



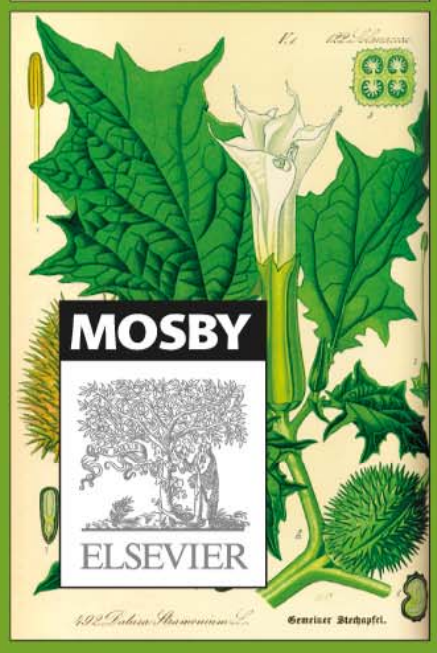
PHARMACOLOGY FOR HEALTH PROFESSIONALS

4th Edition

Bronwen Bryant and Kathleen Knights





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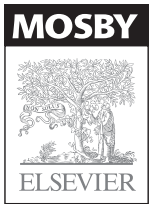

Mosby
is an imprint of Elsevier

Elsevier Australia. ACN 001 002 357
(a division of Reed International Books Australia Pty Ltd)
Tower 1, 475 Victoria Avenue, Chatswood, NSW 2067

National Library of Australia Cataloguing-in-Publication entry

Bryant, Bronwen Jean, author.

Pharmacology for health professionals / Bronwen Bryant, Kathleen Knights.
4th edition.
9780729541701 (paperback)
Pharmacology--Textbooks.
Drugs.
Knights, Kathleen M. (Kathleen Mary), author.

615.1

Content Strategist: Melinda McEvoy
Content Development Specialists: Martina Vascotto and Amanda Simons
Project managers: Anitha Rajarathnam and Rochelle Deighton
Edited by Linda Littlemore and Laura Davies
Proofread by Elaine Cochrane
Tech-checked by Lynne MacKinnon and Jerry Perkins
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Cover images reproduced with kind permission from Kurt Stüber, www.biolib.de <http://www.biolib.de>
Illustrations by Michael Towey
Index by Robert Swanson
Typeset by Midland Typesetters, Australia
Printed in China by China Translation and Printing Services

DEDICATIONS

To my daughters Rosemary, Philippa and Alison, who continually inspire, encourage and amaze me; and to their children, as representatives of future generations to benefit from medical research and scholarship.

Bronwen J Bryant

To the Discipline of Pharmacology that has provided the foundation of my academic career and to those who enrich my life, my husband John and my family and friends.

Kathleen M Knights

ABOUT THE AUTHORS

Bronwen Bryant

Bronwen became fascinated with pharmacology while studying pharmacy at the University of Sydney, and completed an Honours year then a Master of Science degree under the supervision of Associate Professor Diana Temple, with research in the areas of biochemical and cardiovascular pharmacology. After two years' research at Riker Laboratories in Sydney, and work in both community and hospital pharmacies to gain registration and experience as a pharmacist, she moved to London and worked as a medical translator and editor.

Returning to Australia, Bronwen carried out research in the laboratory of Professor Michael Rand and Dr David Story at the University of Melbourne, where she completed a PhD on negative feedback control of central autonomic transmission. Academic positions teaching pharmacology followed at the Victorian College of Pharmacy (now Monash University), La Trobe University and the Fiji School of Medicine in Suva. Along the way she has taught students of virtually every health profession, and has managed to do sporadic research in clinical pharmacology on adverse drug reactions and interactions, non-steroidal anti-inflammatory drugs and psychotherapeutics.

Bronwen currently holds the position of Honorary Fellow in the Department of Pharmacology and Therapeutics, Faculty of Medicine, Dentistry and Health Sciences at the University of Melbourne.

Kathleen Knights

Kathie completed a Bachelor of Science (Honours) degree at North East London Polytechnic (NELP), majoring in pharmacology, while working as a research assistant at Guy's Hospital, London. On returning home to Adelaide she accepted a research position in the Department of Anaesthesia and Intensive Care in the School of Medicine at Flinders University. Following receipt of an Australian Commonwealth Postgraduate Research Scholarship, Kathie completed a PhD investigating the hepatotoxicity of the inhalational anaesthetic agent halothane.

Her academic career has continued to develop throughout her time at Flinders, progressing from her initial appointment as Lecturer to her current position of Professor in Clinical Pharmacology. She is passionate about the discipline of pharmacology and her teaching crosses discipline boundaries, covering medicine, nursing, nutrition and dietetics and paramedic sciences. She was the recipient of a Carrick Award (2007) for Outstanding Contribution to Student Learning for the development of a pharmacology package delivered online to Masters students in rural and remote areas of Australia.

Kathie's research interests centre on drug metabolism, specifically the metabolism of non-steroidal anti-inflammatory drugs and their mechanisms of renal toxicity. An invited speaker at national and international conferences, she has published over 70 research articles and reviews in peer-reviewed international journals and five book chapters.

CONTENTS

PREFACE

The use of drugs for their curative properties, for their social effects and, indeed, in many instances for sinister purposes has no cultural, historical or social boundaries. Pharmacy practices during the ancient Egyptian civilisation are recorded in the *Ebers Papyrus* dating back to 1500 BC; the 15th century German physician Paracelsus used mercury to treat syphilis; courtesans of the French court frequently used a preparation of *Atropa belladonna* to dilate their pupils and enhance their mystical qualities. Indigenous people of South America perfected the preparation of curare and used it as a poison on the tips of their arrows when hunting wild animals and to test the strength of their warriors in trials by ordeal. Indigenous Australian people used a native tobacco, from *Duboisia* species, for the atropinic alkaloids it contained. In Fiji, kava (yaqona or 'grog') is drunk ritually and socially for its stress-relieving, relaxing and euphoriant properties. All too often these fascinating aspects of pharmacology are lost in the current fast-paced world.

With advances in drug development, drugs in clinical use continue to have a high rate of obsolescence, and the facts learned for a particular drug may become irrelevant when each year brings new drugs with differing modes of action. The challenge for all health professionals is to stay up to date with advances in the field of pharmacology and their impact on the quality use of medicines. We hope the fourth edition of this textbook makes the challenge enjoyable, interesting and easy, and, as authors, that our continuing fascination with pharmacology is transmitted to you, the readers.

Pharmacology is a universal discipline but the availability of drugs and the patterns of their use differ between countries. Most pharmacology texts are written for health professionals and students in the northern hemisphere; this fourth edition continues to be ideally suited to the needs of all health professionals practising in Australia and New Zealand. The discussion of drugs reflects the names used and their availability and clinical use within the Australasian region, and the material on drug legislation and ethical principles focuses on regional aspects. To complement and enhance this regional flavour, information on traditional medicinal plants and patterns of use of medicines by Indigenous Australian, New Zealand Māori and Pacific Island people is interspersed in relevant chapters.

Pharmacology texts written especially for medical students continue to emphasise selection, prescription and monitoring of drugs based on diagnosis of a condition in a patient, while those written for pharmacy and science students often give detailed descriptions of the chemistry of the drugs and the biochemistry of the pathways and disease processes in which they act. The needs of many students of health sciences lie somewhere between these approaches. We acknowledge that paramedics and practitioners of some other professions, such as nursing, midwifery, podiatry, physiotherapy, optometry and orthoptics, are increasingly being granted limited prescribing rights, and additional information relevant to these emerging roles has been incorporated throughout the fourth edition. With an increasing percentage of the population taking many medications, some prescribed and some self-prescribed, it is essential that all health professionals have knowledge of pharmacology and the important principles that predict how drugs may affect a person's health and lifestyle. Throughout this fourth edition, we have retained both a scientific and a clinical approach, founded on evidence-based medicine, and emphasising always the use and effects of drugs in people.

As much of pharmacology is predicated on an understanding of physiology and biochemistry, the fourth edition showcases fully updated and revised chapters that include the relevant physiology and biochemistry material. The content reflects recent epidemiological data, research findings, introductions of new drugs, withdrawals of old drugs, and changes in recommendations and guidelines from learned bodies on pharmacological management of disease conditions. Many of the figures and diagrams have been redrawn and new figures included to enhance understanding and interest. This new edition also features:

- new and updated Drug Monographs that describe important aspects of either the prototype of a drug group or the most commonly prescribed drug of a group, or drugs that have gained 'drug of first choice' status
- tables containing more details of drug interactions occurring with major drug groups
- information on recent changes in the pharmacological management of major conditions, including asthma, cardiac failure, cancers including melanomas, stroke, dementia, diabetes mellitus, dyslipidaemia, epilepsy, HIV, hypertension, osteoporosis, rheumatoid arthritis, macular degeneration, otitis media, endometriosis, common complications of pregnancy and childbirth, and for anaesthesia in surgery and analgesia and sedation for children
- many new Clinical Interest Boxes, including those that describe items of special interest specific to New Zealand, and references to material from the New Zealand Medicines and Medical Devices Safety Authority (at www.medsafe.govt.nz); and many that describe typical pharmacological treatment of common diseases and conditions

- references to new reviews on drugs and management of major diseases, and guidelines for clinical choice and use of drugs (while retaining references to 'classic' scientific papers and reference material)
- enhanced information on the use of complementary and alternative medicine (CAM) modalities, and on interactions between drugs and CAM therapies
- a fresh new full-colour treatment to distinguish the text elements and to make navigating the text easy.

Information on the clinical use of drugs is based especially on data in the *Australian Medicines Handbook*, the Therapeutic Guidelines series and reviews in *Drugs*, the *Medical Journal of Australia*, *Australian Family Physician* and *Australian Prescriber*. We are confident that this fourth edition will continue to fulfil the needs of students and academics in all health professions for a comprehensive textbook of pharmacology.

Chapter 15
ANALGESICS

CHAPTER FOCUS

Pain is a distressing and incapacitating symptom experienced by most people at some stage. Many chemical mediators are potentially involved. Pain can be classified depending on its aetiology and duration. Fortunately, the main analgesics currently available—opioids such as morphine and non-steroidal anti-inflammatory drugs such as aspirin and paracetamol—are safe and effective when properly selected and administered, based on individual patient needs and responses and on individual drug actions and pharmacokinetics.

KEY DRUG GROUPS

- Adjuncts to analgesics
  antiepileptic drugs, anti-inflammatory agents, psychotropics
- Non-steroidal anti-inflammatory drugs
  aspirin (Drug Monograph 15-3)
  ibuprofen (Drug Monograph 15-4), **paracetamol**
- Opioid analgesics
  codeine, **fentanyl** (Drug Monograph 15-2), **morphine** (Drug Monograph 15-1)
  partial agonists: **buprenorphine**
- Opioid antagonists
  naloxone, **naltrexone**
- Other analgesic drugs
  capsaicin, **gabapentin**, **pregabalin**

KEY ABBREVIATIONS

AMI	acute myocardial infarction
COX	cyclo-oxygenase
EO	endogenous opioids
glu	glutamate
5-HT	5-hydroxytryptamine (serotonin)
LT	leukotriene
M6G	morphine-6-glucuronide
NMDA	*N*-methyl-D-aspartate
NSAID	non-steroidal anti-inflammatory drug
OR	opioid receptor
PCA	patient-controlled analgesia
PG	prostaglandin
TENS	transcutaneous electrical nerve stimulation

KEY TERMS

acute pain
adjuvant analgesic
analgesic
chronic pain
cyclo-oxygenase
endogenous opioids
endorphin
enkephalin
equianalgesic dose
gate control theory
neuropathic pain
nociceptive pain
non-steroidal anti-inflammatory drug
opioid
opioid receptors
opium
pain
patient-controlled analgesia
prostaglandins
salicylate
stepwise management of pain
substance P
tolerance

KEY BACKGROUND

PAIN is defined by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'. This definition emphasises the dual aspects of pain (sensory and emotional); only the person suffering can tell how much pain is being experienced. Pain is an important protective mechanism, warning of potential injury from the environment or from inside the body.

Some general principles applying to treatment of pain, and the main groups of analgesic drugs, are described in this chapter. **Pain management** is a highly specialised and continually evolving area of medicine. The latest Australian *Therapeutic Guidelines: Analgesic* (version 6, 2012) includes specific recommendations for first-choice drugs and dosing regimens in specific conditions: acute severe pain, acute traumatic pain, perioperative pain, acute pain in opioid-dependent patients, procedure-related pain in adults, chronic pain in adults/children/children with cancer/children with developmental difficulties etc. Indicated drugs and dosages suggested in this chapter are guidelines only; specialist advice or local protocols should be consulted and followed.

