

# 8 Symptom management

## 8.2 The management of pain

### 8.2.3 Opioid analgesic therapy

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#### Introduction

Treatment with analgesic drugs is the mainstay of cancer pain management.<sup>(1,2)</sup> Although concurrent use of other approaches and interventions may be appropriate in many patients, and necessary in some, analgesic drugs are needed in almost every case. Drugs whose primary clinical action is the relief of pain are conventionally classified on the basis of their activity at opioid receptors as either opioid or non-opioid analgesics. A third class, adjuvant analgesics, are drugs with other primary indications that can be effective analgesics in specific circumstances. The major group of drugs used in cancer pain management are the opioid analgesics.

During the last 20 years there has been a dramatic increase in our knowledge of the sites and mechanism of action of the opioids. The development of analytical methods has also been of great importance in facilitating pharmacokinetic studies of the disposition and fate of opioids in patients. More recently advances in genomic research have indicated the potential importance of pharmacogenetic factors in the response to opioid analgesics.<sup>(3)</sup> These studies have begun to offer us a better understanding of some of the sources of variation between individuals in their response to opioids and to suggest ways of minimizing some of their adverse effects. Although there are gaps in our knowledge of opioid pharmacology, the rational and appropriate use of these drugs is based on the knowledge of their pharmacological properties derived from well-controlled clinical trials.

#### Terminology

In this chapter and throughout this text, we have adopted the following conventions in terminology.

*Opiate* is a specific term that is used to describe drugs (natural and semi-synthetic) derived from the juice of the opium poppy. For example, morphine is an opiate but methadone (a completely synthetic drug) is not.<sup>(4)</sup>

*Opioid* is a general term that includes naturally occurring, semi-synthetic, and synthetic drugs which produce their effects by combining with opioid receptors and are stereospecifically antagonized by naloxone. In this context we refer to opioid agonists, opioid antagonists, opioid peptides, and opioid receptors.

*Narcotic* is commonly used to describe morphine-like drugs and other drugs of abuse. The term is derived from the Greek *narke*, meaning numbness or torpor. Since this is an imprecise and pejorative term that is not useful in a pharmacological context, its use with reference to opioids is discouraged. The term narcotic is not used in this book.

#### Opioid receptors

Opioids are agonists at highly specific receptor sites, and there is general agreement on the existence of at least three types of opioid receptor: the morphine receptor  $\mu$  (mu), the  $\kappa$  (kappa) receptor at which the prototype agonist is ketocyclazocine, and the enkephalin receptor  $\delta$  (delta). A fourth receptor,  $\sigma$  (sigma), was originally included in this group. However, actions mediated through  $\sigma$  receptors are not reversed by naloxone so it is not a true opioid receptor. The  $\mu$  receptors have been further sub-classified into two distinct sub-types ( $\mu 1$  and  $\mu 2$ ), as have the  $\delta$  receptors ( $\delta 1$  and  $\delta 2$ ). Kappa receptors have been divided into  $\kappa 1$ ,  $\kappa 2$ , and  $\kappa 3$  sub-types. Recently, several of these receptors have been successfully cloned.

In animal models, some laboratories have cloned up to 10  $\mu$  receptor sub-types.<sup>(5)</sup> However, the functional significance of these 'spliced variants' remains unclear at present.

Table 1 shows the putative effects mediated by the three main opioid receptors.<sup>(6)</sup> This classification is based on the original description by Martin et al.<sup>(7)</sup> The effects presumed to be mediated at  $\mu$  receptors have been defined as a result of both human and animal studies, while the effects mediated at  $\kappa$  receptors derive predominantly from animal models.  $\kappa$  Receptors mediate analgesia that persists in animals made tolerant to  $\delta$  agonists;  $\kappa$  agonists produce less respiratory depression and miosis than  $\mu$  agonists. It is assumed that opioid receptors mediate the sedative and mental clouding effects of opioids, in addition to their other pharmacological actions.

