mastectomy	11–57
Inguinal hernia	5–63
Coronary artery bypass	30–50
Caesarean section	6–55
Cholecystectomy	3–50
Vasectomy	0–37
Dental surgery	5–13

Source: Adapted with permission from Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (ANZCA and FPM). 2010. *Acute Pain Management: Scientific Evidence*. 3rd edn. Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM (eds). Melbourne: Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. http://www.fpm.anzca.edu.au/resources/books-and-publications. Accessed October 2013.

[a] Reported incidences vary between studies.

intercostobrachial nerve, respectively, may be damaged. Other operations with a high incidence of PPSP include limb amputation, as already noted, and hernia repair. Besides the type of surgery (most likely linked to risk of nerve damage), other predictive factors for PPSP have been identified.

Preoperatively these include genetic factors, the duration and intensity of pain before surgery, psychological vulnerability (e.g., catastrophizing), preoperative anxiety, pretreatment with opioids, female gender and younger age (ANZCA and FPM, 2010; Theunissen et al., 2012). Postoperatively, the severity of acute pain seems to be the most important predictor—an opportunity to use preventive analgesic techniques (see below). Other risk factors in the postoperative period are psychological, including depression, psychological vulnerability, neuroticism and anxiety, and also radiotherapy to the area of surgery and chemotherapy (Hinrichs-Rocker et al., 2009; ANZCA and FPM, 2010; Theunissen et al., 2012).

The pathophysiology of this progression process is closely linked to central sensitization (discussed in Section 12.1). This is confirmed by the finding that the extent of wound hyperalgesia in the days following surgery correlates with the incidence of PPSP. It is currently thought that hyperalgesia is common after tissue injury and may help to encourage rest of the affected body part, but that it is also usually self-limiting. Development of persistent pain may be a maladaptive version of this normal physiological response. Last but not least, there is increasing evidence for the contribution of reorganization and remapping of the somatosensory cortex following nerve injury, for example, in the development of phantom limb pain and CRPS. Underlying contributing factors to the development of these changes are genetic and/or psychosocial predisposition (Schug and Pogatzki-Zahn, 2011).

12.6 Preventive analgesia

There has been significant interest in strategies aimed at reducing the risk of progression of acute to chronic pain, or at least the severity of chronic pain should it occur.

Initial concepts focused on the provision of *preemptive* analgesia (Katz et al., 2011). These studies compared the effects of administering pain-relieving drugs or techniques prior to an intervention (e.g., surgical incision) with the same drug or technique given after the intervention. This concept was based on findings in animal studies that supported the concept of preemptive analgesia, but it has not been consistently demonstrated in human studies. The reasons for this are many, but of most importance is that this concept ignores the processes of postoperative inflammation and peripheral sensitization that continue to produce pain after surgery and which will not be covered by the single interventions used in preemptive analgesic approaches (Katz et al., 2011).

Therefore, current interest no longer focuses on the timing of analgesic treatment, but on *preventive* analgesic strategies, where the approach aims to prevent peripheral and central sensitization and therefore might reduce the risk of progression to persistent pain. The effects of a preventive intervention exceed the expected duration of action of the drug used, commonly defined as 5.5 half-lives of this drug (Katz et al., 2011). These may be started preoperatively and aim to provide analgesia throughout the postoperative period, but not due to the direct analgesic effect of the drug.

As activation of the *N*-methyl-D-aspartate (NMDA) receptor is a crucial component of central sensitization, it is not surprising that NMDA receptor

antagonists, in particular ketamine, have been of interest. Ketamine may have preventive analgesic effects with perioperative use (Chaparro et al., 2013).

The perioperative use of regional anesthesia and analgesia may also be effective in reducing the incidence of PPSP after some operations. After lower limb amputation, epidural analgesia has been shown to reduce the incidence of severe phantom limb pain (Gehling and Tryba, 2003). There is little evidence for the benefit of other peripheral nerve blocks including sciatic nerve sheath catheters (or "stump" catheter) on reducing phantom limb pain, although they provide excellent postoperative analgesia. There is some evidence that epidural analgesia may have a preventive effect if used during and after thoracotomy and paravertebral blockade after breast cancer surgery (Andreae and Andreae, 2012). This may partially be an effect of local anesthetics, as another metaanalysis reported preventive effects with regional as well as systemic administration (Barreveld et al., 2013).

While the potential preventive effect of perioperative gabapentinoids, shown in a number of RCTs, is still being debated, a Cochrane metaanalysis has concluded that neither gabapentin nor pregabalin reduce the incidence of persistent postoperative pain (Chaparro et al., 2013).

Changes in surgical approach and avoiding repeat or unnecessary surgery may also be of benefit. Techniques that are minimally invasive or minimize nerve damage may decrease the risk of PPSP, for example, laparoscopic versus open surgery. In patients thought to be at risk of neuropathic pain after surgery or injury, it may be worth initiating therapy *before* any clinical features of neuropathic pain develop.

Key points

1. The prevalence of acute neuropathic pain is often underestimated, therefore, acute neuropathic pain is underdiagnosed and undertreated.
2. The diagnosis of neuropathic pain is a clinical one and can be based on careful history taking and a basic clinical examination looking for negative and positive neurological signs.
3. Treatment of neuropathic pain relies more on the so-called coanalgesics such as antidepressants and anticonvulsants than on classical analgesics.
4. Acute pain after surgery and trauma, in particular if caused by nerve injury, has an underestimated high risk of progressing to persistent pain.
5. Preventive analgesia aims to reduce the incidence of persistent postsurgical pain; potentially promising approaches include local anesthetics, regional anesthesia techniques, and ketamine.

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CHAPTER 13

Nonsurgical acute pain

Many of the significant advances in the management of acute pain over the past years have arisen from work that has focused on pain relief after surgery. While there are obviously many other sources of acute pain, the general principles of management that have resulted from this work remain the same, regardless of the cause of the pain.

The aim of this chapter is to touch briefly on some of the causes of nonsurgical acute pain and some of the problems specific to acute pain management in these patients. Common to many of these situations is the presence of both nociceptive and neuropathic pain, requiring a mix of treatment strategies (see Chapter 12). In addition, specific evidence about the best way to manage pain in the acute phase of these illnesses is often lacking and so only generalizations can be made.

13.1 Burns injury

Patients suffering from burns often have a number of different reasons for their pain. Not only are they likely to have variable degrees of constant background pain and incident pain, for example, when moving or coughing, but they are also repeatedly subjected to multiple, often prolonged procedures such as dressing changes and regular physiotherapy over a long period. In addition, the pain will commonly be a mixed one with a nociceptive as well as a neuropathic component (if nerves supplying the skin are injured or exposed).

A considerable number (in the range of 20%) will go on to develop long-term pain (ANZCA and FPM, 2010). Those who have persistent pain are likely to have more severe symptoms of depression and posttraumatic stress and also recall higher levels of procedure-related acute pain (Browne et al., 2011).

Effective management of the different aspects of pain experienced in the acute phase of treatment, as well as the mixed nociceptive and neuropathic pain present in many patients, may require different strategies involving both pharmacological and nonpharmacological therapies.

13.1.1 Pharmacological

13.1.1.1 Initial pain relief

In the initial stages after a burns injury, pain management using intravenous (IV) opioids is usually required, unless the burns are relatively minor. In patients who are hypovolemic, absorption of intermittent subcutaneous (SC) or intramuscular (IM) injections of opioid may be unreliable. Concerns about delays in gastric emptying, which can occur after major injury, may limit the use of oral opioid analgesia, at least in the first instance. Simple measures such as cooling, covering, and immobilizing the burn area may also assist (ANZCA and FPM, 2010).

13.1.1.2 "Background" analgesia

Paracetamol (acetaminophen) should be given if there are no contraindications but routine administration of nonselective nonsteroidal antiinflammatory drugs (NSAIDs) may not be appropriate, either in the initial stages of the burns injury if the patient is hypovolemic (because of an increased risk of renal complications), or if surgery is required, as they could increase the risk of bleeding. Coxibs (COX-2 selective NSAIDs) may be more suitable, as they have no significant effect on platelets and might also limit further risk of stress-induced gastrointestinal ulcers, which are not uncommon in this group of patients.

Parenteral opioid administration may be continued once the patient is comfortable, for example, using patient-controlled analgesia (PCA). For less severe pain or after initial management of more severe pain, oral opioid analgesia may suffice.

Burns pain, as noted above, will often have nociceptive and neuropathic components. In addition, the repeated procedures such as additional surgery and multiple dressing changes, contribute to central sensitization and hyperalgesia. Antihyperalgesic and antineuropathic agents such as ketamine and gabapentinoids can therefore be of benefit. Ketamine has been shown to improve pain relief and reduce hyperalgesia (McGuinness et al., 2011), and pregabalin and gabapentin administration has led to less surface pain, itch, and procedural pain (Gray et al., 2011) as well as improved background and neuropathic pain (ANZCA and FPM, 2010).

Tricyclic antidepressant agents, used as an alternative to night-time benzodiazepines, may help to improve sleep patterns as well as aid in the management of neuropathic pain.

As the burn injuries heal, the patient can experience intense and at times distressing itching. In addition to the release of histamine in the wound, part of the underlying pathophysiology may be similar to that of neuropathic pain (Goutos, 2013) and gabapentin or pregabalin may be effective in patients who have not responded to standard antihistaminics (Gray et al., 2011; Goutos, 2013). The anxiolytic properties of pregabalin may also be of benefit (Baldwin et al., 2013).

Analgesia in the later stages of a burn injury may be provided by slow-release (controlled-release) oral opioids or methadone with additional access to immediate-release oral opioids for breakthrough and incident pain (e.g., associated with physiotherapy or minor dressing changes).

13.1.1.3 Procedural analgesia

Opioids remain an important component of analgesia during procedures such as burns dressings. If IV PCA is prescribed, some patients may benefit from the use of an opioid with a faster onset of action, such as fentanyl or alfentanil (Holtman and Jellish, 2012). Remifentanil has also been tried as it has a very fast onset of action, but also a higher risk of opioid-induced ventilatory impairment (OIVI).

It is not uncommon for higher PCA bolus doses to be required during this time, so that the patient can more easily match their opioid requirement to the inevitable increase in pain. Patients should be observed closely after the procedure ends, as opioid-related sedation and OIVI may follow the decrease in pain stimulus. This will be more likely if sedatives (e.g., midazolam) have also been given during the procedure.

Fentanyl can be administered intranasally if there is no IV access, as the rate of onset can be almost as quick as IV fentanyl (see Chapter 7) (ANZCA and FPM, 2010). Concentrated forms of fentanyl may be needed if adequate pain relief is to be achieved with a small dose volume. If oral or SC/IM opioids are given prior to an intervention such as dressing changes, sufficient time (e.g., 45–60 minutes) should be allowed for them to work before proceeding.

Ketamine (also see Chapter 6), given either as a low-dose infusion or as intermittent bolus doses, is a frequently used adjunct during burns dressing changes. A mixture of ketamine and midazolam is also used in some centers. A combination of ketamine 10 mg/mL and midazolam 0.5 mg/mL administered by PCA has been reported to give good pain relief, but despite the midazolam, 25% of patients reported hallucinations (MacPherson et al., 2008). Sublingual ketamine may also be effective, given either as a lozenge (prepared in the institution) in doses of 25–50 mg, or as the solution from a ketamine ampoule (10–20 mg) given on demand.

Nitrous oxide is commonly used for pain relief during burn dressings and can be very effective in selected patients, but care should be taken to minimize the risks of nitrous oxide toxicity, in particular with repeated use over longer periods (see Chapter 6).

Regional analgesic techniques have been instituted for the management of burns pain but their use is limited, in part because of concerns about infection, but also because of the length of time over which good pain relief will be required.

13.1.2 Nonpharmacological

Immediately after the injury, simple procedures such as cooling and covering the burn, and immobilization of injured limbs, will help with pain relief. Other techniques that have been used, especially in the treatment of procedural pain, include hypnosis, distraction, and other stress-reducing strategies (see Chapter 8).

13.2 Spinal cord injury

Acute pain resulting from spinal cord injury can also be a mix of nociceptive (e.g., associated with musculoskeletal injury related to the trauma) and neuropathic pain.

Neuropathic pain associated with spinal cord injury is classified as "at-level" and "below-level" (Finnerup and Baastrup, 2012) and may be reported early after the injury, or later in the recovery and rehabilitation stages. At-level pain arises from injury to the spinal cord or nerve roots and therefore may have both central and peripheral components. It usually presents early after the injury as a band of pain in the dermatomes at the level of the injury. Below-level pain is a central pain resulting from spinal cord damage. It is often more diffuse and its onset may be delayed for up to 12 months. As with other patients with neuropathic pain, patients with a spinal cord injury may report burning, tingling, shooting, stabbing pain, "pins and needles," or dysesthesia (unpleasant and abnormal sensations). Allodynia and hyperalgesia are commonly associated with at-level pain, but will also be present below the level of the injury if spinal cord damage is incomplete.

13.2.1 Management of pain associated with acute spinal cord injury

There is no specific evidence to guide the treatment of either acute nociceptive or neuropathic pain in patients with a spinal cord injury.

Treatment for nociceptive pain would be as for any other patient and include simple analgesics and opioids. These patients are at increased risk of gastric ulceration, so NSAIDs, if indicated, should be used with care. Coxibs may be more suitable as they have no significant effect on platelet function and can be combined with a proton pump inhibitor to further decrease the risk of gastric ulceration.

To a large extent, suggestions for the management for acute neuropathic pain following spinal cord injury are based on strategies used to manage chronic neuropathic pain in general. Of the commonly used antineuropathic agents (see Chapters 6 and 12), pregabalin and amitriptyline have been shown to be effective (Finnerup and Baastrup, 2012) and tramadol, ketamine, and, if needed lidocaine, may also be of use (ANZCA and FPM, 2010; Kim et al., 2013).

Gastric stasis may develop in the acute stage of the spinal cord injury, which will limit the use of oral medications until normal gastric emptying resumes.

13.3 Other specific conditions

13.3.1 Abdominal pain

13.3.1.1 Renal and biliary colic

A common misconception has been that pethidine (meperidine) is the preferred opioid for the management of renal or biliary colic. There is, however, no evidence to support this.

The initial treatment of choice for renal colic is an NSAID (the onset of effect will be faster if given IV), although in some patients opioids may also be required (ANZCA and FPM, 2010). Anticholinergic antispasmodic drugs (e.g., hyoscine) appear to be of no additional benefit.

Similarly, NSAIDs and/or opioid are more effective than antispasmodics for the treatment of pain from biliary colic (ANZCA and FPM, 2010).

13.3.1.2 Pancreatitis

The pain associated with chronic pancreatitis has both nociceptive and neuropathic components, and histological studies show inflammation of and damage to intrapancreatic nerves (High and McIlwrath, 2013).

While there is no good information specific to the management of pain in acute pancreatitis, it seems reasonable to treat this also as a mixed pain—for example, adding ketamine, a gabapentinoid and maybe a tricyclic antidepressant to opioids and simple analgesic regimens. In severe cases in patients with impaired respiratory function due to pain, thoracic epidural analgesia has been proven effective.

13.3.2 Herpes zoster

Herpes zoster (HZ) ("shingles") is caused by reactivation of the varicella zoster (chickenpox) virus, which can lie dormant in the dorsal root and the cranial nerve

ganglia following the primary infection, usually contracted in childhood. When the virus is reactivated, it travels along the sensory nerves to infect epithelial cells causing a painful vesicular skin rash in the area of dermatome supplied by the sensory nerve. There is also inflammation of cells within the infected ganglion. The pain that results is therefore a mixed acute nociceptive and neuropathic pain, and it may precede or accompany the rash or appear after the rash is first noticed. A chronic form of neuropathic pain called postherpetic neuralgia (PHN) can follow.