Physiology of pain

Pain and suffering

Understanding the actions of **analgesics** (pain-relieving drugs) requires first an understanding of how pain is generated. The physical component, the sensation of pain (nociception), involves peripheral and central nerve pathways; and the psychological component, the emotional response to pain, involves factors such as a person's anxiety level, previous pain experiences, age, sex and culture. Suffering, a broader term, may include physical pain, emotional and spiritual fears (fear of the unknown, fear of dying, fear of dying alone, lack of social supports, loss of independence or integrity) and social conflicts (unresolved conflicts with family and friends). These may be addressed by interdisciplinary teams in pain management programs, hospices and palliative care centres (see Chapter 42).

People have a relatively constant pain threshold; for example, heat applied to the skin at an intensity of 45–48°C will initiate the sensation of pain in most people. By contrast, pain tolerance—the point beyond which pain becomes unbearable—varies widely among individuals and in a single person under different circumstances. Pain tolerance is lowered (pain is made worse) by anxiety, fear, anger, depression, isolation, fatigue, communication difficulties, previous pain experiences and adverse reactions to analgesic drugs. Tolerance to pain is increased by many medications (analgesics, anaesthetics, adjuncts, antianxiety agents, antidepressants) as well as coping strategies such as distraction, sleep, rest and empathy from carers.

Generation and transmission of pain

Tissue injury in the periphery releases many mediators and is detected by nociceptors (pain receptors), which transmit signals to the spinal cord via A-delta (δ) fibres (mediating sharp, transient, fast pain) or C-fibres (mediating burning, aching, slow, visceral pain). These primary (first-order) afferent fibres terminate in the dorsal horn of the spinal cord, where voltage-gated calcium channels are opened and the transmitter glutamate (glu) released crosses the synaptic gap and activates NMDA receptors on second-order neurons. These neurons cross over and continue upwards in the anterolateral spinothalamic tracts (Figure 15-1, left-hand side) to the thalamus where they synapse with third-order neurons connecting to specific areas of the limbic system and cerebral cortex, where the messages are perceived as pain.

The gate control theory

The **gate control theory** of pain transmission and pain relief, put forward by Melzack and Wall in 1965, proposes that a physiologically analgesic spinal 'gate' mechanism in the dorsal horn of the spinal cord can modify the transmission of painful sensations from peripheral nerve fibres to the thalamus and cortex of the brain. The gate is influenced by descending inhibition from the brain: efferent anti-nociceptive (analgesic) pathways from the cortex descend via the periaqueductal grey matter down the spinal cord (these descending pathways are shown on the left-hand side of Figure 15-1). In the dorsal horn areas they synapse with short interneurons, via the release of noradrenaline and 5-HT as transmitters. The interneurons modify afferent impulses by release of the inhibitory transmitter GABA, thus reducing transmission of incoming pain sensation between the first-order and second-order neurons.

Hyperalgesia (increased pain)

Facilitation in the dorsal horn area results in greatly increased sensitivity (hyperalgesia, or 'opened gate'), which spreads beyond the injured area. Substance P, glutamate and nitric oxide are thought to be involved as transmitters. Pain can be relieved (the gate closed) by afferent stimulation, such as transcutaneous electrical nerve stimulation (TENS), acupuncture and rubbing or 'itching' the skin; these techniques act through inhibitory circuits within the dorsal horn to diminish nociceptive transmission through the C-fibres.

Mediators of pain

Many chemicals are involved in the transmission or relief of pain, especially glutamate, GABA, endogenous opioids, prostaglandins, 5-HT and noradrenaline (see right-hand side of Figure 15-1). Modulation of these chemical mediators is the mechanism for many methods of pain relief, including the use of opioids, NSAIDs, local anaesthetics, γ-aminobutyric acid (GABA) agonists, *N*-methyl-D-aspartate (NMDA) antagonists, tachykinin antagonists, cannabinoids, calcium-channel blockers, α_2-adrenergic agonists

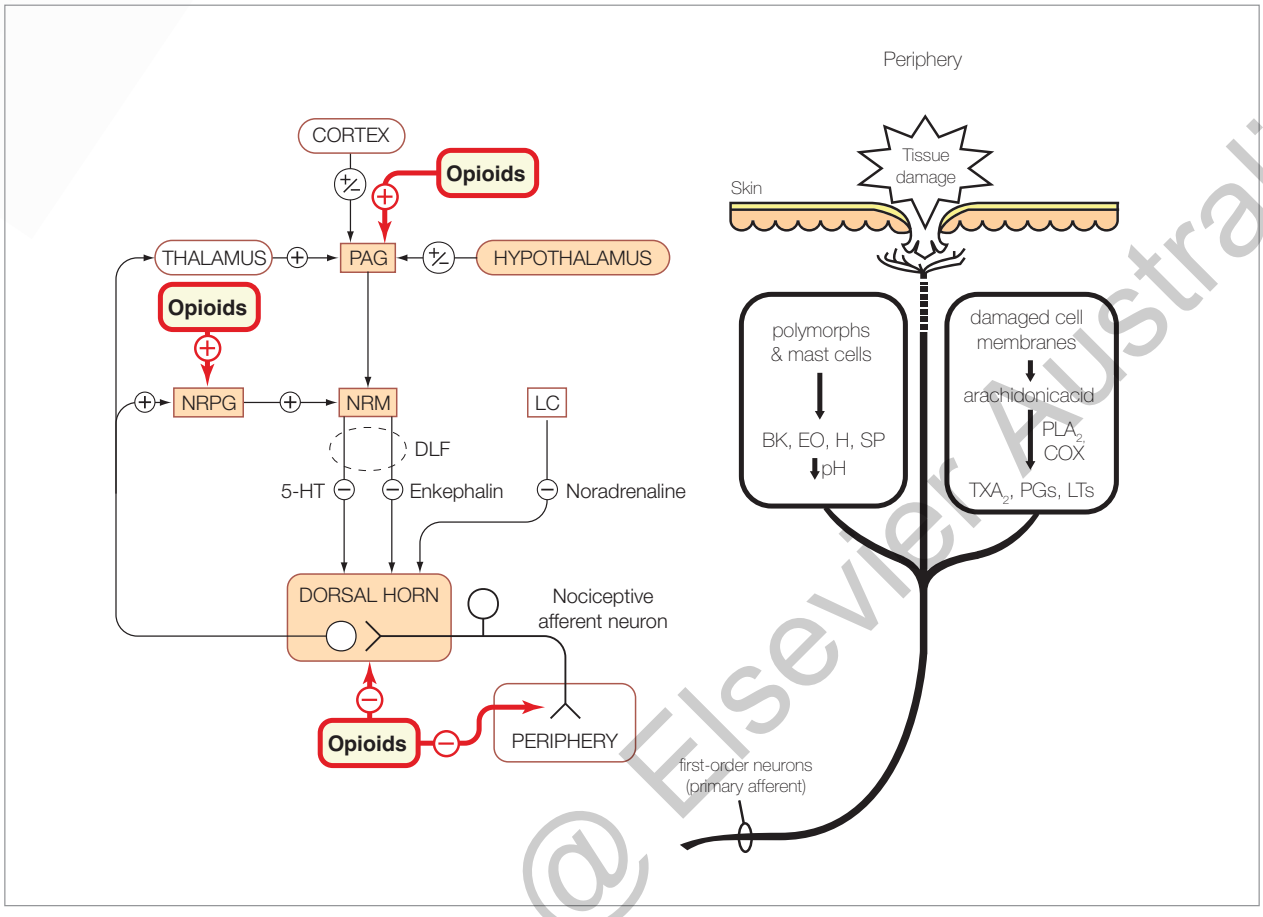


FIGURE 15-1
Right hand side: Periphery - Some mediators, neurotransmitters and nerve pathways involved in pain sensation;
Left hand side: The descending control system, showing the main sites of action of opioids.
Key: 5HT = 5-hydroxytryptamine; BK = bradykinin; COX = cyclo-oxygenase; DLF = dorsolateral funiculus of spinal cord; EO = endogenous opioids; H = histamine; LC = locus coeruleus; LTs = leukotrienes; NRM = nucleus raphe magnus; NRPG = nucleus reticularis paragigantocellularis; PAG = periaqueductal grey matter; PGs = prostaglandins; low pH = increasing acidity; PLA_2 = phospholipase A_2; SP = substance P; TXA_2 = thromboxane A_2.
Adapted from: Argoff (2011); and Rang et al (2007), used with permission.

and non-drug techniques such as TENS, acupuncture and the Lamaze (psychoprophylaxis) technique.

ENDOGENOUS OPIOIDS

Pro-opiomelanocortin (POMC), a 241-amino-acid polypeptide, is a precursor in the body to a wide range of peptides: various cleavage stages produce melanocortins, lipotropins, corticotropin (ACTH), endorphins and met-enkephalin. Other precursor polypeptides are proenkephalin, cleaved to met-and leu-enkephalin, adrenorphin, amidorphin; and prodynorphin (aka proenkephalin B), cleaved to dynorphins A and B, leu-enkephalin, nociceptin and neoendorphin.

The **enkephalins** (pentapeptides), **endorphins** (larger polypeptides: the name implies '**end**ogenous m**orphin**es'), dynorphins and nociceptin are all known as **endogenous opioids** (EOs), as they are produced naturally in the body and have pain-relieving properties. The dynorphins ('powerful endorphins') are stored in large vesicles in parts of the CNS (hypothalamus, medulla, pons, midbrain and spinal cord) and have varying functions involved in analgesia, hypothermia, endocrine and reproductive functions, mood, learning and memory, control of appetite and other physiological functions. They are important natural analgesics, acting via κ-opioid receptors (KORs) and

TABLE 15-1
Comparisons between acute and chronic pain

	ACUTE PAIN	CHRONIC PAIN
Onset	Usually sudden	Long duration (>3 months)
Characteristics	Generally sharp, localised, may radiate	Dull, aching, persistent, diffuse
Physiological responses	Raised blood pressure, respiratory and heart rates; sweating, pallor, dilated pupils; increased muscle tension, tremor	Often absent: normal blood pressure, respiratory and heart rates and pupil size
Emotional/behavioural responses	Increased anxiety and restlessness; focuses on pain, rubs affected part; cries, grimaces, protects part	Person may be angry, depressed, withdrawn, expressionless and exhausted; physical inactivity or sleep; no report of pain unless questioned
Therapeutic goals	Cure of cause; relief of pain; prevent transition to chronic pain; sedation often desirable	Restore functions; tolerance of some pain; improve quality of life; sedation not usually wanted
Drug administration	Usually opioids	Paracetamol, NSAIDs, opioids and/or adjuvants
Timing	Start as soon as possible; assess regularly; patient-controlled analgesia is useful	Regular preventive schedule
Dose	Standard dosages are often adequate; dose reviewed frequently	Individualise according to patient response
Route	Parenteral (IV or SC)	Oral or transdermal

referred to another area of the body (which has sensory nerves running to the same segment of the spinal cord), such as the pain of a myocardial infarction felt initially in the left arm or shoulder. Examples include pain from bowel obstruction, abdominal tumours, ischaemic muscle or major surgery. Visceral pain usually responds well to opioid analgesics.

- Muscle spasm nociceptive pain originates in skeletal or smooth muscle, is mediated by PGs and is worse on movement or when smooth muscle is stretched (colic). Biliary colic, bowel obstruction, spinal cord damage and some types of acute low-back pain exemplify muscle spasm pain, which usually responds to muscle relaxants and NSAIDs.

Neuropathic pain

Neuropathic pain arises from a primary lesion or dysfunction in the somatosensory nervous system pathways, such as nerve compression due to a prolapsed intervertebral disc, inflammation, trauma or degeneration, and occurs in post-herpetic neuralgia, limb amputation, trigeminal neuralgia, diabetic neuropathy or chronic regional pain syndrome. This pain is described as burning, shooting and/or tingling, is often associated with paraesthesia ('pins and needles'), hyperalgesia and allodynia (pain due to a stimulus that does not usually cause pain, e.g. pressure from clothing), and may be accompanied by sympathetic nervous system dysfunction.

Neuropathic pain responds less well to opioid analgesics or NSAIDs, and often requires the addition of adjunct medication such as:

- a tricyclic antidepressant such as amitriptyline or a serotonin–noradrenaline reuptake inhibitor like venlafaxine, to enhance noradrenaline- and 5-HT-mediated descending inhibition of pain stimuli
- an anticonvulsant such as pregabalin, gabapentin or carbamazepine to enhance GABA-mediated inhibition
- a local anaesthetic (lignocaine) to reduce sodium-channel-mediated transmission of nociception
- tramadol, which has both opioid and selective serotonin reuptake inhibitor activities
- topical capsaicin, which gradually depletes substance P levels (see review by Votrubek & Thong [2013]).

Specific pain syndromes

More specific types of pain are treated whenever possible with specific therapies (directed analgesia). Tension headaches, for example, usually respond to over-the-counter analgesics such as aspirin and paracetamol, sinus headaches to NSAIDs plus a decongestant, trigeminal neuralgia to carbamazepine, pain from osteoporotic fractures is helped by the osteoblastic actions of calcitonin, while migraine headaches require specific vasoactive drugs such as sumatriptan or ergotamine (see Chapter 20). Dental pain and toothache usually require treatment of the underlying dental or oral disease; since most dental pain is caused by inflammation, NSAIDs are the preferred analgesics.