Opioid receptors are found in several areas of the brain, particularly in the periaqueductal grey matter, and throughout the spinal cord. Supraspinal systems have been described for  $\mu 1$ ,  $\kappa 3$ , and  $\delta 2$  receptors, whereas  $\mu 2$ ,  $\kappa 1$ , and  $\delta 1$  receptors modulate pain at the spinal level.<sup>(8)</sup> Our understanding of the effect profiles of opioid receptors remains incomplete, as new advances make it clear that their disposition and structure are extremely complex.

#### The molecular pharmacology of opioids

Molecular biology techniques have enabled the primary amino acid sequence of the human  $\mu$ ,  $\kappa$ , and  $\delta$  opioid receptors to be determined. The pharmacological and functional properties of the cloned receptors, the development of 'knockout' animals (which are deficient in a receptor or part of a receptor), and the manipulation and substitution of various amino acids in critical domains of the various opioid receptors are providing new

**Table 1** Responses mediated by activation of opioid receptors

Receptor	Response on activation
$\mu$	Analgesia, respiratory depression, miosis, euphoria, reduced gastrointestinal motility
$\kappa$	Analgesia, dysphoria, psychotomimetic effects, miosis, respiratory depression
$\delta$	Analgesia

information on receptor function and organization that will lead to an increased understanding of opioid neurotransmission at the molecular level and of the factors controlling the development of responses to opioid drugs.

The three opioid receptor genes, encoding mu (MOR), delta (DOR), and kappa (KOR) have been cloned. The binding affinities of a range of opioids to the  $\mu$ -,  $\kappa$ -, and  $\delta$ -opioid receptors and also to the cloned  $\mu$  receptor have been examined in animals. The animal data indicate that while the commonly prescribed opioids (agonists and antagonists) bind preferentially to the  $\mu$  receptor, they also interact with all three receptor types. Morphine and normorphine (a minor metabolite of morphine) show the greatest relative preference for the  $\mu$  receptor. Methadone (which also has some NMDA-receptor blocking activity) shows significant binding to  $\delta$  receptors, while buprenorphine, and to a lesser extent naxolone, avidly bind to all three receptor types. There is evidence (albeit inconsistent) that the D-enantiomer of methadone blocks the NMDAA receptor. The binding affinity of buprenorphine to the  $\mu$  receptor is much greater than that of naloxone, which explains why the latter only partially reverses buprenorphine toxicity.

Animal data also indicate that codeine and diamorphine have very poor binding to opioid receptors, which reinforces the possibility that both are prodrugs where the pharmacologically active species are morphine<sup>(9)</sup> and 6-monoacetyl morphine,<sup>(10)</sup> respectively. Oxycodone may also act through an active metabolite, though there are some data which suggest that this is not the case.<sup>(11)</sup>

Pethidine is considered to be a potent  $\mu$  receptor agonist, but it does bind weakly to all three opioid receptors. Ketobemidone has a lower affinity for the  $\mu$  receptor than does morphine, but it shows greater discrimination for this receptor compared to  $\kappa$  receptors. The binding of both of these opioids to the  $\delta$  receptor is similar.<sup>(12)</sup>

The binding of morphine, methadone, buprenorphine, and naloxone to the cloned human  $\mu$  receptor shows excellent congruence with the animal data.<sup>(13,14)</sup> Fentanyl shows a similar binding affinity, while codeine demonstrates greater binding affinity to the cloned human receptor. Thus, for these commonly administered opioids, there is no great variability in their affinity for the human  $\mu$  receptor.

The clinical relevance of these data is that different opioids act in different ways. We are aware too from anecdotal clinical experience that there is considerable interindividual variability in response to each opioid and this reinforces our need to assess an individual's response to opioid analgesia carefully. It would be premature to extrapolate from laboratory data, which in many instances have not yet been replicated, to the clinic. However, these data increasingly inform the clinical use of these drugs and will be particularly relevant to new approaches to their use such as 'opioid switching'.

## Agonists, antagonists, potency, and efficacy

Based on their interactions with the various receptor sub-types, opioid compounds can be divided into agonist, agonist-antagonist, and antagonist classes (Table 2).