The major risk factor for HZ is increasing age and it is estimated that 50% of individuals who live to 85 years of age will have had HZ; other risk factors include immunosuppression, diabetes, female gender, genetic susceptibility, trauma, and psychological stress (Gershon et al., 2010). The risk of PHN, often defined as pain that is still present three months after the onset of the rash, also increases with age and with severity of acute pain. Up to one third of patients over the age 60 years who have HZ will develop PHN (Boivin et al., 2010).

Antiviral agents (valaciclovir or famciclovir are preferred to acyclovir) will hasten healing of the vesicles, decrease viral shedding (infectivity), and reduce the severity of acute pain, but do not significantly reduce the risk of PHN (Cohen, 2013). It is usually recommended that treatment starts within 72 hours of the onset of the rash, but there may be circumstances where initiation of treatment may still be indicated after this time.

Pain management strategies aiming to treat both nociceptive and acute neuropathic pain may be needed. Paracetamol and NSAIDs may help with mild pain, but in other patients, tramadol or an opioid may be required (ANZCA and FPM, 2010). The management of acute neuropathic pain is summarized in Chapter 13, but use of gabapentinoids (gabapentin, pregabalin) and tricyclic antidepressants has been recommended for the treatment of HZ-related pain; lidocaine patches (applied to intact skin only) is also effective (Boivin et al., 2010; Cohen, 2013). In combination with an antiviral agent, corticosteroids may reduce acute pain and accelerate healing of the skin lesions, but their use remains controversial. Ketamine, either as an infusion or given sublingually, may also be effective.

There is some evidence that early administration of amitriptyline may reduce the risk of PHN (Boivin et al., 2010) but, in general, the efficacy of most preventive strategies is limited.

Epidural or paravertebral local anesthetic/steroid blocks may be effective for the treatment of HZ-related pain and may reduce the incidence of PHN (Dworkin et al., 2013).

13.3.3 Sickle cell disease and hemophilia

Both these hematological diseases are inherited disorders and both can lead to episodes of severe acute pain. The inevitable and recurrent nature of the pain can have significant psychological and social as well as physical consequences for the patient, and a comprehensive management approach should include all involved in the patient's care as well as pain medicine specialists as needed. Individual management plans with agreed treatment algorithms, carried by the patient and held in the patient's hospital (especially the emergency department), can be of value for any patient who may require repeated admissions.

While opioids should only be used with the appropriate precautions in the long term, some of these patients may be opioid tolerant (see Chapter 14) and can require higher than "usual" doses of opioid while in hospital.

13.3.3.1 Sickle cell disease

Sickle cell disease includes a group of inherited disorders of hemoglobin production that can lead to acute "crises" arising from vasoocclusion of the microcirculation resulting in tissue ischemia and infarction. Severe pain may be reported in the back, legs, chest, and arms and pain from involvement of abdominal organs may mimic an acute abdomen (ANZCA and FPM, 2010).

Clinical guidelines for the management of the acute pain episodes may lead to more timely and effective pain relief, but there is only limited evidence available. A summary of that evidence (Ballas et al., 2012) suggests that opioids (other than pethidine) remain the mainstay for the treatment of severe pain during a crisis. Although IV opioid PCA is commonly used for the management of acute pain in sickle cell disease, oral opioids are also effective (ANZCA and FPM, 2010). The choice will depend on the severity of the pain. As with any severe acute pain, IV "loading" with opioids should precede the maintenance opioid regimen.

Although hypoxia can precipitate a sickle cell crisis, as can dehydration, infection, and hypothermia, there is no evidence of benefit from rehydration or oxygen administration (Ballas et al., 2012). As nocturnal oxygen desaturation has been associated with a significantly higher rate of painful sickle cell crises in children (ANZCA and FPM, 2010), oxygen administration while receiving an opioid in particular may be prudent.

There is little specific information about the benefits or otherwise of paracetamol and NSAIDs (Ballas et al., 2012). Case reports have suggested that in severe crises, where pain is unresponsive to other measures, epidural analgesia may offer an effective alternative (ANZCA and FPM, 2010).

13.3.3.2 Hemophilia

Hemophilia is an inherited disorder of coagulation characterized by spontaneous and posttraumatic bleeding. Most common are recurrent painful joint bleeds although bleeding into muscle and other sites may also occur. Repeated bleeds can lead to chronic synovitis and a severe joint arthropathy and associated chronic pain. The lack of specific evidence about the management of both acute and chronic pain in these patients has led to the development of consensus-based rather than evidence-based guidelines (Riley et al., 2011; Holstein et al., 2012). However, these are a good basis from which to start.

Acute pain is often treated with infusion of a factor concentrate, ice packs, elevation and compression and, unless pain is severe, the patient may not require admission to a hospital. Aspiration of the joint may be appropriate in some circumstances. Recommended analgesics include paracetamol and NSAIDs. Nonselective NSAIDs should not be used during bleeding periods, but coxibs may be appropriate in some cases. Opioids can be commenced if required—oral administration is preferred to intermittent injections.

13.3.4 Neurological disease

Pain associated with some neurological diseases, for example, multiple sclerosis, Guillain–Barré syndrome, following a stroke, or associated with a peripheral neuropathy (e.g., diabetic neuropathy, HIV/AIDS neuropathy) is usually neuropathic in nature, although nociceptive pain (e.g., musculoskeletal) may also be present.

13.3.4.1 HIV/AIDS

Pain is a common symptom in over half of patients with HIV/AIDS and can result from a number of different pathological causes (Parker et al., 2014). These include the direct effect of the virus on the central or peripheral nervous system, complications resulting from immunosuppression (infection, cancer) or the neurotoxic effects of antiretroviral treatments. The most frequent neurological diagnosis is a distal symmetrical polyneuropathy (DSP) and common clinical features include reduced or absent ankle reflexes and decreased sensation in the extremities, as well as nonpainful paresthesias and pain in a "glove and stocking" distribution (Schutz and Robinson-Papp, 2013).

In general, the pain from DSP is difficult to treat and most of the medications used to treat neuropathic pain have not necessarily been shown to be effective in this patient group (Schutz and Robinson-Papp, 2013). However, even if complete relief of pain is not possible, it is worth trying those agents commonly used to treat neuropathic pain in general. High-concentration capsaicin patches may also be useful.

Management may be made a little more complex because of the possibility of interactions between drugs used for analgesia and those prescribed for the treatment of HIV/AIDS or some of its related complications, as well as the possibility of nonprescribed drug use in some patients.

13.3.4.2 Guillain–Barré syndrome

Guillain–Barré syndrome has a number of different subtypes, but the most common is an acute inflammatory demyelinating polyradiculoneuropathy (Walling and Dickson, 2013). This is usually thought of as a primarily motor neuron disease, leading to progressive muscle weakness and sometimes respiratory failure requiring ventilation. However, more than half of patients report severe pain.

Severe widespread neuropathic pain may be described, often without the features of a peripheral neuropathy, as well as musculoskeletal pain. As these patients may sometimes have severe acute pain, treatment with systemic ketamine and/or lidocaine as well as gabapentin/pregabalin and carbamazepine may be of benefit in the acute phase (ANZCA and FPM, 2010).

13.3.4.3 Multiple sclerosis

Pain is reported by over half of all patients with multiple sclerosis and it is often severe (Foley et al., 2013). The type of pain may vary (nociceptive and/or neuropathic) and commonly relates to headache, back pain, painful spasms, and neuropathic pain in the extremities. Acute presentations are unusual but in the absence of good specific evidence, the usual treatments for both pain types can be instituted.

Key points

1. Acute pain associated with burns and spinal cord injury as well as pain related to some other diseases such as herpes zoster, HIV/AIDS, and multiple sclerosis often has both nociceptive and neuropathic elements and treatment should aim at managing mixed pain.
2. Treatment of acute neuropathic pain should be based largely on evidence from the management of chronic neuropathic pain.

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CHAPTER 14

More complex patients

The general principles of acute pain management apply to most patients in most acute pain settings. However, there are some groups of patients for whom effective and safe management of pain can be more complex. The aim of this chapter is to touch briefly on some of these groups, highlighting where concerns may arise and possible changes that might be required in acute pain treatment regimens.

14.1 Older patients

The proportion of older people (defined by the United Nations as aged 60 years or over) in the world is growing rapidly and is expected to increase from nearly 12% in 2013 to just over 21% by 2050 (United Nations Department of Economic and Social Affairs, 2013). The percentage of "oldest-old" (persons aged 80 years or over) is estimated to rise from 14% to 19% over the same period. In terms of total numbers, there will be more than twice as many older persons in 2050, seven times as many oldest-old and nearly eight times as many aged 100 years or more than there were in 2013. As a result of these changes, an ever-increasing proportion of patients presenting for major operations or after major injuries for which they will require pain relief, will be in the older age groups. Medical conditions that often lead to acute pain are also more common in older people, including osteoporotic fractures of the spine, ischemic heart disease, and peripheral vascular disease.

Older patients are at particular risk of having their acute pain inadequately managed (Coldrey et al., 2011). A number of factors may combine to make control of pain more complex than in their younger counterparts. These include:

- Changes in pain perception and reporting of pain as well as methods of pain assessment, including patients with cognitive impairment.
- Age and disease-related changes in physiology, diminished physiological reserves and concurrent medications, all of which may alter the pharmacokinetics and pharmacodynamics of some analgesic medications and techniques of administration used in acute pain management.

Most research that has been done looking at management of acute pain in older patients has grouped individuals on the basis of age only. However, it maybe that biological "fitness" rather than chronological age is of most importance. While it is known that older age correlates with a higher incidence of poor postoperative outcomes, other factors such as frailty, which can be measured with validated scales, independently predicts the risks (Hubbard and Story, 2014).

14.1.1 Assessment of pain

The assessment of pain and evaluation of pain relief may be more difficult in the older patient owing to differences in perception and reporting of pain, cognitive impairment, and difficulties in measurement.

14.1.1.1 Perception of pain

Pain thresholds change in older patients. Thresholds to experimental pain are generally increased, although results are inconsistent and may be stimulus-specific. While the significance of these results in the clinical setting remains uncertain, they could indicate some deterioration in the "early warning" function of pain. This could mean a greater delay in the time between identification of the pain stimulus and recognition of a stimulus that might cause tissue injury. There are a number of clinical reports suggesting that some older patients may report no pain or less pain in conditions that are normally associated with severe pain. For example, the risk of painless angina or myocardial infarction increases with older age, and severe pain is less likely to be a presenting symptom in patients with significant acute abdominal pathology (e.g., intestinal obstruction, peritonitis, pancreatitis) (ANZCA and FPM, 2010). Older patients may also report less pain after surgery and some procedures.

Pain that is reported needs treatment as for the younger patient, especially as the development of persistent pain and/or any interference with acute rehabilitation may affect the older patient to a much greater extent.

14.1.1.2 Reporting of pain

Many factors may lead to under-reporting of pain in older patients. These include psychological and cultural factors such as fear, anxiety and depression, quality of social support available, implications of the disease, loss of independence, cultural and ethnic differences, and cognitive impairment (Catananti and Gambassi, 2010; Coldrey et al., 2011). There may also be attitudinal barriers as the older person and their carers may see pain as an inevitable and normal part of aging and something to be endured.

14.1.1.3 Cognitive impairment

Cognitive function declines with age. Patients who have cognitive impairment are known to be at greater risk of under-treatment of acute pain than their cognitively intact counterparts of the same age (ANZCA and FPM, 2010). In part, at least, this is probably due to under-reporting and difficulties in pain assessment, as there may be no difference in the pain experienced (Cole et al., 2006). The placebo component of pain relief may be reduced in these patients.

Delirium (or confusion) is a form of acute cognitive impairment. It is characterized by acute disturbances in mental state or consciousness associated with decreased cognition, which develop over a short time and tend to fluctuate. It is more common in older patients during acute illnesses or in the postoperative period, leading to increased morbidity and hospital stays (Coldrey et al., 2011). While the exact cause may be unknown, a number of risk factors have been identified (Table 14.1) (ANZCA and FPM, 2010; Chaput and Bryson, 2012; Shim and Leung, 2012). If a patient becomes confused while taking opioids, a common

Table 14.1 Risk factors for the development of delirium

- Older age
- Frailty
- Preexisting dementia or depression
- Some medications—for example, benzodiazepines, opioids, tramadol, and drugs with anticholinergic side effects
- Withdrawal from alcohol or sedatives
- Infection
- Fluid and electrolyte imbalances
- Hypoxemia
- Sleep deprivation
- Poorly controlled acute pain

Source: From Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (ANZCA and FPM). 2010. *Acute Pain Management: Scientific Evidence*. 3rd edn. Macintyre PE et al. (eds). Melbourne. http://www.fpm.anzca.edu.au/resources/books-and-publications; Chaput AJ, Bryson GL. 2012. *Canadian Journal of Anesthesia* **59**(3): 304–20; Shim JJ, Leung JM. 2012. *Best Practice and Research Clinical Anaesthesiology* **26**(3): 327–43.

reaction is to withhold further doses. However, as confusion may be the result of many other factors and as severe pain is a risk factor for delirium, it is important to continue providing good pain relief.

14.1.1.4 Measurement of pain

Accurate and repeated assessments of pain are necessary for effective pain management. As with younger patients, the older patient's self-report is the best way to assess pain. Measures of pain in common use in the acute pain setting, such as the visual analog scale (VAS), verbal numerical rating scale (VNRS), numerical rating scale (NRS; a calibrated VAS), verbal descriptor scale (VDS), and Faces pain scale (see Chapter 3) have all been used for assessment of pain in the older patient. The VDS and NRS may be better tools to use in this age group (ANZCA and FPM, 2010; Herr, 2011).

Older patients with mild-to-moderate cognitive impairment may be able to understand and use the VDS, but need more time to think about and respond to questions, and repeated questioning may be required (Coldrey et al., 2011). They may be able to assess pain reliably at the time when asked (present pain), but recall of pain may be less reliable (Herr, 2011).

In patients with more severe cognitive impairment, when self-report measures fail, observer-rated assessment tools can be employed (see Chapter 3). These tools commonly use behaviors such as restlessness, tense muscles, frowning or grimacing, and grunting or groaning, to assess pain severity. However, while these may be a reasonable indicator of the presence of pain, they do not necessarily indicate pain severity (ANZCA and FPM, 2010). There could also be other reasons for distress and such behaviors.

Observation of function, such as the ability to take deep breaths and cough, as well as tolerate physiotherapy and walk, is important and may help to determine adequacy or otherwise of analgesia.

14.1.2 Changes in pharmacokinetics and pharmacodynamics

There can be significant variations in the way older individuals both handle and respond to analgesic medications. Differences in pharmacokinetics (how individuals deal with a drug) as well as pharmacodynamics (how individuals respond to a drug) can mean that changes are sometimes needed in the approaches to pain relief.

14.1.2.1 Pharmacokinetics

Age-related changes in the pharmacokinetics (absorption, distribution, metabolism, and excretion) of many drugs are common. This is due primarily to two factors—the progressive physiological decline that occurs with increasing age and the increasing likelihood of concurrent disease.

The physiological changes are progressive, but the rate of decline can be highly variable as physiological aging may or may not parallel chronological aging. It is also difficult to separate changes due to age from those that result from the higher incidence of degenerative and other diseases that is inevitable in older patients. The changes that are of most significance to the pharmacokinetics of drugs used in acute pain management relate to renal function in particular, although other changes may also have some effect.

For a summary of the more important age-related physiological changes and pharmacokinetic consequences, and their possible effect on analgesia and analgesic regimens, see Table 14.2. Concurrent diseases and/or use of other medications may further alter these factors.