Cancer pain relief requires a multimodal approach of palliative care (see Chapters 41 and 42), possibly involving analgesics and anaesthetics, other cancer therapies (radiotherapy, hormones, surgery, chemotherapy), physical therapies (splints, electrotherapy, occupational therapy) and psychological support for patients and their carers.

Psychogenic pain has psychological, psychiatric or psychosocial causes as its primary aetiology: anxiety, depression and fear of dying have been known to cause severe pain. Although

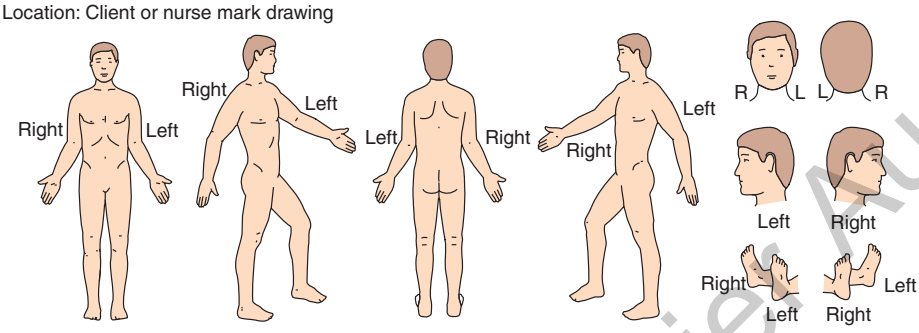
Date _____

Client's Name _____ Age _____ Room _____

Diagnosis _____ Physician _____

Nurse _____

I. Location: Client or nurse mark drawing



II. Intensity: Client rates the pain. Scale used _____

Present: _____

Worst pain gets: _____

Best pain gets: _____

Acceptable level of pain: _____

III. Quality: (Use client's own words, e.g., prick, ache, burn, throb, pull, sharp) _____

IV. Onset, duration variations, rhythms: _____

V. Manner of expressing pain: _____

VI. What relieves the pain? _____

VII. What causes or increases the pain? _____

VIII. Effects of pain: (note decreased function, decreased quality of life)

Accompanying symptoms (e.g., nausea) _____

Sleep _____

Appetite _____

Physical activity _____

Relationship with others (e.g., irritability) _____

Emotions (e.g. anger, suicidal, crying) _____

Concentration _____

Other _____

IX. Other comments: _____

X. Plan: _____

FIGURE 15-2
Pain assessment chart.
Developed by: McCaffery and Pasero (1999); from Salerno (1999).

previous pain experiences. In infants and toddlers, observers can estimate pain by various scales taking into account behaviours, vital signs, sleep patterns and consolability. In older children, a pictorial scale can be used, with faces to 'show how much it hurts' (Figure 15-3 III).

General principles of pain management

Some important principles in **pain management**, based on the World Health Organization Guidelines on Analgesic Use, are summarised below (see Editorial, *Palliative Medicine* (2004):

- Treat the cause of pain where possible, not just the symptom.
- Make accurate assessment of pain extent and type, to ensure appropriate analgesic prescription. Traditional analgesics (NSAIDs and opioids) are used for nociceptive pain; anticonvulsants and antidepressants with opioids for neuropathic pain; and a 'whole patient', multimodal approach for cancer pain or psychogenic pain.
- Keep the patient pain-free: patients recover faster if pain is anticipated and relieved, and they should not have to suffer pain before being allowed the next dose of analgesic. Analgesic effect should be optimised, starting with a low oral dose and titrating upwards depending on the patient's response and adverse effects. In prescription notation, the dose should be 'qs' (sufficient quantity) to prevent pain, not 'prn' (only when necessary).
- Dose at regular specified intervals: particularly for chronic pain, analgesics should be given prophylactically on a regular basis to prevent pain, to optimise drug blood levels and analgesia and to reduce the conditioning reaction in which pain leads to drug-seeking behaviours (e.g. dose every 6 hours, not prn).

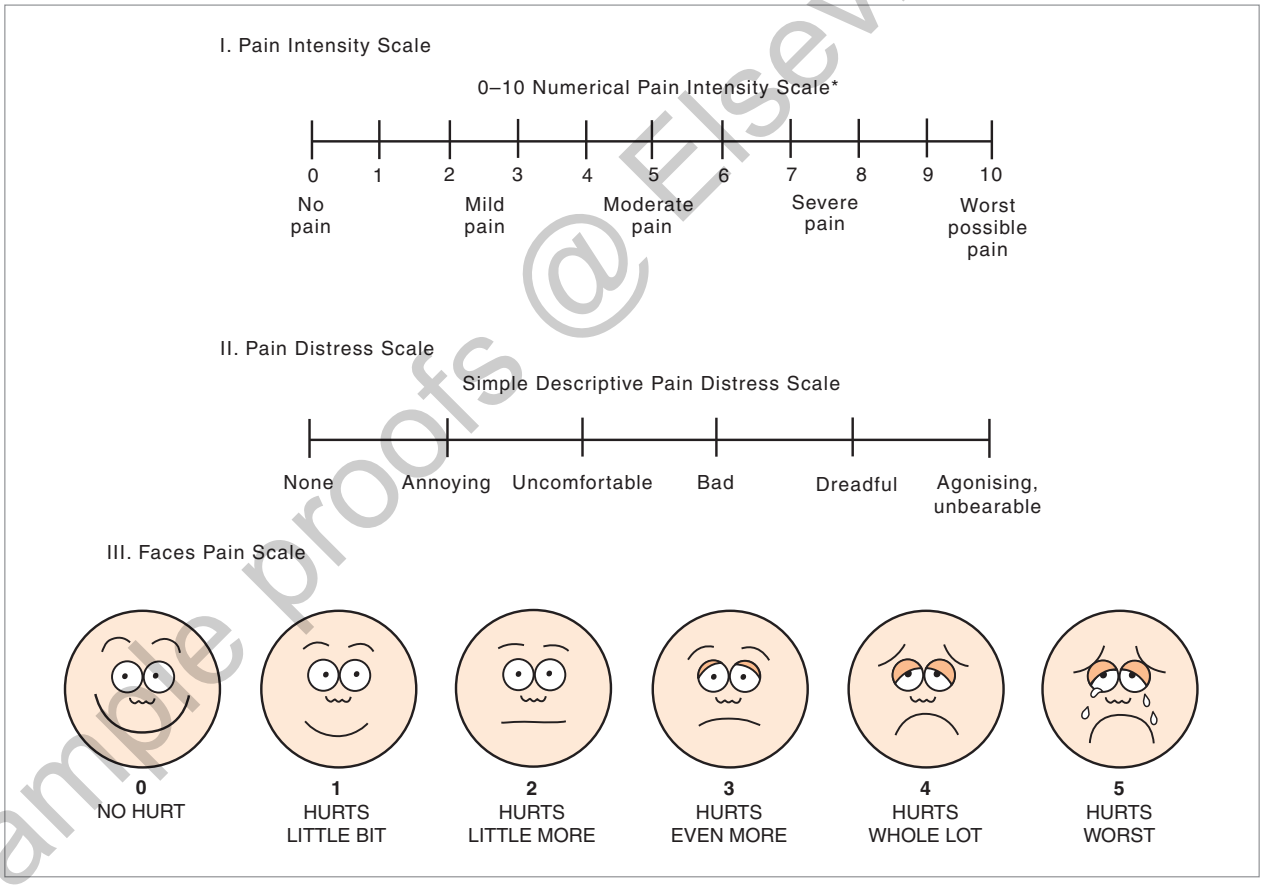


FIGURE 15-3
Scales for rating the intensity and distress of pain. In the Faces Pain Scale used for paediatric patients, the gradation in 'hurt' or 'pain' is explained to the child, with increasing pain shown from left to right; the child is asked to point to the face that shows how much she/he hurts now.

Adapted from: Salerno (1999); Carr et al (1992); Wong et al (2001); reproduced with permission.

- Avoid the chronic pain cycle, disability and 'sick role' by integrating analgesia into a comprehensive patient management plan with a multidisciplinary approach and involvement of a pain-control team if appropriate. An antidepressant may help stabilise sleep patterns and enhance analgesia, whereas sedatives may impair participation in pain management programs.
- **Stepwise management**: doses should be stepped up the 'analgesic ladder' (Figure 15-4) as required for increasing pain or development of tolerance:
  - Step 1—for mild pain, start with non-opioids (soluble aspirin, paracetamol, NSAID) with or without adjuvant drugs (antidepressants, anticonvulsants, antipsychotics, antispasmodics)
  - Step 2—for mild to moderate pain, substitute or add an oral low-dose opioid (codeine or oxycodone)
  - Step 3—for moderate to severe pain use a strong opioid (morphine as slow-release tablets/capsules or IV or SC, fentanyl SC or patch, or tramadol capsules, injection or sustained-release tablets); increase the dose of opioid, plus adjuvant drugs.
- Prevent adverse effects of opioids rather than allowing them to occur and then treating them. Constipation commonly requires a bowel management program with attention to high-fibre diet, high fluid intake and laxatives. An antiemetic and analgesic may prevent the postoperative patient from vomiting and opening up a wound. Respiratory depression may be problematic in patients with asthma or chronic obstructive airways disease. Tolerance and dependence can occur even after one week on continuous opioid therapy, and higher doses may be needed. Addiction rarely becomes a problem with medical use of opioids and is not an issue in terminal care.

Avoid under-treatment of pain

Despite healthcare providers being legally as well as morally responsible for pain relief, and although effective pain

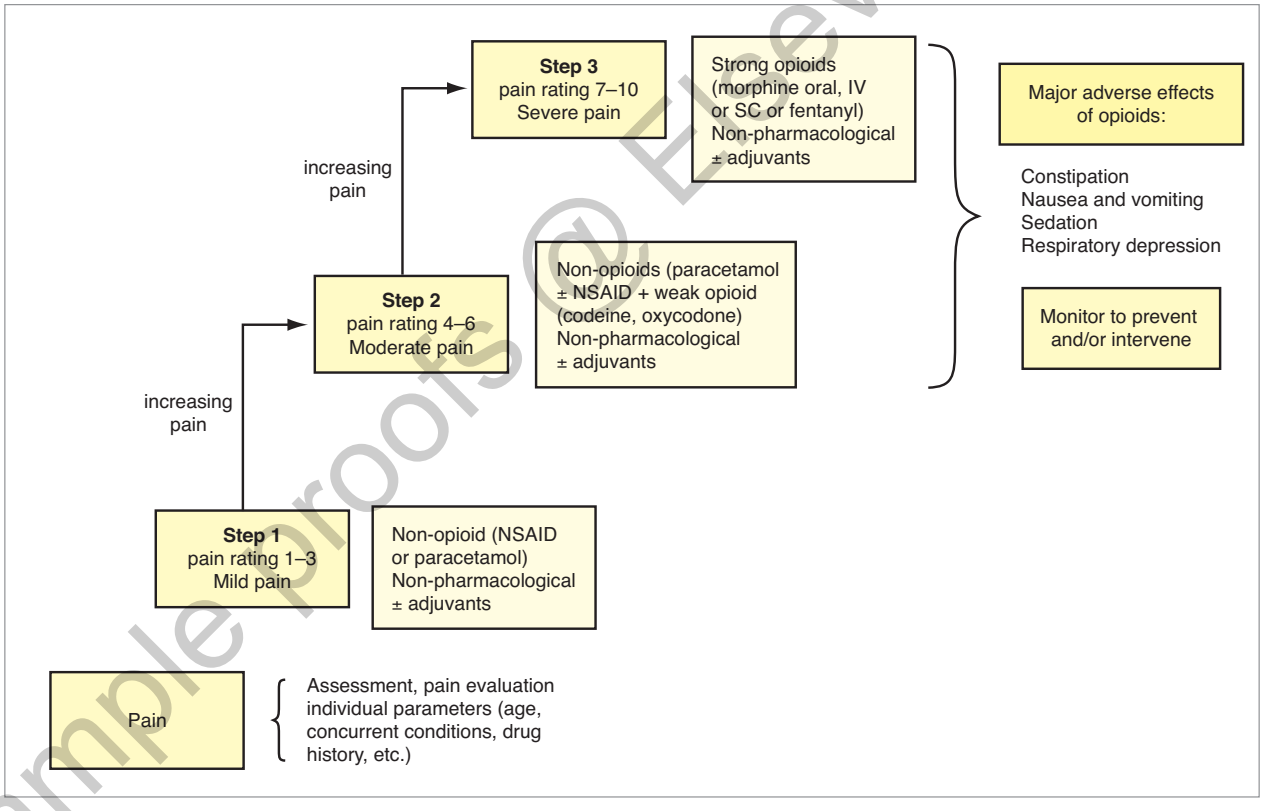


FIGURE 15-4
Flowchart for the 'stepwise' pharmacological management of pain. Analgesic dosage is commenced at the lower end of the range, and increased depending on the patient's responses. Adjuvants may include antidepressants, anti-inflammatories, antianxiety agents and local anaesthetics; non-pharmacological techniques include physiotherapy, acupuncture, psychotherapeutic methods and complementary and alternative therapies.
IV = intravenous; NSAID = non-steroidal anti-inflammatory drugs; SC = subcutaneous.
Adapted from: Salerno and Willens (1996); *Therapeutic Guidelines: Analgesic* (2012).

management techniques are available, many patients still suffer pain. Some reasons for under-treatment of pain are summarised in Clinical Interest Box 15-2.