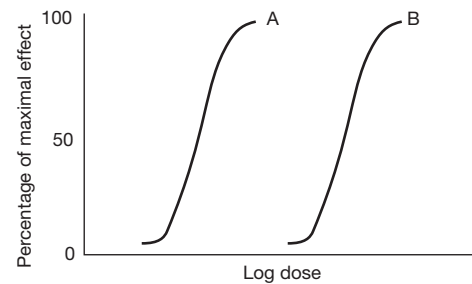
### Agonists

An agonist is a drug that has affinity for and binds to cell receptors to induce changes in the cell that stimulate physiological activity. The agonist opioid drugs have no clinically relevant ceiling effect to analgesia. As the dose is raised, analgesic effects increase in a log linear function, until either analgesia is achieved or dose-limiting adverse effects supervene. Efficacy is defined by the maximal response induced by administration of the active agent. In practice, this is determined by the degree of analgesia produced following dose escalation through a range limited by the development of adverse effects. Potency, in contrast, reflects the dose-response relationship. Potency is influenced by pharmacokinetic factors (i.e. how much of the drug enters the body systemic circulation and then reaches the receptors) and by affinity to drug receptors.

The concepts of efficacy and potency are illustrated in Fig. 1, which shows the dose-response curves for two drugs A and B. If the logarithm of

**Table 2** Classification of opioid analgesics into agonist, agonist-antagonist and antagonist classes

Agonists	Partial agonists
Morphine	Buprenorphine
Codeine	Agonist-antagonists
Oxycodone	Pentazocine
Dihydrocodeine	Butorphanol
Oxymorphone	Nalbuphine
Pethidine	Dezocine
Levorphanol	Meptazinol
Hydromorphone	Antagonists
Methadone	Naloxone
Fentanyl	Naltrexone
Dextropropoxyphene	
Diamorphine (heroin)	
Tramadol	
Phenazocine	
Dextromoramide	
Dipipanone	



**Fig. 1** Dose-response curves for two full opioid agonists (A and B) similar in efficacy but different in potency (A is more potent than B).

dose is plotted against response an agonist will produce an S-shaped or sigmoid curve. The efficacy of the two drugs, defined by maximum response is the same. Drug A produces the same response as B but at a lower dose, and therefore is described as more potent.

### Antagonist

Antagonist drugs have no intrinsic pharmacological action but can interfere with the action of an agonist. Competitive antagonists bind to the same receptor and compete for receptor sites, whereas non-competitive antagonists block the effects of the agonist in some other way.

### Agonist-antagonist

The agonist-antagonist analgesics can, in turn, be subdivided into the mixed agonist-antagonists and the partial agonists, a distinction also based on specific patterns of drug-receptor interaction. Both the partial agonist and agonist-antagonist drugs have a ceiling effect for analgesia, and although they produce analgesia in the opioid-naive patient, in theory they can precipitate withdrawal in patients who are physically dependent on morphine-like drugs. For these reasons, they have been considered generally to have a limited role in the management of patients with cancer pain.

### Mixed agonist-antagonists

The mixed agonist-antagonist drugs produce agonist effects at one receptor and antagonist effects at another. Pentazocine is the prototype agonist-antagonist: it has agonist effects at  $\kappa$  receptors and weak  $\mu$  antagonist actions. Thus in addition to analgesia, pentazocine may produce  $\kappa$ -mediated psychotomimetic effects not seen with full or partial  $\mu$  agonists.

When a mixed agonist–antagonist is administered together with an agonist, the antagonist effect at the  $\mu$  receptor can generate an acute withdrawal syndrome.

### Partial agonists

A partial agonist has low intrinsic activity (efficacy) so that its dose–response curve exhibits a ceiling effect at less than the maximum effect produced by a full agonist. Buprenorphine is the main example of a partial agonist opioid. Increasing the dose of such a drug above its ceiling does not result in any further increase in response. This phenomenon is illustrated in Fig. 2 in which C is a partial agonist. C is more potent than B (in the lower part of the curve it will produce the same response at a lower dose), but is less effective than both A and B because of its ceiling effect.