14.1.2.2 Pharmacodynamics

Age-related changes in pharmacodynamics also occur, although the mechanisms behind them are not yet fully understood. It appears that brain sensitivity to opioids is increased by about 50% in older individuals. However, it is not clear whether this difference is due to alterations in the number and/or function of opioid receptors in the central nervous system (CNS), or whether it is due to other factors.

14.1.3 Analgesic drugs

As with younger patients, a range of analgesic and adjuvant agents may be used in the management of acute nociceptive and neuropathic pain. These drugs are covered in more detail in Chapters 4 through 6. The pharmacokinetic and pharmacodynamic changes described above may affect the doses required and the adverse effects seen. However, these variations in addition to the presence of comorbidities and other medications mean that broad generalizations only can be made about their use in older patients.

The phrase "start low, go slow" is often used in reference to the selection and alteration of drug doses in these patients. However, it does *not* mean they should stay low or that change should be too slow. Doses may need to be titrated upwards in some older patients and it is important for this to be recognized and unnecessary delays avoided.

14.1.3.1 Opioids and tramadol

If opioids are to be used effectively yet safely in the older patient, a number of factors must be considered.

Table 14.2 Pharmacokinetic consequences associated with physiological changes of aging

Physiological variable	Change	Potential PK consequence	Example of possible effects on analgesia/ analgesic strategies
Cardiac output (CO)	↓ Or unchanged	↓ CO = ↑ Peak plasma concentrations with intravenous (IV) bolus dose	↓ Initial IV bolus dose of CNS depressant drugs (e.g., opioids) ↓ Speed of IV injection
Hepatic clearance	↓ Liver mass and blood flow ↓ Phase I metabolism ↔ Phase II metabolism	↑ Oral bioavailability ↓ Clearance (CL) =↑ plasma concentrations for some, not all, high extraction drugs (e.g., morphine, fentanyl) ↓ CL some low extraction (e.g., ibuprofen)	Dose reductions necessary with some drugs; limited/no adjustment needed for most analgesic and adjuvant drugs
Renal clearance	↓ Size and functional capacity of kidneys ↓ In renal blood flow ↓ Glomerular filtration rate (GFR)	↓ CL =↑ plasma concentrations of renally cleared drugs and metabolites	Caution with renally cleared drugs (e.g., gabapentinoids, some NSAIDs) or drugs with renally cleared active metabolites (e.g., morphine, pethidine, dextropropoxyphene)
Body composition	↑ Body fat ↓ Body water	↑ Volume of distribution and half-life of lipophilic drugs	Drug specific—dose based on total body weight (lipophilic drugs) or lean body weight (hydrophilic drugs)

(*continued*)

Table 14.2 (continued) Pharmacokinetic consequences associated with physiological changes of aging

Physiological variable	Change	Potential PK consequence	Example of possible effects on analgesia/ analgesic strategies
	↓ Muscle mass (elderly may range from obese to frail)		
Protein binding	↓ Albumin ↑ Alpha-1-acid glycoprotein Drug-specific binding changes	Volume of distribution changes ↑↓ Hepatic CL of low extraction drugs Half-life changes Altered cerebral uptake of drug	Possible change in clinical effect related to altered free drug fraction NSAIDs and many local anesthetics and opioids are highly (>90%) protein bound
Oral and transmucosal absorption	Generally unaffected in the absence of disease		No change in absorption
Transdermal absorption	↓ For hydrophilic drugs ↔ For lipophilic drugs	No change in time-to-peak concentration for lipophilic drugs	No change required for transdermal fentanyl
Intramuscular absorption	Muscle perfusion unchanged	No change	Limited evidence. Predict minimal change in absorption
Subcutaneous absorption	Skin perfusion unchanged at normal temperatures	No change	Limited evidence. Predict minimal change in absorption

Source: Reprinted from Coldrey JC, Upton RN, Macintyre PE. 2011. Advances in analgesia in the older patient. *Best Practice and Research Clinical Anaesthesiology* **25**(3): 367–78.

14.1.3.1.1 Choice of drug

Any opioid agonist could be used in the older patient. However, for increased safety, given the steady decline in renal function associated with increasing age, those without significant amounts of renally excreted active metabolites are often preferred (see Chapter 4). Fentanyl, oxycodone, hydromorphone, and buprenorphine appear to be reasonable choices (Pergolizzi et al., 2008).

The elimination half-life of tramadol is known to be slightly prolonged in older individuals and the active metabolite, O-desmethyltramadol (commonly known as M1), is also dependent on the kidney for excretion. Therefore, lower daily doses of tramadol may be required.

14.1.3.1.2 Opioid dose and dose intervals

Opioid requirements decrease with increasing patient age (Macintyre and Jarvis, 1996). Age-related differences in the pharmacokinetics of some opioids have been shown, but these variations are not enough to account for the twofold to fourfold decrease in the dose of opioid required by older patients to get the same degree of pain relief as younger patients (Coldrey et al., 2011). As discussed in Chapter 4, the main reasons for the reduced requirements appear to be pharmacodynamic.

Although total daily opioid doses are likely to be less than those needed by younger patients, older patients still exhibit a wide interpatient variability in the doses and blood concentrations required for effective analgesia, and so titration to effect for each patient will still be needed. While it is suggested that initial opioid doses should be lower in older patients (see Chapter 7 for examples relating to the different routes of administration), if analgesia is inadequate and in the absence of side effects, these can be increased if needed.

14.1.3.1.3 Side effects of opioids

The fear of causing opioid-induced ventilatory impairment (OIVI) in the older patient may lead to inadequate doses of opioid being given. However, as with other patients, significant OIVI can generally be avoided if appropriate monitoring is in place and the drugs are appropriately titrated.

The incidence of nausea and vomiting as well as pruritus seems to decrease with increasing age. Tramadol and pethidine may lead to a higher incidence of cognitive dysfunction compared with morphine and there may be a lower risk with fentanyl (Coldrey et al., 2011).

14.1.3.2 Other analgesic and adjuvant drugs

Changes in other drug treatment regimens used in acute pain management may also be required. Some of these are summarized in Table 14.3 (American Geriatrics Society, 2009; ANZCA and FPM, 2010; Barkin et al., 2010; Coldrey et al., 2011).

14.1.4 Specific analgesic techniques

14.1.4.1 Patient-controlled analgesia

Patient-controlled analgesia (PCA) should not be withheld from older patients simply because of their age. As long as there are no contraindications to the use of PCA (see Chapter 8) and as long as the patient is able to comprehend the

Table 14.3 Other analgesic and adjuvant drugs and their use in the older patient

Local anesthetics	Decreased absorption from site of delivery, decreased clearance
	Decreases in peripheral nerve fiber density and conduction velocity, sensory neuron degenerative changes and loss of myelin in the dorsal horn of the spinal cord are among the changes seen, which can lead to an increased motor and sensory block and a longer duration of block for a given volume/concentration
	Possible need to use lower doses and infusion rates to obtain same degree of block
Paracetamol (acetaminophen)	Age-related changes in the pharmacokinetics of paracetamol have been reported
	In the absence of significant renal impairment there is probably no need for routine dose reductions in most older patients unless frail, especially for short-term use
NSAIDs	Risks and severity of NSAID-related adverse effects are increased in older patients
	Most NSAIDs taken in the long-term increase the risk of cardiovascular and cerebrovascular events; short-term use to treat acute pain appears not to, although no NSAIDs should be given after cardiac surgery
	The risk of renal impairment with all NSAIDs is increased in older patients, especially if combined with other medications such as diuretics and angiotensin-converting enzyme (ACE) inhibitors; short-term use in older patients with normal renal function is reasonable
	The incidence of NSAID-related gastrointestinal side effects is also higher in older patients; risks are greater with long-term use and less with coxibs
	In frail older patients, NSAIDs may cause cognitive dysfunction

TCAs	Increased risk of side effects such as sedation, confusion, orthostatic hypotension, dry mouth, constipation, and urinary retention (incidence is lower with nortriptyline compared with amitriptyline)
	Initial doses should be lower than for younger patients (e.g., start with 10 mg nortriptyline), any increases should be titrated slowly as tolerated
	More likely to have diseases that require TCAs to be administered with caution (e.g., prostatic hypertrophy, narrow-angle glaucoma, cardiovascular disease)
Gabapentin, pregabalin	More likely to develop side effects such as sedation and dizziness
	Reduction in renal function may affect the clearance of the drugs
	Initial doses should be lower than for younger patients and any increases should be titrated slowly
Ketamine	Probable increased CNS sensitivity with age
	Lower doses suggested
Nitrous oxide	Older patients are more likely to have a vitamin B_{12} deficiency, putting them at increased risk of a nitrous oxide-induced neuropathy

Source: Information obtained from the American Geriatrics Society. 2009. *Pain Medicine* **10**(6): 1062–83; Barkin RL, Beckerman M, Blum SL et al. 2010. *Drugs Aging* **27**(10): 775–89; Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (ANZCA and FPM). 2010. *Acute Pain Management: Scientific Evidence*. 3rd edn. Macintyre PE et al. (eds). Melbourne. http://www.fpm.anzca.edu.au/resources/books-and-publications. Coldrey JC, Upton RN, Macintyre PE. 2011. *Best Practice and Research Clinical Anaesthesiology* **25**(3): 367–78.

Note: NSAIDs: nonsteroidal antiinflammatory drugs including nonselective NSAIDs and coxibs.
TCAs: tricyclic antidepressants.

technique, PCA is a safe and effective form of pain relief. Although the proportion of older patients who can effectively use PCA may be less than in younger age groups, age by itself does not limit the ability to use PCA successfully. Older patients should be followed closely to ensure that they understand the concept of self-administration and to ensure that they are obtaining adequate pain relief.

In the older patient (over 70 years) it is suggested that the size of the PCA bolus dose be reduced (e.g., by 50%). If a patient becomes confused PCA should be stopped, as it may no longer be used correctly.

14.1.4.2 Epidural and intrathecal analgesia

Older patients are at particular risk of complications after surgery or major trauma and they are therefore most likely to benefit from an analgesic technique, such as epidural analgesia, that might improve outcome (see Chapters 1 and 9) and provides better pain relief than systemic opioid analgesia and possibly improved mental status (ANZCA and FPM, 2010).

As with parenteral opioids, epidural opioid requirements decrease with increasing patient age. In addition, for a given volume and concentration, the spread of local anesthetic drug in the epidural space is greater in the older person and the degree of motor and sensory block is increased (Coldrey et al., 2011). Therefore, whether these drugs are used alone or in combination, age-based dose or infusion rate regimens are recommended (see Chapter 9).

The older patient may be more at risk of some of the adverse effects of epidural analgesia, including hypotension, because of their increased sensitivity to the drugs used and age-associated physiological changes or diseases (e.g., they may be less able to compensate for hypovolemia).

As with any patient, minimization of hemodynamic change (including orthostatic hypotension), early ambulation, and early recognition of any major complication will be made easier if the drugs are titrated to provide sufficient pain relief without motor or sensory block.

If closely supervised by an acute pain service team, with appropriate patient monitoring, staff education, and dosing regimens, older patients with epidural and intrathecal analgesia can be safely managed in general surgical wards.

14.1.4.2.1 Anticoagulant drugs

The doses required and duration of effect of anticoagulant drugs may be different in older individuals. This may be clinically important when these drugs are used in patients receiving continuous epidural and regional analgesia. Low molecular weight heparins are primarily eliminated by the kidney, so clearance may be reduced in the older patient. Age-related decreases in warfarin requirements may also be seen. Concurrent medical problems, including cardiac and renal disease, and interactions with other drugs (both more likely in the older patient) can lead to an increased sensitivity to warfarin therapy.

14.1.4.3 Other regional analgesia

Other continuous regional analgesia (e.g., brachial or lumbar plexus, sciatic or femoral nerve, paravertebral) may be as effective as epidural analgesia in the older patient, but lead to a lower incidence of side effects. As with epidural analgesia, the duration of a local anesthetic block may be prolonged and the motor block more intense (Coldrey et al., 2011).

Key points

1. Pain in older patients is best assessed using the verbal descriptor or numerical ratings scales.
2. In patients with significant cognitive impairment, use of observer-assessed behavioral ratings of pain may be required.
3. Age-related changes in physiology leading to differences in pharmacokinetics and pharmacodynamics in older patients, as well as the higher incidence of comorbid diseases and other medications, should influence the choice of drug, dose and analgesic technique used for the management of acute pain; each must be carefully adjusted to suit each patient.
4. Opioid and local anesthetic requirements are reduced in older patients and the use of lower doses of some other analgesic and adjuvant agents may also be appropriate.

14.2 Opioid-tolerant patients

In earlier chapters emphasis has been placed on the large interpatient variation in the amount of opioid required for effective analgesia and the need to titrate opioid dose to effect for each patient. When individuals have been taking opioids for a prolonged period (whether legally prescribed or illegally obtained), effective titration can be much more difficult. Many of these patients will be tolerant to and physically dependent on these drugs, and some will have an addiction to opioids. In this chapter, for the purpose of clarity, patients taking long-term opioids are referred to as "opioid-tolerant" rather than "opioid-dependent," as the latter term is sometimes used for those with an addiction to opioids—that is psychological as well as physical dependence.

The prescription of opioids, particularly for the treatment of chronic noncancer pain, has continued to rise rapidly in many if not most of the developed countries in the world, at rates that markedly exceeds the rate of population growth (Huxtable et al., 2011). There has also been an associated large increase in the number of individuals using opioids for nonmedical purposes and those in opioid substitution programs for treatment of an addiction to opioids. If this trend continues, an ever-increasing proportion of patients requiring acute pain relief will be opioid tolerant.

Management and provision of effective analgesia in these patients can be a more complex task and may require treatment for longer periods and significant deviation from standardized protocols. Adding to the challenge is the small proportion of patients who exhibit significant aberrant drug-taking behaviors. These behaviors may not just be seen in some patients with a known addiction to opioids or other substances, but may also arise in other patients on long-term opioid therapy. Additional information specific to the management of a patient with an addiction disorder is covered in Section 14.3.

14.2.1 Opioid tolerance, hyperalgesia, dependence, and addiction

14.2.1.1 Tolerance and opioid-induced hyperalgesia

Patients on long-term opioid therapy may have developed a tolerance to the drug, meaning that higher doses are required in order to obtain good analgesia. Opioid-induced hyperalgesia (OIH) might also be present, which will have the

Table 14.4 Definitions of tolerance, opioid-induced hyperalgesia, dependence and addiction

Tolerance	A decrease in sensitivity to opioids resulting in less effect from the same dose, or the need for progressively larger doses to maintain the same effect.
Opioid-induced hyperalgesia	The development of increased sensitivity to pain (hyperalgesia) associated with the long-term use of opioids.
Physical dependence	A physiological adaptation to a drug characterized by the emergence of a withdrawal (abstinence) syndrome if the drug is abruptly stopped, reduced in dose, or antagonized.
Addiction	A pattern of drug use characterized by aberrant drug-taking behaviors and the compulsive use of a substance in order to experience its psychic effects, or to avoid the effects of its absence (withdrawal). There is continued use despite the risk of physical, psychological, or social harm.
Pseudoaddiction	Drug-seeking behavior resulting from a need for better pain relief.

opposite effect and increased doses will not improve pain relief. For the definitions of each see Table 14.4, and for more information on tolerance and OIH, see Chapter 4. After continuous exposure to an opioid, some degree of tolerance is probably seen after 10–14 days (Schug, 2012).

The clinical significance of tolerance to opioids versus OIH is difficult if not impossible to determine in any particular patient. However, if opioid analgesia is inadequate in patients receiving additional opioids for management of their acute pain, tolerance should be assumed as long as there are no other identifiable reasons for the pain (e.g., postoperative complication, acute neuropathic pain). In this situation, opioid doses should be increased as appropriate and/or coanalgesics considered.