Endpoints of treatment

Pain assessment charts and scales are useful for monitoring pain intensity during treatment and to assess the need for ongoing analgesia. Doses are titrated depending on clinical responses and adverse effects; after opioid doses, depth of sedation indicates likely depth of respiratory depression. The aim is to maintain comfort for the patient, avoiding peaks and troughs of pain relief and relapses. When administration is initiated in hospital, the cessation date and/or date for review should be specified and a letter sent to the patient's general practitioner outlining a discharge and weaning plan. If adequate pain relief cannot be achieved, the patient should be referred to a multidisciplinary pain or palliative care clinic.

Routes of administration of analgesics

If it is possible to deliver an analgesic drug directly to the site of pain or to the sensory nerve pathway, this will localise the effects, minimise the dose required and reduce the time to onset of action. Examples are epidural administration of local anaesthetics and opioids, intra-articular administration of corticosteroids and topical administration of local anaesthetics and NSAIDs. Generally, analgesics must be administered systemically to be circulated to the required site of action, whether in the painful tissues or in the CNS.

Oral route

The oral route is preferred as being the most acceptable and has the advantage of minimising IV drug-related problems. Opioid drugs may undergo significant hepatic metabolism after oral administration (first-pass effect), so higher doses are required than for parenteral administration; however, if the metabolites are pharmacologically active they contribute to the analgesic effects. Sustained-release preparations (e.g. morphine sulfate controlled-release tablets, Drug Monograph 15-1) help prolong the half-life of morphine from 3–4 hours to 12–24 hours, and are useful for stable, chronic pain.

Parenteral routes

Intravenous injection is obviously the fastest route for rapid pain control and dosage titration, as it avoids the absorption phase. IM and SC injection routes are common for opioid analgesics, the latter having a slower onset of action. Relatively poor lipid solubility delays the onset of analgesia when morphine is administered by epidural or intrathecal injection. The risk of inducing respiratory depression is greater by the intrathecal route than by epidural administration, so patients must be monitored for at least 24 hours after intrathecal administration.

CLINICAL INTEREST BOX 15-2
Fears or myths about pain and pain management

Many mistaken ideas contribute to the mismanagement of pain:

Fear of inducing addiction to opioids leads to patients being inadequately treated for pain and developing a pattern of drug-seeking behaviours ('pseudo-addiction') to achieve adequate pain control. The risk of addiction in hospitalised patients with severe pain receiving opioids at regular intervals is minimal.

Tolerance to opioids (the need to increase the dose of an analgesic to maintain the desired effect) is not usually seen in 'opioid-naïve' patients with severe acute or chronic pain from a physical cause such as trauma, tumour growth or surgery; increase in pain is usually due to disease progression or complications.

Respiratory depression rarely develops if opioids are carefully prescribed and monitored; in patients with severe pain requiring very large doses of opioids, tolerance develops to respiratory depressant effects.

Under-assessment of pain severity may lead to under-treatment, especially in children, women, elderly people and minority groups.

Inadequate reporting of pain due to stoicism, dementia or other cognitive impairment leads to inadequate treatment.

Legal regulation of opioids due to their potential for abuse and illegal diversion may limit prescribing, leading to under-treatment of pain even in patients with severe pain.

The wish to reserve strong analgesics for later use: patients need to be reassured that it will be possible to treat more severe pain with higher doses and/or combinations of analgesic methods.

Continuous infusion of opioids

Continuous opioid infusions by SC or IV routes may be used when there is intractable vomiting; for severe pain not relieved by oral, rectal or intermittent parenteral dosing; or for pain management in the postoperative period.

Opioids may be infused by a microdrip infusion set and pump (Figure 2-4) or by a **patient-controlled analgesia** (PCA) unit. PCA is commonly ordered in a hospital or hospice setting, usually after surgery or for chronic cancer pain. It is a microprocessor-controlled injector programmed to deliver a predetermined IV opioid dose when the patient triggers the pump mechanism. The dose is based on the prescriber's order and a lock-out interval (5–20 minutes), which protects the patient from overdosing. The unit may record all patient dosing attempts so the prescriber can evaluate the need for analgesia. For children or other patients unable to control their own dose regimen, nurse-controlled analgesia set-ups can be used.

CLINICAL INTEREST BOX 15-3
Opium, opiates, opioids and narcotics

A note on terminology: **opium** is the dried extract of seed capsules of the opium poppy ***Papaver somniferum*** (meaning 'the poppy bringing sleep'). Opium contains many pharmacologically active alkaloids (nitrogenous compounds), including morphine, codeine and papaverine. The term '**opiate**' strictly refers only to opium derivatives, whereas '**opioid**' means any opium-like compound and includes endogenous pain-relieving substances as well as synthetic drugs mimicking opiates.

The medicinal effects of opium have been known in many cultures for over 6000 years. Opium (which contains 8–14% morphine) was almost literally 'the panacea for all ills', as it is effective against pain, diarrhoea, cough and sleeplessness—what more could a sufferer want? A Latin synonym for opium preparations was 'laudanum', meaning praiseworthy. A doctor's bag could have contained many opium preparations, such as Tincture of Opium, Aromatic Chalk with Opium Mixture, Compound Aspirin and Opium Tablets, Gall and Opium Ointment, Ipecacuanha and Opium Powder (Dover's Powder), Opiate Squill Linctus and Opium and Atropine Suppositories. Opium was widely advertised and available well into the 20th century for even mild conditions such as coughs and infants' teething pains.

Opium preparations were standardised in terms of their morphine content (see Chapter 4, 'Standardisation of drugs'). It is now considered preferable to administer pure forms of single drugs (e.g. morphine) rather than crude extracts (opium) that contain varying amounts of several active ingredients plus unknown amounts of contaminants.

Pharmacologists too have known (and experimented with) morphine and similar drugs for many decades, naming and classifying the 'morphine receptors', probably without stopping to wonder why evolution endowed the human CNS with receptors for a poppy extract! It was not until 1975, when Hughes and Kosterlitz in Aberdeen, Scotland, succeeded in isolating from mammalian brain two pentapeptides that competed with and mimicked the actions of morphine, that the body's natural analgesic compounds, the enkephalins, were discovered. Since then, the receptors mediating pain relief have been referred to as opioid receptors.

The term '**narcotic**' has also suffered misuse and confusion: literally, it means a compound causing numbness or stupor; hence 'narcotic analgesics' was the group name for the morphine-like drugs, which cause pain relief with sedation, to distinguish them from the non-narcotic (aspirin group) analgesics. (Morphine was named after Morpheus, the Greek god of sleep and dreams.) The term 'narcotic' was later extended to refer to all drugs causing addiction and likely to be abused, so it now includes stimulants like cocaine as well as sedatives like morphine. The term is probably best avoided in the medical context.

Because of their addictive potential, opium and opioids are tightly controlled worldwide. Most opioids (except low-dose codeine, pholcodine, dextropropoxyphene, diphenoxylate and tramadol preparations) are 'Controlled Drugs' (Schedule 8) in Australia and New Zealand, requiring strict controls on storage and supply (see Appendix 5).

in the membranes of central neurons (also in peripheral tissue, especially in the gut) are responsive to various opioid agonists. On the basis of their actions at **opioid receptors**, drugs may be classed as opioid agonists (natural or synthetic agents that have a full morphine-like effect), antagonists or partial agonists such as buprenorphine, having a less than maximal effect at mu (μ) receptors.

Opioid receptors (OR) are G-protein-coupled transmembrane receptors, activation of which inhibits adenylate cyclase and reduces cyclic adenosine monophosphate (cAMP) levels. G-protein coupling also promotes opening of potassium channels and inhibits opening of calcium channels, which reduces neuronal excitability and inhibits release of excitatory (pain) transmitters, leading to inhibitory effects at the cellular level. Effects that appear to be excitatory are probably actually due to suppression of firing of inhibitory neurons. Tolerance to opioid effects may be due to both a gradual loss of inhibitory functions and an increase in excitatory signalling. Withdrawal effects may be due to a rebound increase in cAMP formation activated via delta opioid receptors by chronic administration of opioid.

OPIOID RECEPTOR SUBTYPES

Subtypes of opioid receptors are classified by responses to different agonists and antagonists (just as there are several subtypes of noradrenaline receptors). The main CNS opioid receptors are named by the Greek letters μ (m; mu), κ (k; kappa) and δ (d; delta): MOR, KOR and DOR, respectively (Dietis et al [2011]). A new member, the 'opioid receptor-like 1 receptor' (ORL-1, aka the nociceptin-opioid receptor), discovered in the Human Genome Project, is being studied as a potential target for new agents involved in analgesia, anxiety and drug addiction. Analgesia and constipation have been associated with all three receptors, while euphoria (feeling good) is associated mainly with actions at MOR and dysphoria (feeling bad) at KOR. What were formerly thought to be specific sigma (σ) OR are now considered general 'psychotomimetic receptors', associated with unwanted effects such as dysphoria, hallucinations and confusion.

AGONISTS AND ANTAGONISTS

The agonist analgesics (e.g. morphine, pethidine) activate both the μ and κ receptors, while partial agonist agents

TABLE 15-2
Opioid receptor responses

RECEPTOR	DRUG EXAMPLES	RESPONSE
mu (μ) MOR	Strong agonists: morphine, fentanyl, methadone, hydromorphone, β-endorphin Partial agonist: buprenorphine Weak agonist: pethidine	Supraspinal analgesia, euphoria, respiratory depression, sedation, constipation, miosis, drug dependence
	Antagonists: naloxone, nalorphine, naltrexone	Reverses opioid effects, induces acute withdrawal in opioid dependency
kappa (κ) KOR	Agonists: morphine, β-endorphin, dynorphin, asimadoline Little or no activity: methadone, pethidine	Spinal and peripheral analgesia, sedation, miosis, dysphoria, respiratory depression
	Antagonists: naloxone, naltrexone	Reverses opioid effects, induces acute withdrawal in opioid dependency
delta (δ) DOR	Agonists: enkephalins, β-endorphin	Spinal analgesia, respiratory depression, constipation; neuroprotection, cardioprotection
	Antagonist: naltrexone	

such as buprenorphine activate one type of receptor (agonist effect) and have minimal effects on other receptors, but may induce undesirable effects associated with σ-receptor activity. Pure antagonists (naloxone, naltrexone) antagonise all opioid receptors. A summary of opioid receptor responses is shown in Table 15-2; the situation is complicated by the fact that some drugs show varying effects in different tissues or species.

Pharmacological effects of opioids

Considering the widespread distribution of opioid receptors in peripheral and central tissues, it is not surprising that opioids have a broad spectrum of actions. (Aspects of opioid actions relevant to drug dependence and social pharmacology are discussed in Chapter 21.)

Central effects

Effects of opioids in the CNS include:

- analgesia—the main clinical use
- suppression of the cough reflex—another useful effect, e.g. codeine or pholcodine cough linctuses
- suppression of the respiratory centre in the medulla—a major adverse effect leading to toxicity; the commonest cause of death from overdose
- sedation and sleep, hence the term narcotic analgesics; a useful clinical effect if pain is keeping the patient awake, but not helpful with daytime activities
- euphoria, the feeling of contentedness and wellbeing, which contributes to the analgesic actions and dependence
- dysphoria (unpleasant feelings, hallucinations, nightmares)
- miosis (pupillary constriction); 'pinpoint pupils' are a diagnostic sign of an opioid-dependent person
- nausea and vomiting—mediated through the chemoreceptor trigger zone; tolerance develops to these effects
- prolongation of labour—not usually a problem clinically
- hypotension and bradycardia occurring after large doses, mediated via the medulla
- tolerance and dependence or addiction, mediated by μ receptors; tolerance develops after a few doses of morphine; physical dependence is shown by a marked withdrawal syndrome after doses are missed for 1–2 days.

Peripheral effects

Effects of opioids in the PNS include:

- actions via opioid receptors in the gut, leading to decreased motility and increased tone in smooth muscle; severe constipation is a common adverse effect; these effects may be useful in treating diarrhoea—the antidiarrhoeal agents loperamide and diphenoxylate are mild opioids (see Chapter 30)
- spasms of sphincter muscles, which can lead to delayed gastric emptying, biliary colic or urinary retention
- suppression of some spinal reflexes
- release of histamine, causing bronchoconstriction and severe itching[1] (this effect of morphine is not mediated by opioid receptors).

Adverse drug reactions

The most serious adverse effects of opioids are respiratory depression, excessive sedation, dysphoria, constipation, nausea and vomiting, tolerance and dependence. The cause of death from acute toxicity after an overdose of an opioid such as heroin is usually respiratory failure (see Clinical Interest Box 15-4).