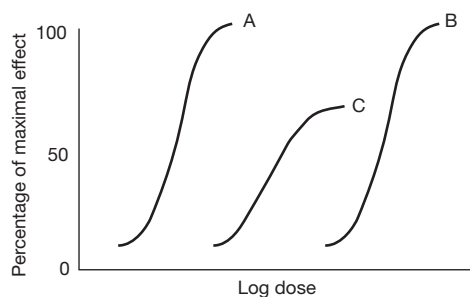
When a partial agonist is administered together with an agonist, displacement of the agonist can cause a net reduction in pharmacological action which may be sufficient to generate an acute withdrawal syndrome. Whilst this is a theoretical possibility with morphine and buprenorphine, no such interaction has been reported. Similarly, it has been suggested that the effects of morphine may be blocked in a patient switched from buprenorphine, because of the prolonged action of buprenorphine and the assumption that it will ‘antagonise’ the effect of morphine. This has been one of the reasons why buprenorphine has not been in cancer pain management. However, the recent development of a transdermal formulation of buprenorphine may encourage its use in chronic cancer pain (and chronic non-cancer pain). An analgesic ceiling with buprenorphine is only reached at doses of 8–16 mg or more in 24 h.<sup>(15)</sup> When used in usual recommended doses (for example, two patches of 70  $\mu\text{g}/\text{h}$  of transdermal buprenorphine, equivalent to 3–4 mg per 24 h) buprenorphine can be considered a full  $\mu$  agonist since at these doses its effect will lie on the linear part of the dose–response curve.

### Relative potency and equianalgesic doses

Relative potency is the ratio of the doses of two analgesics required to produce the same analgesic effect. By convention the relative potency of each of the commonly used opioids is based upon a comparison with 10 mg of parenteral morphine. Data from single- and repeated-dose studies in patients with acute or chronic pain have been used to develop an equianalgesic dose table (Table 3) that provides guidelines for dose selection when the drug or route of administration is changed. The information contained in the equianalgesic dose table does not represent standard doses, nor is it intended as an absolute guideline for dose selection. Many variables may influence the appropriate dose for an individual patient, including intensity of pain, prior opioid exposure in terms of drug, duration, and dose (and the degree of cross-tolerance that this confers), age, route of administration, level of consciousness, metabolic abnormalities (see below), and genetic polymorphism in the expression of relevant enzymes or receptors.

### Dose–response relationship

As noted above, there is no ceiling to the analgesic effects of full agonist opioids. As the dose is raised, analgesic effects increase as a log linear



**Fig. 2** Dose–response curves for two full opioid agonists (A and B) and a partial opioid agonist C.

function. In practice, the appearance of adverse effects, including confusion, sedation, nausea, vomiting, or respiratory depression, imposes a limit on the useful dose of an opioid agonist. Thus the efficacy of any particular drug in an individual patient will be determined by the degree of analgesia produced following dose escalation to intolerable and unmanageable side-effects.

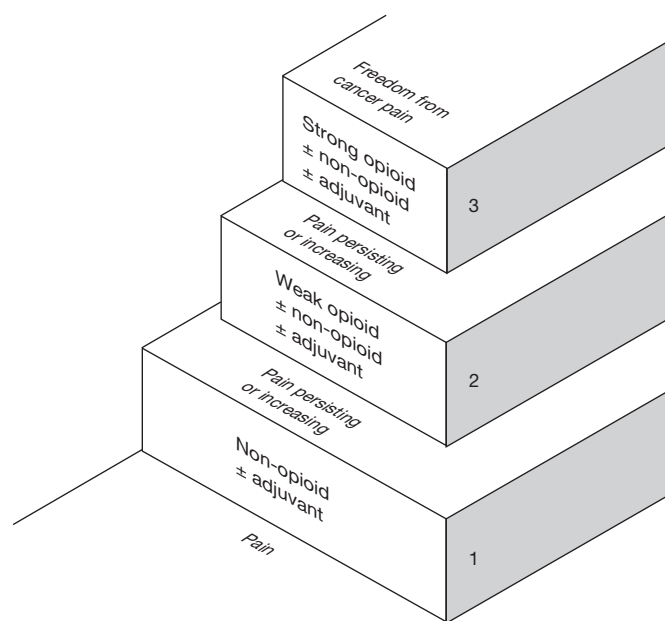
## The role of opioids in the management of cancer pain

Analgesic therapy with opioids, non-opioids, and adjuvant analgesics is developed for the individual patient through a process of continuous evaluation so that a favourable balance between pain relief and adverse pharmacological effects is maintained.