14.2.1.2 Physical dependence

Like tolerance and OIH, physical dependence is a natural biological consequence of repeated opioid use and does not imply abuse or addiction (see definitions in Table 14.4). It should also be presumed to develop if repeated doses of an opioid are given for more than 10–14 days. However, the degree of withdrawal, if the opioid was abruptly stopped, would depend on the doses that had been used.

In acute pain management, withdrawal in opioid-tolerant patients can be prevented if their usual opioid (or equivalent) is continued, although situations can arise when high doses of opioids are abruptly stopped or reduced. For example, postoperative pain in a patient on long-term opioid therapy may be managed using some form of continuous regional (including epidural) or intrathecal analgesia. In most cases, the amount of opioid delivered by these routes is much less than that required to prevent the onset of withdrawal. Additional systemic opioids are required in these circumstances.

However, development of physical dependence in the acute pain setting is usually unimportant. Most patients, even if opioids have been required for several weeks, tend to reduce their opioid intake as pain becomes less. That is, steady tapering of opioid usually occurs naturally and planned dose reductions are not required.

14.2.1.2.1 Withdrawal (abstinence) syndrome

Signs and symptoms of withdrawal syndrome include yawning, sweating, lacrimation, rhinorrhea, anxiety, restlessness, insomnia, dilated pupils, piloerection, chills, tachycardia, hypertension, nausea and vomiting, crampy abdominal pains, diarrhea, and muscle aches and pains (ANZCA and FPM, 2010). Piloerection results in the appearance of gooseflesh so that the skin resembles that of a plucked turkey. Thus, the expression "going cold turkey" is used to describe the syndrome of abrupt withdrawal from opioids.

In patients with a physiological opioid dependence, withdrawal may occur as soon as 4–6 hours after the last dose of a short-acting opioid, but will occur later if methadone or slow-release opioid preparations are ceased. Prevention of withdrawal syndrome is discussed later in this chapter.

14.2.2 Aims of treatment

In general, the main requirements for managing acute pain in opioid-tolerant patients are (ANZCA and FPM, 2010; Huxtable et al., 2011):

- An adequate review and assessment prior to initiating acute pain therapies
- Provision of effective analgesia (including attenuation of tolerance and hyperalgesia)
- Prevention of withdrawal from opioids (and from other drugs as needed)
- Involvement of multidisciplinary and/or other specialist teams (including pain medicine and addiction medicine specialists, psychiatrists, and the patient's community doctors) and treatment of comorbidities (e.g., depression and other mental health illnesses including addiction) as needed
- Organization of appropriate management on discharge

14.2.3 Review prior to commencement of pain relief

Before initiating analgesia in the opioid-tolerant patient, it is important to seek information about all usual medications (opioid and nonopioid) and their doses. In some circumstances (e.g., emergency admissions) this may not be immediately possible. It should be done at the first opportunity and/or information sought from family or friends. As with all patients, questions should also be asked about any nonprescribed drug use, including over-the-counter medications, illicit drugs, and alcohol (Huxtable et al., 2011).

The doses of all prescribed medications should be verified before prescription so that the correct amount can be given. In the case of opioids this will also help guide the dose ordered for pain management as well that needed to avoid withdrawal. Information about prescribed medication doses can be obtained from a variety of sources including the dispensing label on the drug box or bottle (a recent one), the patient's treating doctor and their dispensing pharmacist. It is also worth checking that the opioids are used as prescribed. Some patients may take more or less than the confirmed amount and some may chew an SR tablet, for example, in order to get quicker release of the opioid. Much less commonly the drug might be injected or smoked. This information should be obtained in a nonjudgmental way along with an explanation that the information will help provide good pain relief.

In patients with preexisting pain it is also helpful to gain an understanding of that pain, including pain scores and functional status. Some may be hoping for improved management of their chronic pain. It can be worth explaining that the primary focus of treatment, in the first instance at least, will be to manage their acute pain episode as effectively, but also as safely as possible. Knowledge about the patient's psychiatric and medical comorbidities is also important as these may influence the choice of acute pain management regimen.

14.2.4 Effective analgesia

As with all patients, acute pain in opioid-tolerant individuals needs to be treated as effectively and quickly as possible. In general, multimodal analgesic regimens will be of most benefit and the use of nonopioid analgesics (paracetamol and nonsteroidal antiinflammatory drugs [NSAIDs]), drugs that may attenuate hyperalgesia and tolerance (ketamine and gabapentinoids), and regional analgesic techniques should be maximized in these patients. However, as with any patient, opioids will be the mainstay of good management for moderate-to-severe acute pain. Therefore, most of the following discussion centers on this group of drugs. If the doses of opioid needed for the treatment of acute pain are expected to be significantly higher than in opioid-naive patients, consideration also needs to be given to the best place to nurse the patient (e.g., general ward or high-dependency unit).

14.2.4.1 Opioids and tramadol

Most pure opioid agonists are suitable for use in these patients. The exception is pethidine (meperidine), where doses would have to be limited because of potential problems with norpethidine (normeperidine) toxicity (see Chapter 4). Pethidine is best avoided in the treatment of pain. Using an opioid other than the one the patient is taking long term (opioid rotation—see below) may offer some advantage in some circumstances.

Tramadol may also be of use, although its sole administration instead of any opioid is not recommended as it may not prevent opioid withdrawal.

14.2.4.1.1 Opioid doses

Opioid requirements will often be much higher than "average." The amount needed can be difficult to judge but it may be three or more times greater in opioid-tolerant patients compared with those who are opioid-naive (Rapp et al., 1995). The dose prescribed should take into account the patient's current opioid requirement, although these estimates are difficult to obtain when illicit drugs are involved. It is best to start with a conservative estimate and then rapidly titrate the drug aiming for patient comfort based on repeated assessments. In the short term and in the absence of any contraindication, the total dose should be increased until satisfactory analgesia is obtained or until side effects limit further increases. If high opioid requirements are expected, delivery via PCA is easier and more effective.

Examples of ways to estimate initial bolus doses for PCA are given in Section 14.2.5.1. A background (continuous) infusion can be used to deliver the equivalent of a patient's long-term oral opioid if oral administration is not possible.

The patient should be assured that staff will aim for good analgesia, but that their safety is paramount and so the onset of sedation will indicate that further opioid cannot safely be given even if they are still uncomfortable. In some patients the pain may not be completely responsive to opioids, as is the case with

neuropathic pain. In these cases other drugs or interventional methods of pain relief may be needed.

14.2.4.1.2 Monitoring for effect and side effects

Pain scores tend to be higher in opioid-tolerant patients, especially those with chronic noncancer pain (ANZCA and FPM, 2010) and are, therefore, not always be a reliable guide to alterations in therapy as high pain scores will not necessarily dictate further increases in opioid dose (Huxtable et al., 2011). An objective assessment of function (using functional activity scores [FAS]—see Chapter 3) such as ability to cough or ambulate after a laparotomy or with fractured ribs, may be a better guide to treatment once other reasons for pain (e.g., postoperative complication or acute neuropathic pain) have been considered. Comparison with preadmission pain scores can also be helpful in patients with preexisting pain. If the patient has very small pupils, it is reasonable to explain that this means the drug may already be exerting its near-to-maximal effect in the CNS (see Chapter 3) and that further increases in opioid doses may, therefore, not be safe and alternative strategies will need to be tried.

Tolerance develops to opioid-related side effects as well as analgesia, but to varying degrees and at varying rates. Tolerance to nausea and vomiting, cognitive impairment, sedation, and OIVI occurs rapidly; tolerance to constipation and miosis develops very slowly, if at all.

Despite tolerance to the effects of opioids, side effects can occur in opioid-tolerant patients, including OIVI. This seems especially likely if doses are suddenly and markedly increased above usual "baseline" levels, as might be needed in the acute pain setting. In a study comparing opioid-tolerant and opioid-naive patients given postoperative PCA morphine and using excessive sedation as an indicator of OIVI, opioid-tolerant patients were much more likely to become oversedated even though they reported less nausea, vomiting, and pruritus (Rapp et al., 1995). In a comparison of patients taking buprenorphine or methadone for the management of their opioid addiction, much higher-than-expected rates of excessive sedation were also reported (Macintyre et al., 2013).

If a patient becomes oversedated when given their usual and confirmed preadmission dose of opioid, the possibility that the patient has not been taking all their prescribed opioid prior to admission should be considered.

14.2.4.2 Attenuation of tolerance and hyperalgesia

There are a number of strategies that may help to attenuate opioid tolerance and hyperalgesia to a certain degree and improve analgesia. Those that might be of some use in the acute pain setting include:

- Attempting to reduce the amount of opioid required by addition of nonopioids including paracetamol, NSAIDS and gabapentinoids, and/or use of regional analgesic techniques (see Chapters 6, 9, and 10)
- Use of agents known to modify tolerance and hyperalgesia (ketamine, gabapentinoids)
- Opioid rotation

14.2.4.2.1 Antitolerance and antihyperalgesic medications

The *N*-methyl-D-aspartate (NMDA) receptor is thought to be involved in the development of tolerance and NMDA receptor antagonist drugs such as ketamine may be able to attenuate that tolerance. Ketamine (see Chapter 6) has been

shown to prevent or reverse opioid tolerance in rodents and there is evidence that it can reduce opioid requirements and improve pain relief in opioid-tolerant patients (ANZCA and FPM, 2010; Loftus et al., 2010). It also has antihyperalgesic properties.

Therefore, ketamine administered in low doses of 50–200 mg/24 hours or at a starting infusion rate of 0.1 mg/kg/h by IV or subcutaneous (SC) infusion is a useful adjunct in some opioid-tolerant patients, with few, if any, side effects. It may be of more benefit in patients taking higher opioid doses rather than lower doses prior to admission (Loftus et al., 2010). Doses can be increased as tolerated to provide better analgesia.

While there is no good specific information about the use of gabapentinoids in opioid-tolerant patients they have proven antihyperalgesic properties and may be a useful addition to the treatment regimen (Schug, 2012). Their anxiolytic effect may also benefit some patients (Baldwin et al., 2013).

14.2.4.2.2 Opioid rotation

Opioid rotation (switching from one opioid to another) is common practice in palliative care settings. The aim is to improve pain relief and reduce the incidence of opioid-related adverse effects. The mechanisms behind this effect are thought to include differing receptor activities and the fact that incomplete cross-tolerance is likely to exist, so that when a change of opioid is made, the "new" opioid may be more effective and result in a better side effect profile when used less than equianalgesic dose (Huxtable et al., 2011). The "new" opioid is commonly started at about 30–50% of the calculated equianalgesic dose (except for a change to methadone when much lower doses would be used).

Using an opioid that is different from the patient's usual long-term medication for at least the additional opioid required to manage acute pain may be a useful strategy. However, changing to another opioid because of inadequate analgesia in the acute pain setting is probably best left until after increased opioid doses and other analgesic strategies have been tried.

14.2.4.3 Other analgesic agents and techniques

Where appropriate, other adjuvant medications such as a gabapentinoid (pregabalin, gabapentin) and clonidine, or a regional analgesic technique may be of benefit.

14.2.5 Specific analgesic techniques

14.2.5.1 Patient-controlled analgesia

Patient-controlled analgesia can be a useful way of delivering opioids in opioid-tolerant patients, especially if requirements are expected to be high. In addition, if patients are unable to continue their normal long-term opioid medication (e.g., because they are not allowed anything by mouth), a continuous (background) infusion can be used to cover this basal requirement.

There is no easy way to estimate opioid requirements in these patients. Larger-than-average bolus doses will often be needed, although it can be difficult to predict the optimal starting dose. One method is to base the size of the bolus dose on the patient's normal (preadmission) opioid requirement, if necessary using approximate equianalgesic doses if another opioid is ordered. Examples

of this are provided below. The dose regimens given are suggestions only and may not be suitable for all patients or in all situations. If a patient's usual opioid requirements are much greater than those in the examples below, it may be wise to be more conservative and start at lower than estimated doses and background infusion rates.

If a patient is taking methadone on a regular basis, it is much more difficult to calculate an appropriate initial PCA bolus dose, because the very variable half-life of methadone and its long duration of action make any estimate of true "equianalgesic" dose almost impossible. In practice, a "conversion" of "1 mg oral methadone = 1 mg parenteral morphine" for the initial stage of treatment seems to work in most patients, with the PCA regimens adjusted to suit thereafter. This is a working estimate only and not based on possible equianalgesic doses.

Adjustments to the size of the PCA bolus dose should be guided according to the patient's response—see Chapter 8. The use of higher PCA doses is best limited to situations where the patient is being managed by specialist pain services, when there is 24-hour (appropriate) medical cover, when nursing and medical staff have had appropriate education and experience, and when adequate monitoring is available.

Once the patient is tolerating oral fluids, usual opioid regimens can be restarted to replace any background infusion. High PCA dose requirements may mean that there is a delay before the patient can be managed with oral opioids alone.

Example 1

A patient who has been taking 200 mg of slow-release (SR) oral morphine in divided doses daily for a number of years is ordered PCA as part of his multimodal analgesia following fixation of his fractured tibia. He is allowed to drink after the operation and should continue taking his SR morphine as usual.

His 200 mg/day oral morphine is equivalent to around 70 mg/day IV morphine which is nearly 3 mg/h. Therefore, it might be reasonable to commence PCA with a bolus dose of 2 mg rather than the "standard" 1 mg. Alternatively, PCA fentanyl could be prescribed with a bolus dose starting at 40 μg.

If this patient was unable to drink and unable to take his SR morphine, a background infusion could be ordered. An infusion rate of a little less than the calculated "equivalent" dose may be reasonable—in this case starting at 2 mg/h (or 40 μg/h fentanyl).

Example 2

A patient is ordered PCA fentanyl after her total abdominal hysterectomy. She has been using a fentanyl patch 100 μg/h for back pain for the last two years. She was advised, correctly, to leave her patch on before surgery.

The fentanyl patch should be continued. It might be reasonable to commence PCA with a bolus dose of 50 μg fentanyl rather than the "standard" 20 μg. Alternatively, PCA morphine or oxycodone could be prescribed with a bolus dose starting at 2–3 mg.

14.2.5.2 Regional analgesia

A variety of regional analgesic techniques, including epidural and other continuous nerve or plexus infusions, may be used to provide safe and effective pain relief in opioid-tolerant patients. The doses of opioids usually administered by the epidural or intrathecal routes will not necessarily be enough to prevent opioid withdrawal, and replacement of basal opioid requirements may be needed in order to prevent withdrawal. The use of larger-than-usual neuraxial opioids doses has been suggested (ANZCA and FPM, 2010), but it is difficult to determine a safe dose.

14.2.6 Prevention of withdrawal

If patients are unable to continue their usual chronic opioid therapy in the postoperative or posttrauma period (e.g., because they are fasting), sufficient opioid must be given to cover their basal requirement in order to prevent withdrawal. Basal requirements should be provided regardless of reported pain.

If the patient's "usual" opioid is illicit, the doses cannot be confirmed and so basal requirements are unknown. In these circumstances it may be wise to start with conservative opioids doses and no background infusion if PCA is used. Alterations to the analgesic regimen can then be made according to the need.

If there is any doubt about whether the verified dose is being taken in full, the total daily preadmission dose can be given as divided doses (i.e., smaller and more frequent amounts) with the patient closely observed and subsequent doses altered as needed.

If patients have required high systemic doses of opioid for the treatment of acute pain for more than a week or two, they may also be at risk of withdrawal if the drug is abruptly stopped or doses reduced too rapidly. In general, dose reductions of about 20–25% every day or two will allow a tapering of opioid dose without signs and symptoms of withdrawal. Most patients do this anyway as their acute pain improves.