Tolerance to opioid analgesics

Drug **tolerance** is defined as the gradual decrease in the effectiveness of a drug given repeatedly over a period of

1 The sensation of having ants crawling over the body, known as formication—a word that has to be pronounced and spelt carefully.

TABLE 15-3
Selected opioid dosage forms

DRUG/DOSE FORM	USUAL DOSE	DURATION OF ACTION (h)	NOTES
Morphine			The 'gold standard'; analgesic for severe pain, acute and chronic pain; has an active metabolite M6G
Oral solution, tablets CR preparations	5–20 mg 5–100 mg	2–4 12–24	30 mg oral morphine is considered equivalent to 10 mg parenteral morphine
IM/SC/IV	0.5–10 mg	4–6	
Epidural, IT	0.2–5 mg	up to 24	Slow-release form for anaesthetist-only use in hospital, patient requires close monitoring for 48 hours
Buprenorphine			For chronic pain or opioid dependence; slow onset; partial agonist, low dependence liability
IM, IV	0.3–0.6 mg	6–8	
Sublingual	0.2–0.4 mg	6–8	
Transdermal patch	5, 10 or 20 microgram/h	7 days	For moderate-to-severe pain
Codeine			Weak opioid, metabolised to morphine; for mild to moderate pain; cough suppression; diarrhoea
Oral	30–200 mg	4	Combination formulations contain sub-therapeutic doses
Dextropropoxyphene			Weak opioid, toxic active metabolite; no better than paracetamol; not recommended
Oral	30–100 mg	4–6	
Fentanyl			Highly potent (dosed in microgram); for moderate to severe pain, during anaesthesia, chronic pain, breakthrough pain
SC/IV, epidural, IT	50–100 microgram	0.5–2	
Patch	12–100 microgram/h	3 days	Patches release 12–100 microgram/h; not for opioid-naive
Lozenge ('lollipop')	200–1600 mcg	6–8	Absorbed via buccal mucosa; for breakthrough pain and children
Hydromorphone			Less sedative
Oral: regular, CR	6–8 mg	2–4	24 h for CR formulations
IM/SC/IV	1–2 mg	4–5	
Methadone			Severe postoperative or chronic pain; maintenance of dependence; long half-life, so risk of accumulation
Oral	5–10 mg	4–24	
IM/IV/SC	5–10 mg	4–24	
Oxycodone			Oral bioavailability variable, 50–90%
Oral: regular, CR	15–20 mg	3–4	CR formulations have longer duration of action (12–24 h)
SC IV	2.5–10 mg 0.5–2 mg	4–6	
Rectal	30 mg	6–8	Rectal bioavailability also variable
Pethidine			Risk of excitement, poor oral efficacy; useful in labour, renal and biliary colic pain; interactions with drugs affecting 5-HT levels
IV/IM/SC, epidural	75–100 mg	3–5	
Tramadol			Weak opioid; moderate-to-severe pain; monoamine uptake inhibitor, useful for neuropathic pain; low misuse potential
Oral: regular, CR	50–200 mg	3–6	12–24 h for CR formulations
IM, IV	50–100 mg	5–6	

CR = controlled-release; IM = intramuscular; IT = intrathecal; IV = intravenous; SC = subcutaneous.
Note: Doses need to be titrated depending on age, level of pain, tolerance and renal or hepatic impairment; doses for high-potency opioids buprenorphine and fentanyl are in micrograms or fractions of a mg. *Adapted from:* information in MIMS Online and *Australian Medicines Handbook* (2012).

DRUG INTERACTIONS 15-1
Opioids

DRUG	POSSIBLE EFFECTS AND MANAGEMENT
Alcohol or other CNS depressants (other opioids, anaesthetics, sedatives, psychotropics)	May result in enhanced CNS depression, respiratory depression and hypotension; reduce dosage and monitor closely
Buprenorphine (partial agonist)	May result in additive effect of respiratory depression if given concurrently with low doses of μ- or κ-receptor agonists; avoid concurrent usage. Partial agonists given with an opioid agonist may reduce the analgesic effects of the full agonist or precipitate withdrawal symptoms
Monoamine oxidase inhibitors (phenelzine, tranylcypromine; moclobemide and selegiline)	MAOIs intensify the effects of opioids (especially pethidine, tramadol and fentanyl) and may cause serotonin syndrome; caution should be taken and dosages of opioids reduced
Opioid antagonists (naltrexone, naloxone)	Will produce withdrawal symptoms in patients dependent on opioid medications; avoid concurrent administration
Diltiazem, erythromycin and fluconazole	May inhibit metabolism and increase concentration of alfentanil, thus exacerbating respiratory depression; dose may need to be decreased
Rifampicin	May enhance metabolism and decrease concentration of morphine, codeine and alfentanil, thus reducing their effects; effects should be monitored and dose may need to be increased or another analgesic substituted
Many drugs (including anticonvulsants, antivirals, antifungals, rifampicin and St John's wort)	May enhance metabolism and decrease concentration of methadone, thus reducing its effects; effects should be monitored and dose may need to be increased

injection, oral mixture, controlled-release capsules and tablets (Drug Monograph 15-1); and slow-release epidural injection. Controlled-release preparations are not suitable in acute pain: for acute postoperative pain in a closely monitored situation, bolus IV doses of morphine 1–2 mg can be given at 5-minute intervals (or more frequently) until pain relief is achieved.

Other opioids

CODEINE

Codeine (see Drug Monograph 28-4) is absorbed well after either oral or parenteral administration. Codeine, the 3-methyl ether of morphine, is actually a prodrug, being rapidly metabolised in most people to morphine (by CYP2D6). In the 6–10% of the (Caucasian) population who lack the enzyme to metabolise codeine, it has no analgesic effect, whereas rapid metabolisers may reach toxic concentrations of morphine. Interindividual variation in pharmacokinetics leads to variable effectiveness so codeine is not generally recommended. Constipation is a frequent adverse effect and may limit clinical usefulness.

Codeine is often combined with a non-opioid analgesic such as aspirin, paracetamol or ibuprofen in compound analgesic tablets to provide stronger relief than the NSAID alone can achieve; however, misuse of combination products can lead to toxicity (Iedema 2011). In Australia, tablets containing <10 mg codeine are available over the counter (Schedule 3 Pharmacist-Only Medicine) but at higher doses (30 mg) it must be prescribed (S4: Prescription Only or S8: Controlled Drugs).

FENTANYL

Fentanyl, a very potent opioid with a good adverse-effect profile, has become popular for use as a component of anaesthesia in day-surgery procedures (see Chapter 14) and in breakthrough pain in cancer therapy. Fentanyl is formulated for IM or slow IV injection, intranasal use, as a topical patch (Drug Monograph 15-2) or lozenge ('lollipop') for absorption via the oral mucosa and, in combination with bupivacaine or ropivacaine, for epidural administration for postoperative or obstetric analgesia.

Related drugs are sufentanil, alfentanil and remifentanil. These are used as adjunct opioid analgesics in general anaesthesia, postoperatively and in intensive care situations.

HYDROMORPHONE

Hydromorphone is a semisynthetic opioid with a faster onset and shorter duration of action than morphine. It is prescribed for its analgesic and antitussive effects and is administered as tablets, oral liquid or injection.

METHADONE

Methadone (see Drug Monograph 21-2) is an orally effective analgesic with properties similar to those of morphine; duration of action is usually 4–6 hours, but with repeated oral dosing it may extend to 72 hours (longer in the elderly and in patients with renal dysfunction). To control pain, methadone is administered once or twice daily, based on the individual's response. Accumulation can occur and steady-state concentrations may not be reached for several days. Cardiac dysrhythmias may occur with high doses.

DRUG MONOGRAPH 15-1 • Morphine sulfate controlled-release tablets

Morphine is a strong analgesic with central actions on pain perception; it mimics the actions of enkephalins and endorphins at opioid receptors.

Indications

Morphine is indicated for the treatment of opioid-responsive moderate-to-severe acute and chronic pain, such as after trauma or surgery or for cancer pain. It may be given to suppress an unproductive nagging cough and to patients with lung cancer to treat pain aggravated by coughing, when the sedative and euphoriant actions are also useful. Morphine increases GIT tone and decreases peristalsis and glandular secretions so is useful in treating diarrhoea. In the pre-hospital and emergency situation, morphine is commonly carried in ambulances and administered by paramedics IV, IM or by IV infusion, for acute pain relief, sedation to enable and maintain intubation and in suspected left ventricular failure with shortness of breath.

Pharmacokinetics

Morphine may be administered by many routes—PO, IM, IV, SC, epidural, intrathecal and rectal. It is rapidly absorbed and is subject to extensive first-pass metabolism in the liver, leading to poor bioavailability (about 40% when taken orally), so the oral dose may need to be 2–6 times the parenteral dose (see Table 15-3). The main metabolites are active morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G).

Morphine is distributed widely in most body tissues but only a small fraction crosses the blood–brain barrier. Metabolites are excreted primarily via the kidneys, with 7–10% undergoing enterohepatic circulation, which extends the half-life. The mean elimination half-life is 2–3 hours but this is increased with slow-release preparations (tablets, capsules, oral suspension), such that the peak morphine concentrations during chronic use occur 4–8 hours after dosing and therapeutic effects may extend for 16–24 hours.

Drug interactions

See Drug Interactions 15-1.

Adverse reactions

The most common adverse reactions reported are constipation, nausea and vomiting, itch, urinary retention, sedation, circulatory and respiratory depression and miosis (pin-point pupils); overdose with opioids can cause cessation of respiration (as in Clinical Interest Box 15-4). Tolerance occurs to analgesia as well as to depressant effects (but not to constipation), requiring higher dosages. Constipation should be pre-empted with prophylactic laxative or a diet high in fibre. Respiratory depression, dependence and withdrawal reactions are not usually problems when opioids are used clinically for relief of severe pain.

Warnings and contraindications

Avoid the use of opioids in patients with known opioid drug hypersensitivity, acute respiratory depression, acute alcoholism or head injury. Use opioids with caution in patients with acute asthma, chronic obstructive pulmonary disease (COPD) or other respiratory impairment or a history of drug abuse, and in patients with elevated intracranial pressure (may be exacerbated), biliary colic or pancreatitis (may cause spasm of biliary tract muscle and sphincter), acute abdominal conditions or severe inflammatory bowel disease (risk of obscuring the diagnosis, or risk of toxic megacolon). Doses need to be reduced in patients with renal or liver impairment and in the elderly and children. Administration during pregnancy may result in dependence in the infant; use during labour may cause respiratory depression in the infant, treated with naloxone.

Dosage and administration

Standard morphine doses are 10 mg IV/IM/SC or 30 mg orally; higher doses are required for tolerant patients.

Because of its oral bioavailability and extended half-life, methadone is approved for use in opioid detoxification and maintenance programs in individuals who are physiologically dependent on heroin or other opioids. Oral administration in liquid form is preferred as this removes the need for injections (see Chapter 21).

OXYCODONE

Oxycodone is a potent synthetic opioid about 10 times more potent than codeine; it is available in many different strength tablets, as capsules and oral liquid. It is well absorbed through the rectal mucosa, making the suppository dosage form (30 mg) useful for night-time analgesia and in patients unable to swallow. (*Note*: Suppositories should not be cut (divided up) to reduce the dosage, as pieces may not contain an even distribution of the drug.) Doses may need to be reduced in renal impairment.

Controlled-release combinations with naloxone (an opioid antagonist) are indicated for moderate-to-severe chronic pain when constipation is refractory to treatment with regular laxatives.

PETHIDINE

Pethidine (known as meperidine in the USA) is an effective analgesic for short-term use but is unsuitable for oral administration because of low bioavailability. It is less likely than morphine to release histamine or raise biliary tract pressure, so is useful for patients with acute asthma, biliary colic or pancreatitis. A metabolite (norpethidine) is neurotoxic and can accumulate, so pethidine is used only in acute pain such as for obstetric analgesia. Pethidine has serotonergic actions, and concurrent use of MAO inhibitors may result in unpredictable life-threatening reactions,

CLINICAL INTEREST BOX 15-5 Brompton's cocktail

This traditional oral mixture for pain relief dates back to the 19th century when pulmonary tuberculosis (TB) was endemic among poor and malnourished populations in overcrowded cities, and antibiotics to treat *Mycobacterium tuberculosis* infection had not yet been discovered (see Clinical Interest Box 4-3). Chronic TB caused granulomatous reactions and necrosis commonly in lungs, airways, bones and marrow, bowel, liver, lymph nodes, meninges and genital tracts.

The disease could have a silent course or manifest as fever, weakness, dyspnoea and destruction of lung tissue, with productive cough and haemoptysis (coughing up of blood). The only treatment was removal of the patient to fresh air in a sanatorium and to trust the immune system to overcome the infection. In many 19th century operas and novels, the heroine afflicted with 'consumption' (pulmonary TB) dies tragically but musically—think of Mimi in *La Boheme*, Violetta in *La Traviata*, Fantine in *Les Miserables*, Beth in *Little Women* and (later) Satine in the movie *Moulin Rouge*.