### The analgesic ladder

An expert committee convened by the Cancer and Palliative Care Unit of the World Health Organization (WHO) proposed a structured approach to drug selection for cancer pain, which has become known as the ‘WHO analgesic ladder.’<sup>(16)</sup> When combined with appropriate dosing guidelines, this approach is capable of providing adequate relief to 70–90 per cent of patients.<sup>(17–23)</sup> Emphasizing that the intensity of pain, rather than its specific aetiology, should be the prime consideration in analgesic selection, the approach advocates three basic steps (Fig. 3):

1. Patients with mild cancer-related pain should be treated with a non-opioid analgesic, which should be combined with adjuvant drugs if a specific indication for these exists. For example, a patient with mild to moderate arm pain caused by radiation-induced brachial plexopathy may benefit when a tricyclic antidepressant is added to paracetamol (acetaminophen).<sup>(24,25)</sup>
2. Patients who are relatively non-tolerant and present with moderate pain, or who fail to achieve adequate relief after a trial of a non-opioid analgesic, should be treated with an opioid conventionally used for mild to moderate pain (formerly known as a ‘weak’ opioid). This treatment is typically accomplished using a combination product containing a non-opioid (e.g. aspirin or paracetamol) and an opioid



**Fig. 3** The WHO three-step analgesic ladder. (Reproduced with permission from ref. 2.)

**Table 3** Opioid analgesics (pure  $\mu$  agonists) used for the treatment of chronic pain

Morphine-like agonists	Equi-analgesic doses <sup>a</sup>	Half-life (h)	Peak effect (h)	Duration (h)	Toxicity	Comments	Oral bioavailability (%)	Active metabolites
Morphine	10 s.c. 20–60 p.o. <sup>b</sup>	2–3 2–3	0.5–1 1.5–2	3–6 4–7	Constipation, nausea, sedation most common; respiratory depression rare in cancer patients	Standard comparison for opioids; multiple routes available	20–30	M6G
Sustained-release morphine	20–60 p.o. <sup>b</sup>	2–3	3–4	8–12		Twice daily administration	20–30	M6G
Sustained-release morphine	20–60 p.o. <sup>b</sup>	2–3	4–6	24		Once-a-day morphine approved in some countries	20–30	M6G
Hydromorphone	1.5 s.c. 7.5 p.o.	2–3 2–3	0.5–1 1–2	3–4 3–4	Same as morphine	Used for multiple routes	35–80	No
Oxycodone	20–30	2–3	1	3–6	Same as morphine	Combined with aspirin or acetaminophen, for moderate pain in USA; available orally without coanalgesic for severe pain	60–90	Oxymorphone
Sustained-release oxycodone	20–30	2–3	3–4	8–12				Oxymorphone
Oxymorphone	1 s.c. 10 p.r.	— —	0.5–1 1.5–3	3–6 4–6	Same as morphine	No oral formulation		Glucuronides
Meperidine (pethidine)	75 s.c.	2–3	0.5–1	3–4	Same as morphine + CNS excitation; contraindicated in those on MAO inhibitors	Not used for cancer pain due to toxicity in higher doses and short half-life	30–60	Norpethidine
Diamorphine	5 s.c.	0.5	0.5–1	4–5	Same as morphine	Analgesic action due to metabolites, predominantly morphine; only available in some countries		Morphine
Levorphanol	2 s.c. 4 p.o.	12–16	0.5–1	4–6	Same as morphine	With long half-life, accumulation occurs after beginning or increasing dose		No
Methadone <sup>c</sup>	10 s.c. 20 p.o. (see text)	12–>150	0.5–1.5	4–8	Same as morphine	Risk of delayed toxicity due to accumulation; useful to start dosing on p.r.n.	60–90	No
Codeine	130 s.c. 200 p.o.	2–3	1.5–2	3–6	Same as morphine	Usually combined with non-opioid	60–90	Morphine
Propoxyphene HCl (dextropropoxyphene)	—	12	1.5–2	3–6	Same as morphine plus seizures with overdose	Toxic metabolite accumulates but not significant at doses used clinically; usually combined with non-opioid	40	Norpropoxyphene