More rapid tapering with symptomatic management of withdrawal symptoms can be achieved if the patient is given clonidine (an α_2-adrenergic agonist—see Chapter 6) (ANZCA and FPM, 2010).

Some patients may have a physical dependence on other drugs such as benzodiazepines or alcohol. Treatment must also aim to prevent withdrawal from these drugs.

14.2.7 Involvement of multidisciplinary and other specialist teams

Opioid-tolerant patients may have significant emotional and psychiatric comorbidities. In many of these patients, management of behavioral, psychological, medical, social, and other factors may be needed in addition to analgesia. Assistance from other specialist teams, including chronic pain, palliative care, drug and alcohol and psychiatric services, may be advisable.

14.2.8 Discharge analgesia

The requirements for management of discharge analgesia may be a little more complex in some opioid-tolerant patients—see Chapter 15.

Key points

1. The main principles of acute pain management in opioid-tolerant patients include a thorough assessment prior to initiating acute pain therapies, provision of effective analgesia, prevention of withdrawal from opioids (and from other drugs as needed), involvement of multidisciplinary and/or other specialist teams, and assistance with appropriate discharge planning.
2. Preadmission opioid regimens should be confirmed and then maintained where possible, or an equivalent alternative organized.
3. Multimodal acute pain management in opioid-tolerant patients should be based on nonopioid analgesic drugs (NSAIDs, paracetamol), antitolerance and antihyperalgesic agents (ketamine, gabapentinoids) and regional analgesic techniques as well as opioids.
4. Opioid-tolerant patients may require much higher opioid doses than opioid-naive patients for treatment of acute pain and inter-individual differences in the doses needed may be even greater. The risk of OIVI may be higher in these patients.
5. Pain scores are often higher and acute pain may last for much longer in opioid-tolerant patients; pain should be assessed using a combination of pain scores and assessment of patient function.

14.3 Patients with an addiction disorder

The term addiction (see definition Table 14.4) is used in this book rather than the alternative terms substance dependence or substance abuse. This is to more clearly separate the behavioral components that are part of addiction from tolerance and physical dependence, which are predictable and physiological consequences of long-term opioid use (ANZCA and FPM, 2010). Addiction is not only influenced by the characteristics of the drug used but the genetic, psychological, social and environmental vulnerability of the individual (ANZCA and FPM, 2010).

Patients who are addicted to opioids will usually be tolerant to their effects and physically dependent on the drugs, but management may be further complicated by associated psychological and behavioral factors as well as the presence of other drugs of abuse, medications that assist with drug withdrawal and rehabilitation, and possible other problems related to drug abuse, including infectious diseases.

Common psychological comorbidities in patients who abuse drugs or alcohol are depression, anxiety, and borderline personality disorders (Macintyre et al., 2014) and these can be exacerbated during the acute pain episode. However, it is their aberrant drug-taking behavior and loss of personal control that distinguish patients with an addiction from other patients on long-term opioid therapy. A wide variety of aberrant drug-taking behaviors have been described, some of which are said to be less common but more suggestive of addiction, and others more common but less suggestive (Table 14.5) (Passik, 2009). The latter are more likely to reflect undertreated distress of some kind (e.g., pain or psychological distress).

Occasionally, staff may report that a patient is "becoming addicted" to opioids or "seeking drugs" when the patient appears to be demanding pain-relieving drugs and exhibiting aberrant drug-taking behaviors similar to those seen in patients

Table 14.5 Spectrum of aberrant drug-taking behaviors

More suggestive of addiction	Less suggestive of addiction
• Concurrent abuse of alcohol or illicit drugs	• Aggressive complaining about the need for more drugs
• Evidence of a deterioration in the ability to function at work, in the family, or socially that appears to be related to drug use	• Drug hoarding during periods of reduced symptoms
• Injecting oral formulations	• Openly acquiring similar drugs from other medical sources
• Multiple dose escalations or other nonadherence with therapy despite warnings	• Requesting specific drugs
• Obtaining prescription drugs from nonmedical sources	• Reporting psychic effects not intended by the physician
• Prescription forgery	• Resistance to a change in therapy associated with tolerable adverse accompanied by expressions of anxiety related to the return of severe symptoms
• Repeated resistance to changes in therapy despite clear evidence of drug-related adverse physical or psychological effects	• Unapproved use of the drug to treat another symptom
• Repeatedly seeking prescriptions from other physicians or emergency departments without informing prescriber	• Unsanctioned dose escalation or other nonadherence with therapy on 1 or 2 occasions
• Selling prescription drugs	
• Stealing or borrowing drugs from others	

Source: Reproduced with permission from Passik SD. 2009. *Mayo Clinic Proceedings. Mayo Clinic* **84**(7): 593–601. Mayo Foundation for Medical Education and Research©.

with an addiction. Undertreatment of acute pain may lead to iatrogenic drug-seeking behaviors that are really pain-avoidance behaviors because pain relief is inadequate. This has been termed *pseudoaddiction* (Weissman and Haddox, 1989).

Assistance in the management of patients with an addiction disorder from other specialist teams, including chronic pain, palliative care, drug and alcohol, and psychiatric services, may be advisable.

14.3.1 Use of opioids in patients with a past addiction disorder

If a patient has been addicted to opioids in the past, they may be concerned that the use of opioids for pain relief will lead to the reinstatement of a craving for drugs and their addiction. They can be advised that the use of opioids for analgesia while in hospital is not necessarily a risk factor for readdiction, and that while the use of local anesthetic blocks and nonopioid medications can be maximized and may suffice in some patients, the primary concern must still be good pain relief. An explanation about the need to use opioids in effective doses if pain is severe and that ineffective analgesia may lead to anxiety, drug-seeking behaviors and demands as well as pain, may help allay concerns. An assurance that their ongoing care will be coordinated with their treating doctor after discharge from hospital and that assistance will be given with appropriate dose tapering may also help.

14.3.2 Withdrawal from other drugs

It is not uncommon for patients who have an addiction to opioids to be addicted to other drugs (e.g., alcohol, benzodiazepines, cannabis, and amphetamines).

Monitoring of signs and symptoms that indicate withdrawal from these drugs is suggested, and prevention or treatment regimens should be instituted as necessary.

Early signs of alcohol withdrawal usually appear between six and 24 hours after the last intake of alcohol. The onset of withdrawal from benzodiazepines will vary because of differences in the half-life of the drugs in this class and because some benzodiazepines have active metabolites. Clinical features common to withdrawal from both alcohol and benzodiazepines include tremor, anxiety/agitation, sweating, sleep disturbances, hypersensitivity to stimulation, visual disturbances and, in severe cases, delirium and seizures (O'Brien, 2005; Carlson et al., 2012).

Benzodiazepines may be required for the management of withdrawal from alcohol, benzodiazepines or, less often, cannabis. If concurrent opioids are given, the patient's level of sedation should be monitored closely as the risk of OIVI will be increased. If patients are at risk of seizures, other medications that are known to lower seizure threshold (e.g., tricyclic antidepressant agents, tramadol) should be used with care.

Withdrawal from amphetamine can lead to marked sedation and possible difficulties in safely obtaining adequate analgesia with opioids.

14.3.3 Management of aberrant drug-taking behaviors

Individualized treatment plans that help with effective and safe yet compassionate treatment can benefit the small proportion of patients who exhibit significant aberrant drug-taking behaviors while in hospital. These treatment plans, which should be firmly but fairly applied, should be discussed with the patient. They should include an assurance that attempts will be made to provide good pain relief, but that there may need to be realistic goals for analgesia (complete pain relief is usually not realistic), expected duration of treatment, plans for dose reductions, and choice of drugs available. All medical and nursing staff involved in treating the patient should agree with and adhere to the plans. These plans also often need to include behavioral boundaries to limit abuse of staff and/or ensure personal safety of staff in potentially violent situations.

The dangers associated with tampering with equipment, or the use of illicit drugs in addition to prescribed medications, should also be explained. If use of illicit drugs is suspected at any time, the patient may need to be monitored more closely as there could be an increased risk of OIVI if sedative medications or other opioids were taken. Staff looking after these patients should be aware of relevant hospital protocols relating to the possession of prohibited substances by patients and visitors.

14.3.4 Drugs used in the treatment of opioid addiction

Patients in treatment programs for their opioid addiction are often prescribed methadone or buprenorphine as opioid substitutes—opioid substitution therapy (OST) and some will be given naltrexone (Tetrault and Fiellin, 2012).

14.3.4.1 Methadone

Methadone is a long-acting pure opioid agonist usually used in syrup form for OST patients and given once a day. This will usually suppress opioid withdrawal for at least 24 hours, but the duration of analgesia is probably shorter (ANZCA

and FPM, 2010). The patient's usual methadone dose should be continued while additional opioids are given for management of acute pain. Temporary administration of the methadone in two or three divided doses during the day may provide a more stable "background" analgesia.

If the patient is unable to take their methadone by mouth, smaller "equivalent" dose of methadone (about 60% of the oral dose) can be given parenterally, either by an IV infusion or, sometimes more easily, as three or four divided doses by intermittent SC injection (ANZCA and FPM, 2010).

Changes to a patient's OST methadone dose should only be done in consultation with the authorized (registered) prescriber or an addiction medicine specialist.

14.3.4.2 Buprenorphine

Buprenorphine is also increasingly being used as OST, either as a sublingual tablet or mucoadhesive film. It is now more commonly given in combination with naloxone rather than alone (Macintyre et al., 2013). Naloxone is poorly absorbed via the sublingual route, but if injected will reverse the effects of the buprenorphine.

Buprenorphine OST is also usually given once a day, but its long duration of action means that some patients require it only second daily. Again, temporary administration in two or more divided doses throughout the day may provide a background analgesic effect while additional opioid are being given.

Its high affinity for and slow dissociation from μ-opioid receptors have led to concerns that buprenorphine may block the analgesic effects of pure opioid agonists. Its classification as a partial μ-agonist (clinically it appears to behave as a full μ-agonist for analgesia—see Chapter 4) has also led some to believe it would antagonize the effects of other pure agonist opioids given at the same time. However, neither of these concerns appears to be well-founded in clinical practice and coadministration with another opioid will reduce the amount of additional opioid needed (Macintyre et al., 2013). The patient's usual buprenorphine should therefore be continued while other opioids are added as required for management of acute pain. As buprenorphine is given sublingually, it can be continued even if patients are not taking anything by mouth.

If buprenorphine has been ceased, there have been concerns that its reintroduction may precipitate withdrawal if the patient is still taking other opioids. In practice, if small doses are started to begin with and increased to the patient's usual dose over a few days, withdrawal appears not to be an issue (Macintyre et al., 2013).

14.3.4.3 Naltrexone

Naltrexone is a pure opioid antagonist (see Chapter 4) used in the treatment of alcohol and opioid addiction. As it may be difficult to achieve adequate pain relief with opioid drugs, even in high doses, until the effects of naltrexone have abated, naltrexone should be ceased at least 24–48 hours prior to surgery where possible (Macintyre et al., 2013). There is some evidence that patients may become much more sensitive to opioids following cessation of naltrexone, therefore they should be monitored closely if other opioid analgesia is given during this time.

Naltrexone is usually given as a tablet, but implanted pellets of a slow-release naltrexone are also used in some countries (Tetrault and Fiellin, 2012). This can make effective management of moderate-to-severe pain much more difficult unless regional analgesia is possible. Removal of the implant may be

required in some patients, especially if the course of their pain is expected to be prolonged.

14.3.5 Discharge analgesia

The requirements for management of discharge analgesia may be a little more complex in patients with an addiction disorder—see Chapter 15.

Key points

1. Patients who are addicted to opioids will usually be tolerant to their effects and physically dependent on the drugs. It is their aberrant drug-taking behavioral patterns and loss of personal control that distinguish them from other patients on long-term opioid therapy.
2. Patients in treatment programs for their opioid addiction are often prescribed methadone or buprenorphine as opioid substitutes. Both should be continued where possible in addition to other opioids used for acute pain management.

14.4 Patients with obstructive sleep apnea

Obstructive sleep apnea (OSA) is just one aspect of the complex spectrum of sleep-disordered breathing which also includes obesity, hypoventilation, and central apnea syndromes. The prevalence of OSA in the adult population is surprisingly high. Approximately 1 in 5 adults are said to have at least mild OSA and 1 in 15 have moderate-to-severe OSA; around three-quarters of those who could benefit from treatment remain undiagnosed (Young et al., 2004; ANZCA and FPM, 2010).

There is little good evidence to guide "best choice" of acute pain management regimen in patients with OSA. Nonopioid analgesics and regional analgesic techniques are usually recommended (either as the sole means of pain relief or in addition to opioids) because of concerns that the patient with OSA is at increased risk of OIVI if given opioid or sedative drugs. However, as many patients will have undiagnosed OSA, the same standards of pain relief should be applied to all.

Supplemental oxygen given to patients with OSA (not in a perioperative setting) has been shown to be as effective as CPAP in reducing the risk of significant hypoxemia. The routine use of supplemental oxygen would therefore seem appropriate in all patients with OSA, or suspected of having OSA, and receiving opioids for the treatment of their pain. Any patient who has a CPAP machine should use it throughout their hospital stay.

14.4.1 Opioid analgesia and patients with OSA

Patients with OSA are at higher risk of postoperative complications (Chung and Mokhlesi, 2014; Memtsoudis et al., 2014). One common concern is that opioid administration may lead to an increase in the number and severity of obstructive episodes, hypoxia and OIVI in this group of patients. However, good consistent evidence is still lacking. For example, some but not all studies show a greater increase in the number of central apneas than number of obstructive episodes (Macintyre et al., 2011).

There have been a number of case reports of life-threatening or fatal OIVI following opioid administration in patients with OSA (Macintyre et al., 2011). However, when these reports are studied in detail, it would appear that one of the main problems was the lack of appropriate monitoring that would enable the early detection of OIVI. Inappropriate dose regimens also appeared to contribute in some patients (e.g., use of a background infusion with PCA in an opioid-naive individual or coadministration of sedative drugs).

It is known that increasing sedation is the best early clinical indicator of OIVI (see Chapter 3) and yet it would seem, in most if not all of the reports, that inappropriate reliance was placed on monitoring the patient's respiratory rate. In many of the reports, marked sedation and hypercarbia were noted in the presence of a normal respiratory rate, and the significance of increasing sedation was not recognized as an early indicator of OIVI. Had sedation levels been monitored on a regular basis and appropriate measures taken when excessive sedation was first noticed, it may be that severe OIVI could have been averted.

As a result of these cases it has been suggested that monitoring should be improved in high-risk patients such as those with OSA. However, attempting to select out high-risk patient groups may put other patients at risk.

In an analysis of postoperative claims resulting in significant harm (death or severe brain damage in 80% of cases) from OIVI, there was evidence of OSA in 40% of cases, so patients with OSA are at increased risk (Lee and Domino, 2013). However, and importantly, this meant 60% of patients did *not* have evidence of OSA. Also noted were excessive sedation (in 60% of cases), coadministration of nonopioid sedative medications (38%), prescribing of opioids or sedatives by more than one physician (34%) and snoring (16%). Over 60% of the patients were obese and over 50% were aged 18–49 years. A key finding was that 87% of patients who came to harm from OIVI did so on the first day or night after surgery. It was concluded that patient outcomes may be improved if there was a focus on better monitoring of *all* patients in the high-risk postoperative period, rather than only in patients deemed to be high risk.

A variety of screening tools have been developed in an attempt to identify patients at high risk of OSA (Abrishami et al., 2010), but appropriate and effective monitoring of every patient will increase the safety of all. However, it may be prudent to monitor selected patients with OSA in a high dependency setting.