The Brompton Chest Hospital in London developed a powerful analgesic mixture to relieve the terminal pain of pulmonary TB. It became known as Brompton's cocktail, Haustus E or Mist Euphoriens (euphoriant mixture). A typical recipe combined three effective euphoriant/analgesic drugs: opium, cocaine and gin (alcohol).

Many hospital pharmacies still have their own formula for a dose of Brompton's cocktail, such as:

- morphine hydrochloride 15 mg
- cocaine hydrochloride 15 mg
- gin or brandy to 10 mL with the gin or brandy replaced by alcohol, syrups and flavourings.

It is used nowadays to relieve severe terminal pain; the CNS-depressant effects help cloud the patient's consciousness.

including serotonin syndrome.[3] Pethidine is often requested by illicit drug users (who may very effectively mimic the signs and symptoms of severe pain), and prescribers are warned of this drug-seeking behaviour.

TRAMADOL

Tramadol is a relatively new centrally acting synthetic analgesic that is not chemically related to the opioids but binds to μ-opioid receptors; it also inhibits reuptake of noradrenaline and 5-HT so is referred to as an opioid–SNRI (serotonin noradrenaline reuptake inhibitor) analgesic. It is indicated in treatment of moderate-to-severe chronic pain and neuropathic pain, but is less effective and more expensive than morphine; it may have less potential for respiratory depression and drug dependency. Common adverse reactions include nausea, dizziness, hypertension and seizures; precautions are needed in elderly patients as hallucinations are possible. Tramadol is a prodrug, activated by CYP2D6; there are many interactions with other drugs inducing or inhibiting CYP2D6, and with other drugs affecting 5-HT levels, contributing to serotonin syndrome.

A new chemically related drug is tapentadol; it appears to have similar mechanisms of action, indications, adverse effects and contraindications. Both immediate- and sustained-release tablets are available; the SR formulation was similar in trials to controlled-release oxycodone for chronic low-back pain and osteoarthritis. Tapentadol is not currently recommended for labour pain or cancer pain.

PHOLCODINE

Pholcodine (see Drug Monograph 28-4), an opioid chemically similar to the opium alkaloid papaverine, has virtually no analgesic effects but retains other morphine-like effects, including suppressing cough and respiration and causing mild sedation, nausea and vomiting, dependence and constipation. It is used mainly as a cough suppressant, as are dextromethorphan and dihydrocodeine.

DEXTROPROPOXYPHENE

Dextropropoxyphene is a synthetic analgesic structurally related to methadone, previously indicated for treatment of mild-to-moderate pain. It has significant dysphoric effects, accumulation and cardiotoxicity can occur and it has no marked advantages over safer analgesics such as codeine, aspirin or paracetamol, so is not recommended. It has been removed from the market in many countries (UK in 2004, EU in 2009, USA and NZ in 2010), and was recommended by the TGA for removal in Australia; however, after appeals by the drug manufacturer, it is still on the market in Australia as of 2014 (see Buckley and Faunce [2013]).

HEROIN

The case is often put for legalisation of heroin for treatment of intractable pain because of its analgesic and euphoric effects. Some advocates believe it is more potent, faster acting and produces more prolonged euphoric effects than other opioids. Pharmacologically, however, heroin is a prodrug: when administered it is rapidly converted in the liver to morphine and morphine metabolites, which provide its analgesic effects. Due to its greater lipid solubility, heroin crosses the blood–brain barrier faster than morphine, inducing a greater 'rush'; hence it is preferred by opioid-dependent persons; however, it has a shorter duration of action.

Heroin is a popular illegal drug of abuse (Schedule 9), so legalising it brings increased risks of drug diversion, pharmacy burglaries and crime. As heroin offers few (if

3 Serotonin syndrome is an adverse effect due to excessive stimulation of 5-HT_{2A} receptors by drugs such as antidepressants; it is characterised by mental state changes (confusion, delirium, hypomania), GI tract effects (diarrhoea), neuromuscular hyperactivity (hyperreflexia, incoordination, tremor), autonomic instability, sweating, fever and shivering (see Chapter 18 for more detail).

DRUG MONOGRAPH 15-2 • Fentanyl patches

Fentanyl is a strong opioid analgesic with a mechanism and actions similar to morphine; it mimics the actions of endogenous enkephalins and endorphins at opioid receptors.

Indications

Fentanyl is indicated for the treatment of opioid-responsive acute and chronic pain, as an adjunctive analgesic during general anaesthesia, for breakthrough pain in cancer patients (lozenge formulation) and in epidural anaesthesia in combination with bupivacaine or ropivacaine. In the pre-hospital and emergency situation, fentanyl is administered by paramedics by IV injection or intranasal inhalation, for analgesia and sedation to facilitate intubation.

Pharmacokinetics

Fentanyl is released from a transdermal patch at a relatively constant rate, providing continuous systemic delivery for the 72-hour application period. The transdermal patch has a slow onset of action, so shorter acting analgesics should be administered initially; heat and fever increase release of active drug. Serum fentanyl concentrations attained are proportional to the fentanyl patch size. By the end of the second 72-hour application, a steady state serum concentration is reached and is maintained during subsequent applications of a patch of the same size. The plasma-protein binding of fentanyl is about 84%. Fentanyl is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is inactive. Skin does not appear to metabolise fentanyl delivered transdermally. After IV infusion, the apparent half-life is approximately 7 (range 3–12) hours. The half-life is longer after dermal administration, as absorption continues within the skin after the patch is removed; following a 72-hour application the mean half-life ranges from 22 to 25 hours. Elderly or debilitated patients may have a reduced clearance of fentanyl and so the terminal half-life of fentanyl may be prolonged in this patient group. Approximately 75% of fentanyl is excreted in the urine, and about 9% in the faeces, mostly as inactive metabolites.

Drug interactions

See Drug Interactions 15-1. In addition, as fentanyl can contribute to serotonin toxicity, it is contraindicated with MAO inhibitors or other drugs implicated in serotonin syndrome (see under 'Pethidine', and Chapter 18). Azole antifungals can impair the metabolism of fentanyl, leading to prolonged half-lives and risk of adverse effects.

Adverse reactions

The most common adverse reactions are bradycardia and rash and itch from the patch; there is less risk of nausea, vomiting and constipation than with other opioids. Fentanyl has a long duration of action (up to 72 hours), so adverse effects are not easily reversed.

Warnings and contraindications

Avoid the use of fentanyl in patients with bradycardia. Doses do not need to be reduced in patients with renal or liver impairment. Even after 3 days' wearing, patches retain about 50% activity, so used patches should be folded, wrapped and disposed of carefully, as the contents of patches may be retrieved and abused by people addicted to opioids. (Children have died after inadvertently sticking used patches to their skin; recent changes instituted by the Australian Therapeutic Goods Administration to make patches easier to see and less easily leached of active drug should improve safety.) Unused patches should be returned to a pharmacy.

Dosage and administration

Doses may vary widely depending on the indication for which it is given, the route of administration, tolerance developed, level of pain, age and opioid familiarity/naïveté of the patient. Patches come in a great range of doses, from 12 microgram/hour through 25, 50, 75 to 100 microgram/hour, allowing ready titration of dosage. The 12 microgram/hour patch is roughly equivalent to 45 mg morphine PO daily. The date and time of application should be written on the patch before it is applied to dry, hairless skin; after 3 days the patch is removed, disposed of carefully and another applied to a different area of skin.

Based on information from *Australian Medicines Handbook* (2013), and New Zealand Medsafe database (www.medsafe.govt.nz/medicines).

any) advantages over the already marketed opioids, it is Australian policy that legalisation and clinical use of heroin are not essential for optimal treatment of pain.

Partial agonists

Partial agonists produce less than maximal effects at a receptor; for example, buprenorphine is a partial agonist at μ receptors and antagonist at κ receptors (see Table 15-3). Generally, these drugs are less effective analgesics with lower dependency potential and less severe withdrawal symptoms than full opioid agonists. However, their use as analgesics is not recommended, as they may precipitate pain or withdrawal reactions in patients taking other opioids, their actions may not be reversible with an antagonist (naloxone) and patients taking a partial agonist may not respond adequately if a full agonist needs to be given.

BUPRENORPHINE

Buprenorphine is a partial agonist at mixed nociceptin ORs/MORs. It is available as tablets, injection or patches, and is indicated for relief of moderate-to-severe pain and for treatment of opioid dependence. As it has a prolonged onset of action it is not suitable for acute pain; and as a partial agonist, it may precipitate withdrawal in patients dependent on other opioids, and its effects are not readily reversed by naloxone.

DRUG MONOGRAPH 15-3 • Aspirin

Aspirin has analgesic, antipyretic, anti-inflammatory and antiplatelet effects. Its commonest formulation is in tablets containing 300 mg aspirin.

Indications

Aspirin is indicated (in those over 16 years) for the treatment of pain and fever, headaches, rheumatic fever, rheumatoid arthritis and osteoarthritis, and in prevention of AMI, reinfarction or stroke. The advantages of aspirin over paracetamol include its anti-inflammatory effects and its effectiveness in preventing AMI and thrombi. In the pre-hospital and emergency situation, aspirin tablets PO are commonly administered by paramedics for their antiplatelet actions, to reduce thrombus formation and reduce risk of worsening heart attack.

Pharmacokinetics

Aspirin taken orally is rapidly absorbed, partly from the stomach (as the drug is itself acidic), and also from the intestine. Peak serum levels of acetylsalicylic acid are reached within 20–40 minutes. Rapid metabolism by tissue and blood esterases occurs, hydrolysing aspirin to acetic acid and salicylate; the peak plasma salicylate level is reached in 2–4 hours. Salicylate is distributed throughout most body tissues and fluids, including synovial fluid and cerebrospinal fluid, and is 50–90% bound to plasma proteins. Salicylate then undergoes hepatic metabolism to inactive metabolites. The plasma salicylate level required for analgesic and antipyretic effects is about 28 mg/L, whereas 100 mg/L is required for anti-inflammatory effects. Toxic effects (salicylism) are seen above about 200 mg/L.

Common adverse effects

Common adverse effects include gastrointestinal irritation or discomfort and nausea or vomiting. Taking aspirin with a full glass of water helps reduce GIT effects. Toxic reactions due to salicylate poisoning (salicylism) include tinnitus, vertigo, complicated effects on acid–base balance (both respiratory alkalosis and metabolic acidosis) and Reye's syndrome in young people. See Clinical Interest Box 15-6 for clinical management of aspirin overdose.

Drug interactions

There are many potential drug interactions with other drugs affecting platelet function or the blood-clotting process; drugs eliminated mainly by renal excretion; drugs used to treat heart failure (as aspirin can impair renal function); antihypertensive agents (as aspirin can raise blood pressure and impair renal perfusion); other NSAIDs (increased risk of gastric ulceration or bleeding); corticosteroids (may decrease salicylate concentration and clinical effect); drugs affecting blood glucose concentration; probenecid (uricosuric effect may be reduced); valproate (concentration and effects of valproate may be enhanced, as may effects of aspirin on blood parameters). In most cases, low-dose aspirin (e.g. 100 mg daily) is safe with other drugs.

Warnings and contraindications

Precautions with aspirin use are required in heart failure and hypertension, renal impairment, severe liver disease, during surgery and in people predisposed to bleeding, peptic ulcer or asthma, if previous serious adverse effects with salicylates have occurred, and during late pregnancy. It should not be used in children under 16 years, especially those with fever, because of the possibility of rare but potentially fatal Reye's syndrome (severe liver damage and encephalopathy).

Dosage and administration

Aspirin products are available in tablet, effervescent tablet, capsule, enteric-coated and extended-release tablet dosage forms. Aspirin should be taken after food to minimise irritant effects in the gastrointestinal tract (this also has the effect of delaying absorption). The usual adult dose is 1–2 regular-strength tablets (300 mg) every 4–6 hours or as needed. Higher doses are required for anti-inflammatory effects. For prophylactic antiplatelet effects, much lower doses are sufficient, e.g. 75–150 mg/day (¼ to ½ standard tablet).

Paracetamol is an effective analgesic provided that adequate regular doses are maintained; typical adult dosage is two tablets to start, then one tablet (500 mg) every 3–6 hours, with maximum daily intake 4 g (8 standard tablets). The dose is lower for small elderly patients.

Paracetamol is recommended particularly for treatment of mild pain and fevers in children (see Clinical Interest Box 15-8), and in adults in a wide range of conditions causing mild-to-moderate pain (especially of non-inflammatory origin), fever, migraine and tension headache and some forms of arthritis (osteoarthritis; see Day and Graham [2005]). Aspirin or other NSAIDs are preferred in moderate-to-severe arthritis when there is a major inflammatory component, as in rheumatoid arthritis (see Chapter 47).