Propoxyphene napsylate (dextropropoxyphene)	—	12	1.5–2	3–6	Same as hydrochloride	Same as hydrochloride	40	Norpropoxyphene
Hydrocodone	—	2–4	0.5–1	3–4	Same as morphine	Only available combined with paracetamol; only available in some countries		Hydromorphone
Dihydrocodone	—	2–4	0.5–1	3–4	Same as morphine	Only available combined with aspirin or paracetamol in some countries	20	Morphine
Fentanyl	—	3–12	—	—	Same as morphine	Can be administered as a continuous i.v. or s.c. infusion; based on clinical experience, 100 µg/h is roughly equianalgesic to morphine 4 mg/h i.v.	25/buccal <2/oral	No
Fentanyl transdermal system	—	13–22	—	48–72	Same as morphine	Based on clinical experience 100 µg/h is roughly equianalgesic to morphine 4 mg/h; recent study indicates a ratio of oral morphine: transdermal fentanyl of 100 : 1	90/transdermal	No

<sup>a</sup> Dose that provides analgesia equivalent to 10 mg i.m. morphine. These ratios are useful guidelines when switching drugs or routes of administration.

<sup>b</sup> Extensive survey data suggest that the relative potency of i.m. : p.o. or s.c. : p.o., morphine of 1 : 6 changes to 1 : 2–3 with chronic dosing.

<sup>c</sup> When switching from another opioid to methadone, the potency of methadone is much greater than indicated in this table.

(such as codeine, oxycodone, or propoxyphene). This combination can also be coadministered with an adjuvant analgesic. The doses of these combination products can be increased until the maximum dose of the non-opioid analgesic is attained (e.g. 4000–6000 mg paracetamol); beyond this dose, the opioid contained in the combination product could be increased as a single agent, or the patient could be switched to an opioid conventionally used in step 3.

- Patients who present with severe pain, or who fail to achieve adequate relief following appropriate administration of drugs on the second step of the analgesic ladder, should receive an opioid conventionally used for moderate to severe pain (formerly known as a 'strong' opioid). This group includes morphine, diamorphine, fentanyl, oxycodone, phenazocine, hydromorphone, methadone, levorphanol, and oxymorphone. These drugs may also be combined with a non-opioid analgesic or an adjuvant drug. Clearly, the boundary between opioids used in the second and third steps of the analgesic ladder is somewhat artificial since low doses of morphine or other opioids for severe pain can be less effective than high doses of codeine or propoxyphene.

According to these guidelines, a trial of opioid therapy should be given to all patients with pain of moderate or greater severity.

The evidence of the long-term efficacy of this approach and the evidence base underlying its recommendations has been the subject of criticism.<sup>(26)</sup> Several other developments have also contributed to a reevaluation of the WHO ladder. The introduction of low-dose formulations of opioid agonists traditionally used for severe pain, and of other agents such as tramadol has widened the repertoire of agents suitable for the management of moderate pain (step 2). Indeed, many authorities now advocate the use of the same opioid for all pains of moderate or greater intensity.<sup>(27–30)</sup>

Despite these reservations, the guiding principle that analgesic selection should be primarily determined by the severity of the pain remains sound, and continues to be widely endorsed.<sup>(1,27,31)</sup>

## Opioid analgesics

The division of opioid agonists into 'weak' or 'strong' opioids, which was incorporated into the original analgesic ladder proposed by the WHO, was not based on fundamental differences in their pharmacology, but rather reflected the customary manner in which these drugs were used. In this chapter we will refer to opioids for mild to moderate pain and opioids for moderate to severe pain rather than 'weak' or 'strong' opioids. This terminology is now incorporated into the current version of the WHO analgesic ladder.