Key point

1. Patients with OSA may be at higher risk of complications after surgery and from opioid analgesia, but the key to patient safety is to focus on effective monitoring for *all* patients, as it is not possible to identify all patients with OSA.

14.5 Pregnant or lactating patients

14.5.1 Analgesic use during pregnancy

The pregnant woman may require treatment for acute pain for many reasons other than during labor and delivery. The major concern in these patients is that all analgesics will almost invariably cross the placenta to some degree. Therefore,

nonpharmacological therapies should be used where possible. However, if this is not feasible, drugs that pose the least risk to the fetus should be prescribed in consultation with the patient's obstetrician. While most are safe, their administration during two particular periods of pregnancy is of most concern—the first trimester and just before delivery.

In many countries, drugs that might be prescribed during pregnancy have been categorized according to risk of birth defects, undesirable pharmacological effects around the time of delivery (which may or may not be reversible) and problems in later life. These recommendations should be consulted before any drug is used in a pregnant patient. One example of an easily searchable database is the *Prescribing Medicines in Pregnancy Database* from the Therapeutics Goods of Australia (http://www.tga.gov.au/hp/information-medicines.htm#). While the details in each category may vary from country to country, certain generalizations can be made (ANZCA and FPM, 2010):

- Paracetamol is the analgesic of choice.
- NSAIDs should be used with caution in the last trimester of pregnancy and avoided from the last few days before delivery is expected, as they can cause fetal renal problems, increase the risk of premature closure of the ductus arteriosus and delay labor.
- Short-term use of opioids appears to be relatively safe and they can be used in pregnancy if the benefits are considered to outweigh the risks. They can cause OIVI in the newborn and withdrawal after long-term maternal use.
- Most if not all local anesthetic agents are safe to use.
- Of the antiemetics, metoclopramide, dimenhydrinate, and diphenhydramine are the drugs of choice.

14.5.2 Analgesic use during lactation

Many of the analgesic drugs that might be prescribed during lactation will transfer in part to human milk and then to the breast-fed infant. The amount transferred will be greater for those drugs that are highly lipid soluble, have a low molecular weight and are minimally protein bound, however, clinically significant levels are not usually seen (Rowe et al., 2013).

Drugs that might be prescribed during lactation have also been categorized according to risk. One example of an easily searchable database is the National Library of Medicine's *Drugs and Lactation Database (LactMed)* http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. Guidelines such as this should be consulted before analgesic drugs are prescribed for the lactating patient and/or other specialist information services consulted. However, certain generalizations can again be made (ANZCA and FPM, 2010):

- Paracetamol is the analgesic of choice.
- Most NSAIDs can be used: ibuprofen may be preferred and aspirin should be avoided.
- Most opioids may be used safely although pethidine is not recommended and caution is required with codeine as deaths have been reported in infants of breastfeeding mothers who were ultrarapid metabolizers of the drug (see Chapter 4). Both mother and child should be monitored for sedation.
- Local anesthetic agents are safe to use.
- Antiemetics that are safe to use include dimenhyredrinate and metoclopramide.

Table 14.6 Analgesics used in patients with renal or hepatic impairment

	Renal impairment	Hepatic impairment
Opioids	*No dose adjustment required as none, minimal amount, or only weakly active metabolites* • Alfentanil • Fentanyl (good choice if severe renal impairment) • Buprenorphine • Oxycodone (in most patients)[a] • Methadone (unless impairment severe) • Sufentanil *Dose adjustment suggested or, sometimes in preference, use alternative agent* • Codeine • Hydromorphone • Morphine • Tramadol *Avoid* • Pethidine • Dextropropoxyphene	*No dose adjustment required*[b] • Alfentanil • Buprenorphine • Fentanyl • Morphine • Oxycodone • Sufentanil *Dose adjustment may be needed if impairment severe* • Methadone • Tramadol *Avoid* • Pethidine
Local anesthetic drugs	No significant difference in plasma concentrations unless renal impairment is severe	Dose adjustment may be required with repeated or prolonged use

Paracetamol	Safe to use in most patients	Short-term use at therapeutic dose is reasonable in patients with chronic liver disease; reduce dose to 2–3 g/day for long-term use; preferred to NSAIDs
NSAIDs including coxibs	Use with extreme caution if renal impairment and avoid if severe	Reduced doses suggested
Tricyclic antidepressants (TCAs)	Metabolite accumulation may occur but limited evidence about need for dose reductions	Reduced doses suggested if severe hepatic impairment
Gabapentin, pregabalin	Dose adjustment suggested based on creatinine clearance	Suitable for use—nonhepatic metabolism
Ketamine	Limited data but probably no dose adjustment needed	Limited information

Source: Adapted with permission from Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (ANZCA and FPM). 2010. *Acute Pain Management: Scientific Evidence*. 3rd edn. Macintyre PE et al. (eds). Melbourne. http://www.fpm.anzca.edu.au/resources/books-and-publications with additions from Niscola P, Scaramucci L, Vischini G et al. 2010. *Current Drug Targets* **11**(6): 752–8 and Dwyer JP, Jayasekera C, Nicoll A. 2014. *Journal of Gastroenterology and Hepatology* **29**(7):1356–60.

[a] Significant ↑ in half-life especially in end-stage renal disease and may need dose reduction or alternative agent.

[b] Possible increased risk of opioid toxicity in patients with hypoalbuminemia.

Key point

1. The use of medications for pain in pregnancy or during lactation should be guided by published recommendations.

14.6 Patients with renal or hepatic impairment

In patients with renal or hepatic impairment, altered clearance of some analgesic agents or accumulation of their active metabolites may occur. This may influence the choice of drug or the dose used.

While good evidence is sometimes lacking regarding some of the drugs used for pain relief in these patients, certain generalizations can be made. These are summarized in Table 14.6 (ANZCA and FPM, 2010; Niscola et al., 2010; Dwyer et al., 2014). The information given is applicable to most patients but there will be individual variations.

Evidence about the effects of dialysis on most of the drugs is minimal or lacking and much of what is known is based on case reports. Information should be sought on an individual basis as it may also vary with the type of dialysis.

Key point

1. Consideration should be given to choice and dose regimen of analgesic agents in patients with renal or hepatic impairment.

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CHAPTER 15

Opioid analgesia after discharge from hospital

The main aim of the previous chapters has been to provide practical information about the management of patients with acute pain when in hospital. However, many inpatients are now being discharged at an earlier stage after their surgery or after they have suffered a significant injury or medical illness, and many more are undergoing more complex surgery, either on a day-stay or 23-hour-stay basis. So that patients can continue their physical rehabilitation and activities after discharge, some will, quite reasonably, require short-term continuation of an opioid medication as part of their ongoing multimodal analgesia.

However, before postdischarge opioids are prescribed, consideration must be given to whether there are any risks that might be associated with this prescription for each patient, what opioid will be used and for how long, and what information the patient and their treating doctors and other healthcare professionals in the community might need to have.

15.1 Potential risks

15.1.1 Adverse effects of opioids

In addition to the adverse effects that might be seen following opioid administration in the hospital, the use of opioids for ongoing acute pain management in a community setting may carry additional risks.

15.1.1.1 Opioid-related side effects

If the patient has already been given an opioid while an inpatient, in the doses that are similar to those that will be used after discharge, it is likely that side effects such as nausea and vomiting, pruritus, or excessive sedation/opioid-induced ventilatory impairment (OIVI) will have already been recognized. However, if patients will be taking these medications for the first time after discharge (e.g., from a day-surgery procedure) or if they do not reduce their opioid doses as their pain improves, such side effects may first develop after they have left hospital. Each patient should be given appropriate instructions to follow should any of these adverse events occur (see Section 15.3.1).

In hospital it is known that the combination of opioid with any sedative medication will increase the risk of OIVI (Macintyre et al., 2011; Lee and Domino, 2013). This combination (especially with benzodiazepines and alcohol) has also been shown to increase the risk of death in patients with chronic noncancer pain and those using opioids for nonmedical purposes (Gomes et al., 2011; Webster et al., 2011; Rintoul et al., 2013). Therefore, patients prescribed an opioid for after-discharge acute pain management should be advised not to take any sedative medications or to drink alcohol while taking these medications.

Less often considered is the risk of falls, which is known to be higher in patients who have recently started taking an opioid (Soderberg et al., 2013).

15.1.1.2 Inadvertent initiation of long-term use

It is also possible, while the opioid has been prescribed to treat acute pain that is ongoing after discharge, that some patients may, for a variety of reasons, still be taking an opioid long after the pain would still be considered "acute"—in some reports as long as one or two years after their surgery (Macintyre et al., 2014).

There could be a number of reasons for this. For example, the patient may still be experiencing significant pain after their surgery or injury, which should be assessed, or they might have found that the opioid helped other pain that he/she had been experiencing, such as chronic back pain. In others it could also be because they found that the opioid helped them cope with negative emotions and stress (Passik and Lowery, 2011).

The risk of long-term use of an opioid initially prescribed to manage acute pain in the short term may correlate better with psychological factors such as depression rather than duration of the pain (Macintyre et al., 2014). Depression, anxiety, pain catastrophizing, and other mental health problems have also been linked to a higher risk of persistent postsurgical pain (Hinrichs-Rocker et al., 2009; Theunissen et al., 2012), persistent pain after acute musculoskeletal injuries (Rosenbloom et al., 2013), and prolonged opioid use in patients with chronic pain as well as the risk of opioid misuse or addiction (Macintyre et al., 2014).

This does not mean that patients with these psychological conditions should never be given an opioid when they leave hospital. However, it is important that the risk factors for prolonged or inappropriate use are recognized. Closer follow-up of the patient after discharge and assistance with tapering of the doses may be advisable.

The aim of prescribing opioids after discharge is to help the patient manage their acute pain and not start them, albeit inadvertently, on long-term opioid therapy or a path to opioid misuse. A patient who is still requiring opioid for their "acute" pain some months after discharge needs to be evaluated further. This would include an assessment of the pain, whether there is any evidence of a neuropathic component to the pain, and relevant psychological and social factors. Pain persisting for three months is classed as chronic and not acute pain and alternative treatment strategies may be preferable.

15.1.1.3 Effect on driving ability

The effects of opioid medication on driving and driving risks have been studied in detail (European Monitoring Centre for Drugs and Addiction, 2012) and many countries have guidelines relating to driving and opioid medications. In general, most suggest that driving performance will not be significantly impaired once the dose of opioid is stable, but may be impaired if recent alterations have been made to the dose being taken, following acute administration of opioids, or if the driver is also taking a benzodiazepine medication (Drug and Alcohol Services South Australia, 2006; British Pain Society, 2010; National Opioid Use Guideline Group, 2010; Wilhelmi and Cohen, 2012).

The intensity of acute pain both in and after discharge from hospital is likely to vary according to the degree of activity, and should decrease as the patient recovers. Therefore, the dose of opioid that is likely to be needed by the patient may vary within each day and should be decreasing with time overall. As such

the dose is not stable. Patients prescribed an opioid after discharge for ongoing management of acute pain should therefore be cautioned about driving.

15.1.2 Risk of diversion and harm

The increasing problems in the community resulting from diversion, misuse, and abuse of opioids are well-recognized. In many if not most developed countries of the world there has been a rapid rise over time in the number of prescriptions for opioids (Leong et al., 2009; Manchikanti et al., 2012), which has coincided with increases in the number of deaths related to nonmedical use of opioids (Rintoul et al., 2011; Centers for Disease Control and Prevention, 2013) and hospital attendances related to complications from these medications (Roxburgh et al., 2011; Substance Abuse and Mental Health Services Administration, 2013).

To a large extent the "epidemic" of opioid misuse for nonmedical purposes has been attributed to the number of opioid prescriptions written for the management of chronic noncancer pain. However, opioid prescriptions for acute pain, both after discharge from a hospital and in the community generally, are likely to play a part.

It is known that patients prescribed an opioid for discharge after surgery may be given many more tablets than they need and most keep the leftover medication rather than dispose of it properly (Macintyre et al., 2014). This results in a potentially very large reservoir of unused opioid. These may be kept by the patient possibly for future use or, less commonly, to be abused or diverted, with the consequent risk of harm to the patient and others. Around 50% or more of those obtaining opioids for nonmedical use, including those likely to be prescribed for ongoing acute pain management, are able to source them from family and friends (Substance Abuse and Mental Health Services Administration, 2012; Stafford and Burns, 2013).

15.1.2.1 Identification of the "at risk" patient

Before a patient is prescribed an opioid for discharge it is important that risk of diversion and misuse is considered. In some patients a more formal assessment may be advisable and a number of risk-assessment tools are available (Passik et al., 2008; Chou et al., 2009). One that screens for *potential* misuse and abuse of opioids is the opioid risk tool (ORT) (Webster and Webster, 2005)—see Table 15.1.

The ORT includes a number of questions, the answers to which are scored differently depending on whether the patient is female or male. These questions relate to a personal or family history of abuse of alcohol, illegal drugs or prescription drugs, as well as the patient's age and whether they have a diagnosis of attention-deficit disorder, obsessive–compulsive disorder, bipolar disorder, or schizophrenia. A diagnosis of depression is scored separately. The other question asks about preadolescent sexual abuse, which may not be easy or appropriate to ask during a brief visit to assess a patient's acute pain and efficacy of its treatment. A total score of 8 or more is said to indicate that there is a high risk (estimated 91%) risk of opioid-related aberrant behavior (Webster and Webster, 2005).

The ORT may be a less-sensitive screening tool than some others, but it is quick and easy to use in a busy acute pain setting. When considering the risk of diversion or abuse of opioids after discharge, it may be reasonable to widen the definition of "family" and consider the friends with whom a patient may be living and will be returning to with these medications.

Table 15.1 Opioid risk tool

Item	Mark each box that applies	Item score if female	Item score if male
1. Family history of substance abuse			
Alcohol	[ ]	1	3
Illegal drugs	[ ]	2	3
Prescription drugs	[ ]	4	4
2. Personal history of substance abuse			
Alcohol	[ ]	3	3
Illegal drugs	[ ]	4	4
Prescription drugs	[ ]	5	5
3. Age (mark box if 16–45 years)	[ ]	1	1
4. History of preadolescent sexual abuse	[ ]	3	0
5. Psychological disease			
Attention-deficit disorder, obsessive–compulsive disorder, bipolar, schizophrenia	[ ]	2	2
Depression	[ ]	1	1
Total			

Source: Reproduced with permission from Webster LR, Webster RM. 2005. *Pain Medicine* **6**(6): 432–42. Copyright American Academy of Pain Medicine.

Note: Total score risk category:
Low risk 0–3.
Moderate risk 4–7.
High risk >8 (estimated 91% risk of aberrant behavior).

15.2 Choice of discharge opioid regimen

15.2.1 Choice of opioid

There is no evidence to guide the choice of "preferred" oral opioid to be prescribed at discharge, whether immediate-release or slow-release opioid, although immediate-release opioids have been recommended (Thorson et al., 2014). The use of methadone is best restricted to those experienced with its use. Factors that should be taken into account include whether "activity-based" analgesia (where opioid doses can be titrated to periods of activity and the patient encouraged to use them on this basis) or more constant opioid blood concentrations are likely to be of most benefit. Ease of dose tapering with different drug regimens should also be considered.

Opioid "attractiveness" is said to add to the risk that an opioid will be diverted for nonmedical use. However, while factors such as cost, speed of onset, peer preference, and intensity and duration of affect are important in these attractiveness ratings (Butler et al., 2010), availability is probably a key factor (Cicero et al., 2013). Some "abuse-deterrent" formulations of opioids may reduce the risk of the drug being used in other than the intended way or route of administration (Cicero et al., 2012; Butler et al., 2013).