Pharmacokinetics of paracetamol

Paracetamol taken orally is rapidly absorbed, with bioavailability approximately 90%, reaching peak serum levels in 15–60 minutes; its elimination half-life is 1–3 hours. It is metabolised in the liver (see Figure 15-5), and glucuronide and sulfate metabolites are excreted by the kidneys. The usual maximum daily paracetamol dose for adults is 4 g/day (8 × 500 mg tablets); for children, the single dose is 15 mg/kg orally, with a maximum of 1 g/dose. Paracetamol is available in infant, paediatric and adult strengths, as tablets, capsules, chewable tablets, elixirs, suppositories (not recommended due to erratic absorption) and as an injection. Extended-release tablets are available, containing 655 mg paracetamol in a formulation that

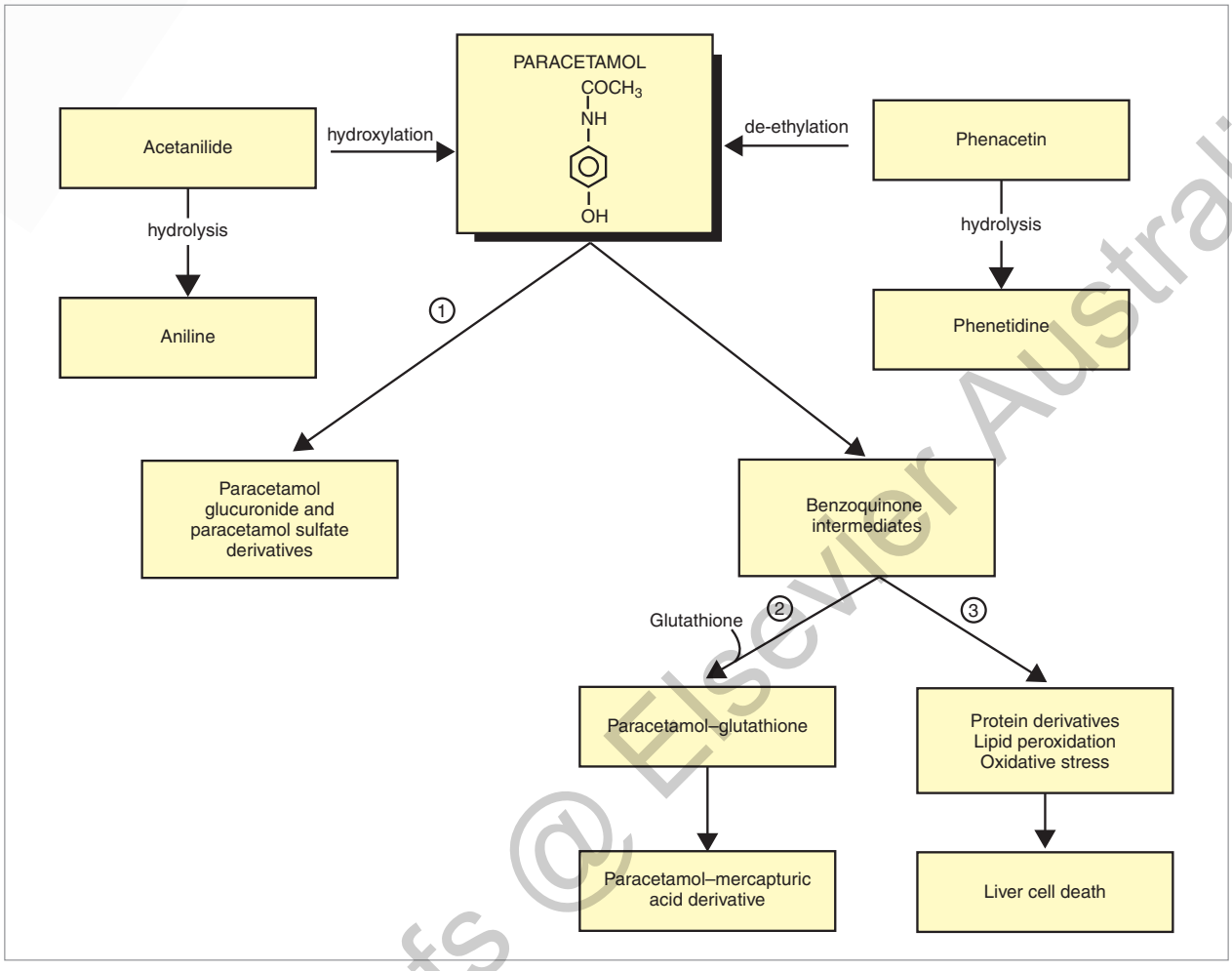


FIGURE 15-5
Metabolic pathways involving paracetamol. In normal doses, paracetamol is conjugated (pathway 1) to non-toxic glucuronide and sulfate derivatives. In higher doses, pathway 1 becomes saturated and a benzoquinone intermediate (BQI) is produced. Combination of the BQI with glutathione (GSH, a gamma-glutamyl-cysteinyl-glycine tripeptide involved in amino acid transport in cells) via pathway 2 produces mercapturic acid metabolites. In large overdoses, GSH reserves are used up and BQIs are diverted via pathway 3, in which toxic derivatives cause potentially lethal reactions in liver cells. Paracetamol overdose is treated with acetylcysteine, a precursor of the natural compound GSH; this replenishes GSH supplies and avoids formation of toxic BQI metabolites.

NSAIDs and polypharmacy

NSAIDs are often included in commercial products such as pain relievers, cough and cold remedies, sedatives and medicines for allergy or (pre)menstrual problems, so patients may be unaware that they are taking several NSAIDs concurrently,[7] for example for headache, fever, arthritis and prophylaxis of AMI or stroke. Taking more than one of these products at the same time, or with a prescribed NSAID, can lead to toxicity. Elderly patients with impaired renal function are particularly at risk of adverse drug reactions and interactions, especially from NSAIDs with long half-lives.

Other pharmacological analgesics

Pregabalin and gabapentin

New analgesics unrelated to opioids or NSAIDs are pregabalin and gabapentin. **Pregabalin** (an analogue of the neurotransmitter GABA) reduces the release of various transmitters via interference with the calcium channels in nerve terminals. Pregabalin is indicated in neuropathic pain

7 A tactful review of the family's drug cabinet or questioning about all the medicines currently being taken, including those bought in pharmacies or supermarkets, often reveals a potentially toxic cocktail of many NSAID preparations (see Clinical Interest Box 2-4, 'Clues in the medicine cabinet').

CLINICAL INTEREST BOX 15-7
Managing paracetamol overdose

Patients suspected of taking an overdose of paracetamol are notoriously unreliable as to the amount taken and the time of ingestion, and may appear well for 1–2 days after an eventually fatal overdose. As there is a specific antidote (acetylcysteine, which replaces depleted glutathione, see Figure 15-5), it is important that any patient with possible paracetamol overdose be tested for plasma paracetamol levels. More than 150 mg paracetamol per kg body weight (about 20 standard 500 mg paracetamol tablets for an average adult) or 10 g total paracetamol is potentially a toxic dose. People with previously impaired liver function (e.g. by alcohol abuse) are more susceptible to liver damage and have a lowered threshold for toxicity.

Symptoms

- Early symptoms are sweating, anorexia, nausea or vomiting, abdominal pain or cramping and/or diarrhoea; these usually occur 6–14 hours after ingestion and last for about 24 hours.
- Late symptoms are swelling, tenderness or pain in the abdominal area 2–4 days after ingestion (indicates hepatic damage).

Treatment

- If less than 1 hour since overdose, gastric lavage or activated charcoal is administered.
- A plasma sample should be obtained for liver function tests and coagulation studies. Determine paracetamol serum levels at 4 hours or more after ingestion, then start acetylcysteine administration. Hepatotoxicity is likely if plasma paracetamol concentration is more than 200 microgram/mL at 4 hours, 150 microgram/mL at 6 hours, 100 microgram/mL at 8 hours, 50 microgram/mL at 12 hours or 5 microgram/mL at 24 hours.
- Administer acetylcysteine IV in 5% glucose from 4 hours after overdose, with a loading dose, then maintenance dose continuing for 21 hours. (See current *Australian Medicines Handbook* or other reference for the nomogram to determine likelihood of paracetamol toxicity from plasma levels, and dosage instructions.)
- Perform liver function tests and prothrombin time determinations to monitor hepatotoxicity. Institute supportive measures as indicated for bleeding disorders, renal failure, cardiac toxicity and hepatic encephalopathy.

DRUG MONOGRAPH 15-4 • Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug with analgesic, anti-inflammatory and antipyretic mechanism and actions similar to aspirin, however with little anti-platelet activity; it inhibits cyclo-oxygenase enzymes non-selectively and thus reduces production of prostaglandins, leading to less pain and inflammation.

Indications

Ibuprofen is indicated for the treatment of pain, especially pain due to inflammation such as headache, and fever, arthritis (osteo-, rheumatoid and idiopathic), heavy menstrual bleeding and period pain.

Pharmacokinetics

Ibuprofen is mainly administered orally, as tablets, capsules, oral liquid or infant drops; also as a topical gel. After PO administration, ibuprofen is well absorbed, with peak levels (taken on an empty stomach) reached in about 45 minutes. The plasma-protein binding of ibuprofen is about 99%; drug interactions are possible with other drugs bound to the same site on plasma albumin. Ibuprofen is metabolised in the liver to two major propionic acid metabolites, both inactive. Approximately 95% of ibuprofen is excreted via the urine, mostly as inactive metabolites. The plasma half-life of ibuprofen is in the range 1.9–2.2 hours.

Drug interactions

Refer to Drug Interactions 47-1. In addition, -conazole antifungals may inhibit the metabolism of ibuprofen, thus increasing its concentration and the risk of adverse effects; dosage may need to be reduced and effects monitored. The antiplatelet activity of concurrent aspirin may be reduced; if regular use is required, an alternative NSAID to ibuprofen may be preferred. The 'triple whammy' combination of an NSAID with a diuretic and an ACE inhibitor or angiotensin receptor inhibitor must be avoided.

Adverse reactions

The most common adverse reactions reported are gastrointestinal (nausea, heartburn, cramping), tinnitus, rash, fluid retention and dizziness.

Warnings and contraindications

Avoid the use of ibuprofen in people with history of gastrointestinal or cardiovascular problems, previous hypersensitivity reactions, with severe renal or hepatic impairment or in third trimester of pregnancy (category C). Precautions should be taken in patients with enhanced risk of cardiovascular events, hypertension or asthma.

Dosage and administration

Oral dose for adults is 200–400 mg 3 or 4 times per day, maximum 2400 mg daily. Topical 5% gel is applied to affected area up to 4 times daily.

Based on information from *Australian Medicines Handbook 2013* and New Zealand Medsafe database (www.medsafe.govt.nz/medicines).

CLINICAL INTEREST BOX 15-8
Analgesia for an injured child

A 4-year-old boy is brought to the emergency department of the local hospital with a swollen, painful and deformed left forearm after falling off a trampoline. He has previously been in good health, with no known allergies, and his routine immunisations are up-to-date. He has a past medical history of infrequent episodic asthma, and his weight is 19 kg. While in the waiting room, he is given a single oral dose of the hospital's combined paracetamol–codeine liquid preparation StopPain, containing 120 mg of paracetamol and 5 mg of codeine phosphate per 5 mL. Clinical assessment shows no additional injuries. Plain film X-rays reveal displaced mid-shaft fractures of his radius and ulna bones, with a moderate degree of angulation. After fasting for 2 hours since his last snack of food or liquid, he has procedural sedation in the department to permit reduction and plastering of his fractured arm; good sedation is safely achieved with a mix of 60% inhaled oxygen and 40% inhaled nitrous oxide for approximately 12 minutes; he is monitored closely for asthma symptoms. He makes a good recovery with rapid return to his normal conscious state, and is discharged home.

His parents ask about pain relief for him for the next few days. They are reminded that immobilising and elevating the injured limb will provide good analgesia especially overnight, and given prescriptions for paracetamol 15 mg/kg qid and ibuprofen 10 mg/kg tds, regularly for 48 hours, then on an 'as necessary' basis.

(Acknowledgements to Dr Philippa Shilson, Paediatrician.)

in diabetic neuropathy and post-herpetic neuralgia, but patient response is variable. It is also useful as adjunctive therapy in partial seizures. The related **gabapentin**, an anticonvulsant drug (see Chapter 17), is also effective in the relief of neuropathic pain. Adverse reactions include dizziness, sedation and incoordination, ocular dysfunctions and weight gain. Doses need to be reduced in renal impairment, and prescribers are warned against stopping the drugs abruptly.

Capsaicin

Capsaicin, an alkaloid found in chilli peppers, is formulated into topical creams for treatment of neuralgias, arthritic pain and pain associated with cystitis and HIV infection. It is said to activate capsaicin receptors; on application it causes an initial release and then a depletion of substance P from nerve fibres, which eventually results in a decrease in pain transmission.

Other drugs useful for their analgesic effects

- Local anaesthetics, e.g. lignocaine, EMLA cream (see Chapter 14)
- General anaesthetics, e.g. sevoflurane, nitrous oxide, ketamine and methoxyflurane (see Chapter 14)
- Cannabinoids, i.e. derivatives of the marijuana plant *Cannabis sativa*, main active ingredient Δ^9-tetrahydrocannabinol (THC; see Chapter 21); its psychopharmacological actions include analgesic effects mediated via δ- and κ-opioid receptors. THC enhances the analgesic potency of morphine, and allows lower doses of opioids to be used in pain syndromes resistant to opioids alone. A mouth spray formulation is being trialled in cancer pain
- Specific antimigraine drugs, including 5-hydroxytryptamine (5-HT, serotonin) agonists (sumatriptan) and antagonists (methysergide), and vasoconstrictors (ergot alkaloids) (see Chapter 20)
- Natural remedies, in addition to opium and willow bark that provide morphine and aspirin, respectively, include clove oil, feverfew and kava (see Clinical Interest Box 15-9 later), and sugar solutions for infants (described earlier).

New approaches

New pharmacological approaches to pain management include drugs that:

- enhance the inhibitory effects of adenosine on nociceptors
- mimic the actions of analgesic neuropeptides, e.g. nociceptin/orphanin FQ, the natural ligand of the opioid receptor-like 1 receptor
- inhibit enzymes inactivating enkephalins or endorphins (opiorphin)
- inhibit fatty acid amide hydrolase, and thus prolong the actions of endogenous cannabinoids.

Adjuvants to analgesics

Adjuvant medications are used in combination with opioid or NSAID analgesics to enhance pain relief or to treat symptoms that exacerbate pain. **Adjuvant analgesic** medications include anticonvulsants, antidepressants, antihistamines, corticosteroids, antidysrhythmics, psychostimulants and clonidine as follows:

- Tricyclic antidepressants and membrane-stabilising agents, such as some anticonvulsants and antidysrhythmic agents, may be useful in neuropathic pain and are often used in combination with opioids for cancer-associated nerve pain; the mechanism is via blockade of sodium channels. The analgesic actions of nimodipine and gabapentin may be due to blockade of calcium channels.
- Corticosteroids such as dexamethasone help relieve pain associated with inflammation, swelling and space-occupying lesions, e.g. for cancer pain that originates in a restricted area such as intracranially, alongside a nerve root or in pelvic, neck or hepatic areas.
- Psychoactive drugs, including phenothiazines and benzodiazepines, may be useful for their sedating, antianxiety and muscle-relaxing properties.

- Bisphosphonates (which reduce bone turnover) are sometimes useful for metastatic or osteoporotic bone pain, and antispasmodics (which relax smooth muscle) for colic pain.
- Clonidine, a centrally acting α_2-adrenergic agonist and antihypertensive agent, has been tried for the treatment of pain associated with reflex sympathetic dystrophy, diabetic neuropathy, post-herpetic neuralgia, spinal cord injury, phantom pain and pain in cancer patients who are opioid-tolerant. Clonidine is administered to enhance spinal anaesthesia via spinal injection, which minimises cardiovascular and other autonomic effects, and is effective in treating opioid withdrawal reactions by reducing autonomic hyperactivity. It was formerly used as a preventive treatment in migraine, but clinical trials have failed to prove benefit.
- NMDA receptor channel modulators, such as dextromethorphan, phencyclidine and amantadine derivatives, are showing promise as analgesics in neuropathic pain by inhibiting NMDA receptors involved in pain transmission. Ketamine, a general anaesthetic (see Chapter 14), is an antagonist at NMDA receptors and, in sub-anaesthetic doses, helps relieve chronic neuropathic pain; other NMDA receptor antagonists are being developed.

Non-pharmacological analgesic techniques

Non-pharmacological analgesic methods include:

- first aid techniques: RICE (**r**est, **i**ce, **c**ompression, **e**levation); heat packs and cold packs (Garra et al 2010)
- physiotherapy: exercise techniques that improve strength and flexibility, muscle relaxation techniques, massage, trigger-point therapy and hydrotherapy
- counter-irritants: scratching, liniments, rubefacients (substances that redden the skin by causing vasodilation)
- transcutaneous electrical nerve stimulation (TENS): passing small electrical currents into the spinal cord or sensory nerves via electrodes applied to the skin
- acupuncture: a technique from traditional Chinese medicine in which needles are inserted into the skin at specific points; acupuncture releases endorphins and enkephalins and may also block gates in the dorsal horn regions (possibly via inhibitory 5-HT pathways); excitatory amino acid and autonomic neurotransmitters and inflammatory mediators are also affected, and there is a major placebo effect (see Lin and Chen [2008])
- psychotherapeutic methods: hypnosis, behaviour modification, biofeedback techniques, assertiveness training, art and music therapy, meditation and the placebo effects induced by various methods
- surgery: neurosurgical techniques in chronic pain resistant to other management procedures; neurectomy (removal of part of a nerve), leucotomy (removal of part of the white matter of the CNS), sympathetic chain ablation, cortical ablation (removal of part of the cerebral cortex) and neurotomy by radiofrequency
- community support groups, family therapy and support, occupational therapy to assist with activities of daily living and use of orthoses
- complementary and alternative medicine (CAM) in acute pain: effective methods include relaxation, music therapy, self-hypnosis, acupuncture, spinal manipulation, biofeedback and cognitive behavioural therapy
- CAM in the treatment of chronic pain and cancer pain: long-term effects of therapies have rarely been studied; some short-term pain relief of pain, anxiety and depression from herbs and natural supplements (see Clinical Interest Box 15-9), relaxation therapy, aromatherapy, Chinese herbs, acupuncture, therapeutic touch, education, cognitive behavioural therapy and biofeedback (Hassed 2013).

CLINICAL INTEREST BOX 15-9
Herbal remedies for pain

The most important herbal remedies for pain are, of course, morphine and codeine in opium extracts from the poppy *Papaver somniferum* and salicylates from the bark of the willow tree *Salix alba* and from the herb meadowsweet (*Filipendula ulmaria*).

Extracts of bark from trees of the willow family (*Salicaceae*) were used medicinally in ancient times. In the 18th century in England, the Rev Edward Stone searched for a remedy for 'the ague' (fevers, shivering, rigor and rheumatism), and tested extracts of willow bark with great success. Salicin, the bitter glycoside of the *Salix* species, was extracted in 1827 and found to contain saligenin, an active ingredient from which salicylic acid was prepared. Sodium salicylate was first used in 1875, and acetylsalicylic acid was introduced into medicine in 1899 as aspirin. The trade name Aspro was popularised by the Nicholas drug company in Australia. Many other derivatives of salicylic acid have been synthesised and trialled; still in use are methyl salicylate (present in oil of wintergreen), salicylamide and choline salicylate.

Many other plants also have analgesic properties, including the following, which have been clinically tested and proven:

- cloves, the dried flower buds of *Eugenia* species, containing the oil eugenol, which has analgesic, anti-inflammatory, antimicrobial and antiplatelet activities; clove oil has

CLINICAL INTEREST BOX 15-9 Continued

traditional use in dentistry as an analgesic and antiseptic; it depresses nociceptors and inhibits PG synthesis

- feverfew, the leaves and flowering tops of the plant *Tanacetum parthenium*, containing many active ingredients including the terpene parthenolide; feverfew has long been used to treat headaches, arthritis and fever, and is effective prophylactically against migraine headache
- kava kava, a beverage prepared by Pacific Islands people from the root of *Piper methysticum*; the lipid-soluble lactones and flavonoids have mainly CNS effects (sedative and anxiolytic, via various transmitter receptors) as well as analgesic actions (via inhibition of COX enzymes) and local anaesthetic effects
- St John's wort, used since ancient times to rid the body of evil spirits and treat neuralgia, neuroses and depression; the herb is mainly used for its antidepressant actions, which mimic those of the serotonin selective reuptake inhibitors such as fluoxetine; analgesic actions are due to modulation of both opioid receptors and COX enzyme expression
- other natural extracts and supplements with analgesic properties, such as devil's claw, ginger, ginseng, lemon balm, stinging nettle and shark cartilage
- in Australian Indigenous bush medicine, several traditional remedies are available to relieve the symptoms of headaches: the leaves of small-leaf clematis (*Clematis microphylla*), stinkwood (*Ziera* spp.) or *Melaleuca* species are crushed and the vapour inhaled, or leaves bound around the head to relieve pain.

Adapted from several sources, including Braun and Cohen (2010).

DRUGS AT A GLANCE 15: Analgesics

THERAPEUTIC GROUP	PHARMACOLOGICAL GROUP	KEY EXAMPLES	PREGNANCY SAFETY CATEGORY	KEY PAGES
Opioid analgesics (narcotic analgesics)	Opioid receptor agonists	morphine	C	319–325
		codeine	A	342
		fentanyl	C	327, 342
	Opioid/SSRI	tramadol	C	326
Opioid antagonists	Opioid receptor antagonists	naloxone	B1	328
		naltrexone	B3 (avoid)	328
Non-opioid analgesics	Antipyretic analgesics (NSAIDs)	aspirin	C	329–331
		paracetamol	A	329–333
		ibuprofen	C	331, 333
	GABA analogues	gabapentin	B1	332
	Irritants	capsaicin	(may be used on small areas)	334
	NMDA antagonists	ketamine	B3	334,335
Adjuvant drugs	Tricyclic antidepressants	nortriptyline	C	334
	Membrane-stabilising agents, anticonvulsants	carbamazepine	D	334
	Corticosteroids	dexamethasone	A	334
	α_2-adrenoceptor agonists	clonidine	B3	334–335

GABA = gamma-aminobutyric acid; NMDA = *N*-methyl-D-aspartate; SSRI = selective serotonin reuptake inhibitor.
Pregnancy safety categories: Most analgesics are classified in Category C—opioids because they can cause respiratory depression in the newborn infant and prolonged use during pregnancy can lead to withdrawal symptoms in the neonate; and NSAIDs (other than paracetamol) because, when given late in pregnancy, inhibition of prostaglandin synthesis can cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation and delayed labour and birth.

KEY POINTS

- Pain is a common health problem, with sensory and emotional components contributing to suffering that disables and distresses people.
- Physiological theories of pain involve nociceptors, ascending afferent pathways of sensory nerves and spinothalamic tracts and descending efferent pathways from the cortex, which modulate dorsal-horn 'gating' mechanisms.
- Many neurotransmitters and other chemical factors are involved in pain sensation; analgesic drugs in particular affect endorphins and prostaglandins as mediators.
- Pain may be classified by its time course and origin, and assessed by its severity.
- Pain is often inadequately or inappropriately treated because of attitudes, fears and biases of health professionals, patients and family.
- Clinical principles of pain management emphasise the importance of adequate regular doses of appropriate analgesics, stepping up the analgesic ladder as necessary, with adjunctive care.
- Many effective pharmacological and non-drug methods are available for the treatment and/or prevention of pain. Assessment tools, pain scales and clinical guidelines are the basis for an effective pain management program.
- The opioids are strong analgesic drugs that are agonists centrally on opioid receptors. Opioid antagonists are used to treat adverse effects, overdoses or dependence.
- The non-narcotic analgesics, or non-steroidal anti-inflammatory drugs, include aspirin, paracetamol and ibuprofen. These act by inhibiting production of prostaglandins and may also have antipyretic and antiplatelet actions.
- Health professionals need to be informed on the pharmacodynamics and pharmacokinetics of these agents and to be able to discuss choice of appropriate analgesic agents in a wide variety of patient populations and to recognise adverse effects.

REVIEW EXERCISES

1 What are the primary myths or fears that interfere with healthcare professionals providing adequate pain management?

2 Describe the aetiology and recommended drug therapy for nociceptive, neuropathic and breakthrough pain syndromes.

3 Mr Brown is a 59-year-old man with metastatic disease of unknown origin. He reports his pain as 9 on a scale of 1 (least pain) to 10 (most severe pain). His prescriber ordered Panadeine Forte (paracetamol 500 mg with codeine phosphate 30 mg) 1–2 tablets every 6 hours as required for pain. Two hours after receiving two tablets of this medication, Mr Brown is still in very severe pain. Was this order appropriate for the reported pain level? How might the prescription be improved? What adjuvant medications and non-pharmacological interventions would you suggest, and why?

4 Review at least four potential issues to be considered when selecting an analgesic for an elderly patient. Name three analgesics that should be avoided for use in the elderly patient, explaining the reasons.

5 Name the three primary opioid receptors in the CNS and describe effects mediated through stimulation of these receptors.

6 Discuss factors associated with legislative approval of heroin for intractable pain.

7 Describe the transmitters and other chemical factors involved in the pain sensation and explain how the two main groups of analgesic drugs affect these mediators.

8 Compare the main pharmacological actions and common adverse effects of the opioids and of the non-narcotic analgesics.

9 Outline the stages in the stepwise management of pain, giving examples of appropriate drugs.

10 Describe the main symptoms of overdose with the following drugs and the management steps in treatment of overdose: aspirin, paracetamol, morphine.

11 Questions related to the case study in Clinical Interest Box 15-8:

   a Would you need to change your plans for procedural sedation and post-injury analgesia if he had experienced more severe and unpredictable asthma attacks recently?