The combination of an opioid with paracetamol (acetaminophen) may act as a deterrent to abuse as link between high doses and liver damage is relatively well known (Cicero et al., 2013). The risks associated with high doses of NSAIDs and therefore the dangers associated with abuse of NSAID-opioid combination analgesics, appear to be less well understood (Frei et al., 2010).

In general, the choice of which opioid might be better for the ongoing management of acute pain after discharge is probably of less importance than the amount of opioid that is prescribed. This should be based on a judgment of the anticipated severity and duration of pain likely to be associated with specific types of surgery, trauma, or illness. For inpatients, an estimation of the amount to be prescribed should be based on the requirements in the last 24–48 hours before discharge.

The aim is to limit over-prescription and have a minimal amount of unused opioid remaining. It may be better to have repeated prescriptions of a small amount of opioid rather than one prescription for a large amount. In some patients, "interval dispensing" of an opioid (e.g., at one- or two-day intervals) may be required.

15.2.1.1 Opioid-tolerant patients

For patients taking long-term opioids prior to admission for management of chronic pain, the discharge plan would usually aim to minimize alterations to the patient's usual treatment regimen (unless these are thought not to conform to good practice). If a temporary increase in their opioid dose for a short while after discharge, or the short-term addition of an additional opioid is thought to be required, this is best done in consultation with the patient's treating doctor. Similarly, the aim would be to minimize any changes to the doses of methadone or buprenorphine being taken by patients in opioid substitution programs. In many countries, regulatory requirements will dictate that only one physician has the authority to prescribe OST (opioid substitution therapy) for patients outside the hospital and changes should only be made after discussion with that prescriber. Occasionally, in these patients, small amounts of another opioid may be made available but only dispensed in a limited, tapering amount and for a limited time, each time the patient collects their methadone or buprenorphine (Huxtable et al., 2011).

15.2.2 Relevant legislation and regulations

Some countries may have regulations in place that limit prescription of opioids to some patients—for example, those with chronic pain who require opioids for more than a few months or, more commonly, those known or thought to be addicted to a controlled drug (also called controlled substance or dangerous drug depending on the legislation in various jurisdictions) or in a methadone or buprenorphine opioid substitution programs. These regulations may limit in the amount of opioid that can be prescribed when a patient leaves hospital and all prescribers should be aware of the legislation that applies in their place of practice.

Even if no such regulations are in place, an assessment of patients using the ORT may suggest that limitations on the prescription of opioids are warranted.

15.2.3 Duration of treatment

In most instances, acute pain will diminish in intensity as the patient recovers. Opioid doses should therefore be tapered as such recovery occurs, and usually

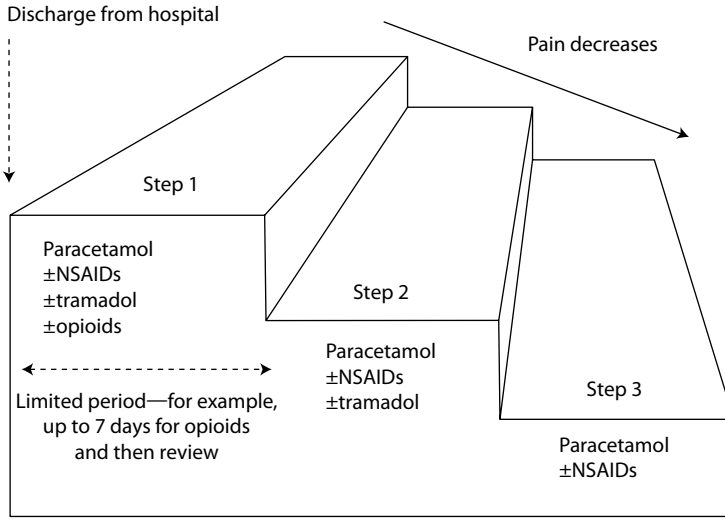

Figure 15.1 "Reverse" pain ladder. (Modified with permission from Huxtable CA, Roberts LJ, Somogyi AA et al. 2011. *Anaesthesia and Intensive Care* **39**(5): 804–23.)

before the tapering of other medications used as part of the patient's multimodal analgesia. If dose reductions are not occurring as expected, the patient should be reassessed before further opioids are prescribed.

One way to explain the concept of tapering to patients and their treating doctors is to use the idea of a "Reverse Pain Ladder" (McQuay, 2004)—see Figure 15.1. This is based on the well-known pain ladder used to describe the steps taken to escalate analgesia in patients with cancer, with the highest step being opioid medications. The reverse ladder simply means these steps are taken in reverse order.

15.3 Information for patients and treating doctors

15.3.1 Patient information

When the patient leaves the hospital with an opioid prescription for continued management of their acute pain, they should be given advice about the safe use of these medications as well as information about the expected duration (short-term only) of therapy and the need to be reassessed by their doctor should they believe they need opioids for a longer period. Ideally, the information should be in both verbal and written forms.

The key points that should be covered in written information given to the patient, for use by the patient as well as their family and friends, include (Royal Adelaide Hospital and SA Health, 2010):

- The expected duration of treatment and the need to taper doses over time.
- The need to avoid taking the opioid in doses that are higher than prescribed or more often than prescribed.
- The need to see their doctor should significant pain continue.

- The significance of increasing or excessive sedation as a sign of OIVI and the steps to take should this occur, including that they should not take any more of the opioid until wide awake and that if they are very sedated they should seek emergency assistance.
- The risks associated with concurrent use of sedative medications or alcohol.
- The need to avoid driving, performing other complex tasks, or making key decisions while taking opioids in varying doses.
- The need to store their opioids safely and not allow others access (especially children).
- The need to dispose of excess opioid medications safely.

These points should of course be written in a language appropriate to the reading level of the patient and others.

15.3.2 Information for the treating doctors

The doctor who will be treating the patient in the community should be given information about the plan for the patient's pain relief when they are discharged. They may welcome advice about the estimated duration of opioid therapy as well as tapering strategies and, for some patients especially, information about the steps to take should problems arise, including where they can seek advice. Referral to a chronic pain medicine center may be appropriate in case of ongoing pain management issues. It is important for this information to reflect that given to the patient so that the patient has the same expectations.

Key points

1. When prescribing an opioid for use after discharge from hospital, the risks of inadvertent long-term use and/or nonmedical use (by the patient or others) must be considered. Patients should be assessed accordingly prior to prescription and appropriate postdischarge management plans formulated.
2. The risk of OIVI is known to increase with coadministration of sedative medications and this risk may continue after discharge from hospital if the patient also takes sedative drugs or alcohol. The patient and their carers should be aware of the significance of increasing sedation.
3. Patients should be cautioned about driving and their ability to perform other complex tasks while taking opioids for ongoing acute pain management as the doses may vary.
4. The patient and their treating doctors in the community should be given the appropriate information about the safe use of opioids and expected duration of treatment.

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CHAPTER 16

Self-assessment questions

As noted in Chapter 2, nursing education and accreditation programs are important if acute pain is to be managed safely and effectively. In particular, such programs are recommended if more advanced techniques such as patient-controlled and epidural analgesia are to be made available on general hospital wards. The questions below are examples of ones that might be used as part of an accreditation assessment.

Select the ONE BEST ANSWER from the four options listed for each question:

1. Predictors of high postoperative pain scores and/or high opioid requirements include all of the following EXCEPT:
   a. Preoperative anxiety
   b. Pain catastrophizing
   c. Older patient
   d. Presence of preoperative pain

2. Potential adverse effects of pain after surgery include:
   a. Decreased myocardial oxygen consumption
   b. Hypoxemia
   c. Hypoglycemia
   d. Increased intestinal motility

3. Simple methods of opioid analgesia (e.g., oral or SC opioids given as needed) can be more effective if there is:
   a. Appropriate staff and patient education
   b. Provision of appropriate guidelines, policies, and monitoring
   c. Regular patient assessment and individualization of treatment
   d. All of the above

4. The least reliable measure of pain in a cognitively intact patient is:
   a. Observation of patient behavior
   b. The verbal numerical rating scale
   c. The verbal descriptor scale
   d. The visual analogue scale

5. Signs and symptoms that suggest a patient may have acute neuropathic pain include:
   a. Pain that is dull or cramping
   b. Pain that is sharp and well localized to the area of injury
   c. Pain that appears to be responding poorly to opioids
   d. Decreased pain in response to a stimulus that is normally painful

6. Opioid-induced ventilatory impairment (OIVI) can lead to high carbon dioxide levels by:
   a. Depression of the respiratory center leading to a decreased respiratory rate
   b. Depression of the CNS in general leading to increasing sedation
   c. Upper airway obstruction (leading to snoring in some patients)
   d. All of the above

7. A patient who is noticed to be snoring after being given an opioid:
   a. Should be woken to have their level of sedation checked
   b. Should be left to sleep as they are probably comfortable
   c. Should be left to sleep as they probably have sleep apnea
   d. Should be given naloxone

8. The most reliable clinical indicator of OIVI is:
   a. A decrease in respiratory rate
   b. Increasing sedation
   c. Increasing confusion
   d. Low oxygen saturation (SpO_2) levels in a patient receiving supplemental oxygen

9. Which patient could have OIVI?
   a. A patient with a respiratory rate of 6/minutes
   b. A patient with a respiratory rate of 12/minutes
   c. A patient with a respiratory rate of 18/minutes
   d. All of the above

10. Which drug given to a patient who is also receiving opioids is unlikely to increase the risk of OIVI?
    a. Promethazine (Phenergan)
    b. A nonsteroidal antiinflammatory drug
    c. Clonidine
    d. A benzodiazepine (e.g., diazepam)

11. Causes of low oxygen saturation levels (SpO_2) in the postoperative period could include all of the following EXCEPT:
    a. OIVI
    b. Postoperative changes in lung function
    c. Anemia
    d. Sleep apnea

12. An oxygen saturation level (SpO_2) of 90% indicates a PaO_2 of approximately:
    a. 90 mmHg
    b. 60 mmHg
    c. 40 mmHg
    d. 26 mmHg

13. A patient wakes easily when you go to give him his medications. He stays awake while you are talking to him. His sedation score is:
    a. 0
    b. 1
    c. 2
    d. 3

14. A patient wakes easily when you go to give him his medications but he appears drowsy and keeps falling asleep while you are talking to him. His sedation score is:
    a. 0
    b. 1
    c. 2
    d. 3

15. A patient is wide awake and has been watching television all afternoon. His sedation score is:
    a. 0
    b. 1
    c. 2
    d. 3

16. The least effective antiemetic drug in the postoperative setting is:
    a. Droperidol
    b. Dexamethasone
    c. Ondansetron
    d. Metoclopramide

17. The best predictor of the amount of morphine an opioid-naive patient is likely to need after major surgery is:
    a. Gender of the patient
    b. Age of the patient
    c. Weight of the patient
    d. Estimated lean body weight of the patient

18. Of the opioids listed below, the least lipid-soluble is:
    a. Morphine
    b. Methadone
    c. Hydromorphone
    d. Fentanyl

19. If an injection of morphine is given IV, the average time it will take for the full effect of the morphine to be seen is around:
    a. 30 seconds
    b. 1 minute
    c. 5 minutes
    d. More than 10 minutes

20. If an injection of fentanyl is given IV, the average time it will take for the full effect of the fentanyl to be seen is around:
    a. 30 seconds
    b. 1 minute
    c. 5 minutes
    d. More than 10 minutes

21. M6G, a metabolite of morphine:
    a. May lead to hyperalgesia and allodynia
    b. Does not accumulate in renal failure
    c. Has analgesic activity
    d. Has a shorter half-life than morphine

22. Codeine, a naturally occurring alkaloid of opium:
    a. Will not result in effective analgesia in over 50% of Caucasian patients
    b. Is metabolized in the liver where it is converted into morphine
    c. Has a high affinity for the opioid receptor
    d. Is useful for the treatment of severe pain

23. Fentanyl is a synthetic opioid that:
    a. Results in more histamine release than other opioids
    b. Has active metabolites that are excreted primarily in feces
    c. Is very effective when administered orally
    d. Can be administered by transdermal patch

24. Norpethidine (normeperidine) is a metabolite of pethidine. Early signs and symptoms of norpethidine toxicity:
    a. Include sedation
    b. Include anxiety and twitching
    c. Are reversible using naloxone
    d. Result from activation of opioid receptors

25. The following statements about tramadol are all true EXCEPT:
    a. The analgesic effect of tramadol is mediated only via its action on opioid receptors
    b. It causes less sedation than other opioids
    c. Has an active metabolite (M1) that is dependent on the kidney for excretion
    d. It is an effective treatment in neuropathic pain

26. All of the following opioids have active metabolites that are excreted by the kidneys EXCEPT:
    a. Fentanyl
    b. Oxycodone
    c. Morphine
    d. Pethidine

27. The following statements about buprenorphine are all true EXCEPT:
    a. It is increasingly being used in opioid addiction treatment programs
    b. In case of an overdose, higher than usual doses of naloxone may be required
    c. It should be given orally and swallowed
    d. It is available as a transdermal preparation for the treatment of chronic and cancer pain

28. A patient is taking 300 mg/day of a slow-release oral morphine preparation. On average, this would be equivalent to:
    a. 300 mg IV morphine
    b. 150 mg IV morphine
    c. 100 mg IV morphine
    d. 50 mg IV morphine

29. A patient is taking 200 mg/day of a slow-release oxycodone preparation. On average, this would be equivalent to:
    a. 200 mg IV morphine
    b. 150 mg IV morphine
    c. 100 mg IV morphine
    d. 50 mg IV morphine

30. Slow-release tablets of morphine or oxycodone:
    a. May take 4 hours or more to reach peak blood levels after administration
    b. Should be ordered on a PRN basis
    c. Are suitable for the rapid titration of acute pain relief
    d. Can be crushed if the patient does not like swallowing tablets

31. Signs and symptoms of local anesthetic systemic toxicity (LAST) include:
    a. Drowsiness
    b. Numbness around the mouth and tongue
    c. Muscle twitching
    d. All of the above

32. Treatment of LAST in a patient in a general ward includes:
    a. Large doses of epinephrine
    b. Use of lipid emulsions
    c. Treatment of ventricular arrhythmias with lidocaine
    d. All of the above

33. The following statements about bupivacaine are true EXCEPT:
    a. It has a greater potential for cardiotoxicity than ropivacaine and levobupivacaine
    b. It is easier to treat cardiotoxicity resulting from administration of bupivacaine than ropivacaine and levobupivacaine
    c. When used in low doses for continuous regional analgesia there are no consistent differences between bupivacaine and ropivacaine in terms of quality of analgesia or degree of motor block
    d. A liposomal formulation of bupivacaine aims to increase its duration of action

34. Paracetamol (acetaminophen):
    a. Should be used with caution in patients with mild-to-moderate renal impairment
    b. Can be given in doses of up to 8 g/day
    c. Has analgesic, antipyretic, and antiinflammatory activity
    d. Is no more effective when given by the rectal route rather than the oral route

35. Nonsteroidal antiinflammatory drugs (NSAIDs):
    a. Should be used with caution in patients with renal impairment
    b. Should not be given concurrently with paracetamol
    c. Result in fewer side effects when given by the rectal route rather than the oral route
    d. Are more effective when given by the rectal route rather than the oral route

36. Nonselective NSAIDs (e.g., ibuprofen and diclofenac):
    a. Do not reduce the incidence or severity of opioid-related side effects when given with opioid medications
    b. Are "opioid sparing"
    c. Inhibit only COX-1 and not COX-2
    d. Do not result in better pain relief when given with paracetamol

37. Risk factors for the development of renal failure in association with the use of NSAIDs include all of the following EXCEPT:
    a. Hypotension
    b. Low urine output

c. Concurrent administration of gentamicin
d. Younger patient age

38. The risk of developing gastric erosions following the use of nonselective NSAIDs is decreased by all of the following EXCEPT:
    a. Concurrent use of proton pump inhibitors (e.g., omeprazole)
    b. Short-term use of the drug
    c. Avoiding use in patients with a history of gastric bleeding
    d. The use of the rectal rather than the oral route for administration of the drugs

39. Selective COX-2 inhibitors (coxibs):
    a. Are more effective analgesics than nonselective NSAIDs
    b. Have a similar risk of renal failure as nonselective NSAIDs
    c. Have the same risk of postoperative bleeding as nonselective NSAIDs
    d. Should not be used in patients with aspirin-exacerbated respiratory disease

40. Ketamine:
    a. Acts on NMDA receptors
    b. Is ineffective in the treatment of neuropathic pain
    c. Increases tolerance to opioids
    d. Has a high incidence of central nervous system side effects when used by infusion in low doses (e.g., 100–200 mg/day in the average adult)

41. Tricyclic antidepressant agents:
    a. Do not lead to sedation
    b. Are not effective for the management of neuropathic pain
    c. Act by inhibiting reuptake of noradrenaline and serotonin
    d. Are useful in the management of acute nociceptive pain

42. Which of the following drugs are the least effective drugs in the management of neuropathic pain?
    a. Gabapentinoids (e.g., pregabalin, gabapentin)
    b. Anticonvulsants (e.g., carbamazepine)
    c. Lignocaine
    d. Selective serotonin reuptake inhibitors (SSRIs)

43. The gabapentinoids (pregabalin and gabapentin):
    a. Are excreted unchanged by the kidney and dose adjustments are required in patients with renal impairment
    b. Have similar half-lives
    c. Do not cause sedation, dizziness, or visual disturbances
    d. Do not reduce postoperative opioid requirements

44. Nitrous oxide is sometimes used as analgesia for short painful procedures. Contraindications to the use of nitrous oxide include all of the following EXCEPT:
    a. Concurrent use of opioids
    b. Vitamin B_{12} deficiency
    c. Pneumothorax
    d. Bowel obstruction

45. Immediate-release opioids such as oxycodone, morphine, and hydromorphone are commonly used in the management of acute pain. When given orally:
    a. Their peak effect will be seen within 10–15 minutes
    b. They should only be ordered at fixed time intervals
    c. They can be given if a patient is fasting prior to elective surgery
    d. The doses used are the same as for the IM dose of each opioid

46. When morphine is given by intermittent SC injection:
    a. Absorption into the blood stream will be slower than following an IM morphine injection
    b. Higher doses of morphine will be needed than if given by IM injection
    c. Morphine should be given in the smallest volume possible
    d. Injection must not be given more often than every 4 hours

47. A 23 year old patient is prescribed "7.5–15 mg SC morphine 1-hourly PRN" for pain relief after a laparotomy for a ruptured spleen the day before. He is wide awake and watching television. His last injection of morphine was 15 mg 90 minutes ago. He says his pain score is 9 and that he cannot cough because of the pain. He would like another injection of morphine. You would:
    a. Suggest he wait another 30 minutes
    b. Give 15 mg morphine
    c. Give 7.5 mg morphine
    d. Give 2.5 mg morphine

48. A 23 year old patient is prescribed "7.5–15 mg SC morphine 1-hourly PRN" for pain relief after a laparotomy for a ruptured spleen the day before. His last injection of morphine was 15 mg 90 minutes ago. When you wake him he says his pain score is 9 and that he would like another injection of morphine but his sedation score is 2. You would:
    a. Not give any more morphine until his sedation score was <2
    b. Give 15 mg morphine
    c. Give 7.5 mg morphine
    d. Give 2.5 mg morphine

49. A patient who is wide awake complains of pain 10 minutes after a SC injection of morphine and asks for another injection. You:
    a. Tell him you will give him another injection now
    b. Tell him that the injection has not yet had a chance to work
    c. Tell him he must wait another 2 hours
    d. Tell him he must wait another 3 hours

50. A patient is ordered 10 mg oral IR oxycodone "strictly 4-hourly." When the patient is due her next dose it is noted that she has a sedation score of 2. You decide the best course of action is to:
    a. Withhold the dose
    b. Give 5 mg oxycodone only
    c. Give naloxone
    d. Give dose as ordered

51. A patient in a general ward is ordered 40 mg slow-release oxycodone BD. When the patient is due her next dose it is noted that she has a sedation score of 3. You decide the best first course of action is to:
    a. Withhold the dose
    b. Give 20 mg OxyContin only

c. Give the dose as ordered
d. Withhold the dose and give naloxone

52. A continuous IV infusion of morphine is ordered at a rate of 2 mg/h. On average, the full effect of the morphine given at that rate of infusion will be seen within:
    a. 15 minutes
    b. 1 hour
    c. 4 hours
    d. 15 hours

53. Transdermal fentanyl patches enable fentanyl to be absorbed through the skin. These patches:
    a. Allow blood concentrations of fentanyl to rise rapidly
    b. Are useful in the routine management of acute pain
    c. Have an effect that may last 24 hours after the patch is removed
    d. Have only small amounts of fentanyl left in the patch after removal

54. Transmucosal routes can be used for opioid administration if:
    a. An opioid is given intranasally it should ideally be delivered in a volume no larger than 200 μL per nostril
    b. The time to peak effect of intranasal (IN) fentanyl is the same as intravenous fentanyl
    c. The IN route is best suited to less lipid-soluble opioids such as morphine
    d. Fentanyl "lollipops" are recommended for treating postoperative pain

55. A patient using PCA with a bolus dose of 1 mg morphine (lockout 5 minutes) complains of severe pain. His sedation score is 0. He is receiving, on average, 5 mg every hour (i.e., five "successful" demands). You would:
    a. Tell him to press the demand button more frequently, as he can get more doses from the machine each hour
    b. Suspect he has an addiction to morphine
    c. Tell him that an increase in the size of the bolus dose is not appropriate
    d. Consider increasing the size of the bolus dose

56. A patient using PCA with a bolus dose of 2 mg morphine (lockout 5 minutes) complains of severe pain when you wake him. He is receiving, on average, 10 mg every hour (i.e., five "successful" demands). He has a sedation score of 2. You would:
    a. Tell him to press the demand button more frequently, as he can get more doses from the machine each hour
    b. Decrease the size of the bolus dose
    c. Increase the lockout interval
    d. Consider the use of a continuous (background) infusion

57. A patient using PCA morphine is found with a sedation score of 3. When you look at the PCA chart you see that the bolus dose is set at 2 mg and that he has been receiving around 14 mg every hour (i.e., seven "successful" demands) for the last 3 hours. His family has been with him during that time. Prior to the family visiting he was receiving on average 6 mg/h. You would:
    a. Assume that he has been awake enough to push the button and has only just become difficult to rouse
    b. Suspect that the machine is faulty

c. Be concerned that a family member might be pushing the PCA demand button
d. All of the above

58. A patient using PCA morphine complains of severe itching over his face and chest. A decision is made to change to PCA fentanyl. If the bolus dose of morphine is currently 1 mg, an appropriate bolus dose of fentanyl would be:
a. 1 μg
b. 5 μg
c. 20 μg
d. 50 μg

59. The following statements are true about IV PCA EXCEPT:
a. Antireflux valves should be used unless a dedicated line is available for PCA
b. Antisiphon valves should always be used in the line between a patient and drug reservoir
c. The volume of the dose delivered cannot be altered in most disposable PCA devices
d. The record of the number of "successful" versus "unsuccessful" bolus dose deliveries is always a useful guide to alterations in the size of the dose

60. The following statements are true about IV PCA EXCEPT:
a. Changing the lockout interval has been shown to improve pain relief
b. Use of an hourly or 4-hourly dose limit will not necessarily prevent overdose of PCA opioid
c. Smaller bolus doses may be appropriate in older patients
d. The routine use of a background infusion increases the risk of OIVI

61. A dose of intrathecal morphine that gives a similar degree of pain relief as 5 mg IM morphine is:
a. 0.1 mg
b. 0.5 mg
c. 1 mg
d. 5 mg

62. Epidural opioids cause:
a. Less nausea and vomiting than epidural local anesthetics
b. More itching than epidural local anesthetics
c. More hypotension than epidural local anesthetics
d. Less sedation than epidural local anesthetics

63. Postdural puncture headache is typically:
a. A result of leakage of blood into the epidural space
b. Usually worse when lying down, compared with sitting
c. Bifrontal or occipital
d. More likely in older patients

64. The following statements about a patient with an epidural abscess are true EXCEPT:
a. The patient will always require surgery
b. The patient may have no neurological signs
c. The patient may be afebrile
d. The patient may present with increasing back pain

65. A patient with an epidural abscess accompanied by leg weakness will have the best chance of full recovery if diagnosis and treatment are carried out within:
    a. 8 hours of the onset of leg weakness
    b. 12 hours of the onset of leg weakness
    c. 18 hours of the onset of leg weakness
    d. 24 hours of the onset of leg weakness

66. A patient is receiving an epidural infusion of bupivacaine 0.1% and fentanyl 2 μg/mL at a rate of 10 mL/h for postoperative analgesia. He tells you that he has some weakness in both of his legs. You would:
    a. Tell him that it is likely to be due to the bupivacaine
    b. Cease the infusion
    c. Consider the possibility of epidural hematoma or epidural abscess
    d. All of the above

67. A patient is receiving an epidural infusion of bupivacaine 0.1% and fentanyl 2 μg/mL at a rate of 10 mL/h for postoperative analgesia. You note that his blood pressure is 80 mmHg systolic. It has not been less than 120 mmHg since his surgery two days ago and the rate of the epidural infusion has not been changed. You would:
    a. Tell him that it is likely to be due to the bupivacaine
    b. Administer naloxone
    c. Consider the possibility of postoperative bleeding
    d. All of the above

68. A patient calls you from her home at 10 pm. She has increasing back pain and is having trouble voiding. She says that you gave her an epidural anesthetic for her hysterectomy three weeks ago. You would:
    a. Tell her to come to your hospital first thing tomorrow morning
    b. Tell her that she must come to the hospital for immediate assessment
    c. Tell her to see her general practitioner
    d. Tell her that back pain is a common problem after epidural anesthesia and that she should take two paracetamol (acetaminophen) tablets every 4 hours and call again in the morning

69. An increased risk of phantom pain is associated with all of the following except:
    a. Male gender
    b. Severe preamputation pain
    c. Chemotherapy
    d. Severe postoperative stump pain

70. A patient is admitted following a motorbike accident. He has no movement in his right arm and an injury to his brachial plexus is suspected. Four days later he says that he has burning and shooting pains in his arm. He also says that the morphine he is getting is not helping the pain nearly as much as it was before. This type of pain is called:
    a. Nociceptive pain
    b. Neuropathic pain
    c. Psychological pain
    d. Phantom pain

71. Phantom pain:
    a. Is more likely to occur weeks after limb amputation than within the first few days
    b. Is more likely after a traumatic amputation
    c. Occurs in about 20% of patients only
    d. May respond to ketamine, gabapentinoids, and calcitonin in the acute stages

72. Preventive analgesia:
    a. Means than an analgesic drug or technique given before an intervention (e.g., surgical incision) results in less pain compared with the technique drug given after the intervention
    b. Means that the analgesic effect of a drug or technique exceeds the expected duration of effect
    c. Is not seen with ketamine
    d. Has not been seen with epidural analgesia

73. First-line treatments for acute neuropathic pain include:
    a. Gabapentoids (pregablin or gabapentin) and tricyclic antidepressant agents
    b. Opioids and tramadol
    c. Ketamine
    d. All of the above

74. First-line treatments for chronic neuropathic pain include:
    a. Gabapentoids (pregablin or gabapentin) and tricyclic antidepressant agents
    b. Opioids and tramadol
    c. Ketamine
    d. All of the above

75. Older patients:
    a. Are likely to report more pain than a younger patient if they have a painful condition such as angina or peritonitis
    b. Are likely to have higher opioid requirements than younger patients
    c. May be at higher risk of some of the side effects of epidural analgesia
    d. Require larger dose of local anesthetic to get the same degree of nerve block (motor and sensory) than younger patients

76. Strategies that may help to improve postoperative analgesia in an opioid-tolerant patient include all of the following EXCEPT:
    a. Addition of drugs such as NSAIDs, paracetamol, and gabapentinoids
    b. Use of ketamine
    c. Use of a benzodiazepine
    d. Use of regional analgesic techniques

77. An opioid-tolerant patient taking 40 mg of slow-release morphine for chronic back pain is ordered PCA for management of their acute pain after surgery for a fractured leg: All of the following statements are true EXCEPT:
    a. The patient's usual (preadmission) opioid(s) should be continued
    b. The dose(s) of the opioid(s) that the patient has been taking prior to admission must be confirmed before they are prescribed
    c. The patient should be asked about all medications they are taking, opioid and nonopioid, as well as the use of nonprescribed drugs
    d. If the patient reports very high pain scores after surgery, the size of their PCA bolus dose should always be increased

78. Patients in a program for treatment of their opioid addiction may be prescribed methadone, buprenorphine, or naltrexone. All of the following statements about their treatment when presenting for surgery are true EXCEPT:
    a. Methadone regimens should be continued where possible
    b. Naltrexone regimens should be continued where possible
    c. Buprenorphine regimens may be continued where possible
    d. They may require treatment for withdrawal from other drugs such as benzodiazepines

79. In patients with moderate renal impairment, which opioid would you choose NOT to use—if you had a choice?
    a. Fentanyl
    b. Oxycodone
    c. Morphine
    d. Buprenorphine

80. Prescription of opioids for ongoing acute pain management after discharge from hospital may be associated with an increased risk of:
    a. Ongoing opioid use way past the time the pain could still be considered acute
    b. Any opioid that is not used by the patient for their acute pain then being available for use at a later stage by the patient or by others
    c. Driving impairment
    d. All of the above

Answers

1. c
2. b
3. d
4. a
5. c
6. d
7. a
8. b
9. d
10. b
11. c
12. b
13. b
14. c
15. a
16. d
17. b
18. a
19. d
20. c
21. c
22. b
23. d
24. b
25. a
26. a
27. c
28. c
29. c
30. a
31. d
32. b
33. b
34. d
35. a
36. b
37. d
38. d
39. b
40. a
41. c
42. d
43. a
44. a
45. c
46. c
47. b
48. a
49. b
50. a
51. d
52. d
53. c
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59. d
60. a
61. a
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64. a
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66. d
67. c
68. b
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74. a
75. c
76. c
77. d
78. b
79. c
80. d

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PAIN MANAGEMENT

"Well-managed acute pain benefits patients' experience, recovery, and long-term outcome. Here is a comprehensive and highly readable reference that can make an acute pain management expert out of any interested provider."

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Acute Pain Management: A Practical Guide provides health professionals with simple and practical information to help them manage patients with acute pain safely and effectively. The book also helps them to identify and manage acute pain in more complex patients, for whom effective treatment can be challenging.

Features

- Combines evidence-based information about acute pain management with practical guidelines and protocols
- Covers the techniques commonly used in acute pain management and the pharmacology of opioids, local anesthetics, and nonopioid and adjuvant analgesic agents
- Discusses management of acute pain in both surgical and nonsurgical acute pain settings, including in patients with spinal cord or burn injuries and selected medical illnesses
- Includes evidence-based information about management of acute pain in some specific patient groups in which treatment may be more complex, including older patients, opioid-tolerant patients, patients with an addiction disorder, pregnant or lactating patients, patients with obstructive sleep apnea, or patients with renal or hepatic impairment
- Discusses the use of opioids in patients discharged from the hospital that require ongoing management of acute pain

In this new edition, chapters have been revised and updated, often extensively, to reflect current knowledge and practice. This resource will undoubtedly be helpful to a variety of professionals in assessing and managing acute pain.

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