## Opioids for mild to moderate pain

### Codeine

Codeine (methylmorphine) is a naturally occurring opium alkaloid used as an analgesic, antitussive, and antidiarrhoeal agent (Fig. 4). Codeine is much less potent than morphine and produces its analgesic effects in part by binding to  $\mu$  opioid receptors but with low affinity and, in part through biotransformation to morphine by cytochrome P-450 CYP2D6 (sparteine oxygenase) which exhibits genetic polymorphism. Approximately 7 per cent of Caucasians lack CYP2D6 activity (poor metabolizers) due to inheritance of two non-functional alleles and in these individuals codeine has a diminished analgesic effect.<sup>(32,33)</sup>

Codeine phosphate is absorbed well from the gastrointestinal tract, but oral bioavailability varies considerably between individuals (from 12 to 84 per cent in one study<sup>(34)</sup>). The main metabolite is codeine-6-glucuronide, with much smaller amounts of norcodeine, morphine, and morphine 3- and 6-glucuronides also being produced.<sup>(35)</sup> The usual oral dose of codeine is 30–60 mg and its duration of action is 4–6 h.

Codeine is not generally given as a single agent when used orally as an analgesic, but is usually combined with a non-opioid and recent systematic

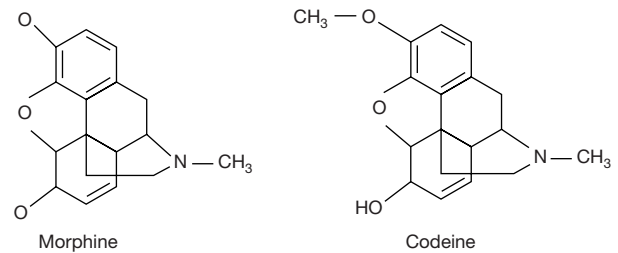


Fig. 4 The chemical structures of morphine and codeine.

reviews confirm that the combination of codeine and paracetamol is more effective than paracetamol alone.<sup>(36,37)</sup> A sustained-release formulation of codeine is available in some countries. When changing from regular administration of a codeine/non-opioid combination to morphine, patients receiving a total daily dose of 240–360 mg codeine are usually started on 60 mg morphine daily.

### Dihydrocodeine

Dihydrocodeine is a semi-synthetic analogue of codeine that is used as an analgesic, antitussive, and antidiarrhoeal agent. When administered by mouth, dihydrocodeine is equianalgesic to codeine. However, when administered parenterally it is approximately twice as potent as codeine. This may be explained by the consistently poorer bioavailability of dihydrocodeine (20 per cent), which probably results from hepatic presystemic metabolism.<sup>(38)</sup>

The usual starting dose is 30 mg every 4–6 h (by mouth), and this may be increased to 60 mg. However, dihydrocodeine appears to have a narrower therapeutic index than codeine, with a high incidence of adverse effects at the 60-mg dose. A controlled-release formulation of dihydrocodeine is available in several countries.

There have been a number of reports of severe toxicity associated with dihydrocodeine in patients with impaired renal function.<sup>(39,40)</sup> The mechanism is not clear because of the limited data available on the pharmacokinetics of this drug, although it seems most likely that the cause is accumulation of active glucuronide metabolites, as occurs with morphine.

There is confusion about the relative analgesic potency of dihydrocodeine. It seems reasonable to assume that oral dihydrocodeine is roughly equipotent to oral codeine, and to use a similar conversion ratio when changing to morphine.

### Dextropropoxyphene

Propoxyphene is a synthetic derivative of methadone, and its dextrorotatory stereoisomer dextropropoxyphene is responsible for its analgesic activity. Dextropropoxyphene is a  $\mu$  agonist with low receptor affinity similar to that of codeine. It is readily absorbed from the gastrointestinal tract with peak serum levels about 2 h after administration. The mean elimination half-life is about 12 h, with steady state levels being reached after 3–4 days of regular administration every 6–8 h. The half-life may be very long (over 50 h) in elderly patients.<sup>(41)</sup>

Dextropropoxyphene undergoes extensive first-pass metabolism. Its principal metabolite is norpropoxyphene, which is active but penetrates the brain to a much lesser extent and has much weaker opioid effects. Norpropoxyphene has a longer half-life (about 23 h) than dextropropoxyphene itself and accumulates in plasma.<sup>(42)</sup> Norpropoxyphene accumulation is associated with excitatory effects, including tremulousness and seizures.

The analgesic efficacy and relative potency of dextropropoxyphene have been questioned. This is in part because single-dose studies comparing aspirin, paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen 400 mg, mefenamic acid 250 mg, and fenoprofen 50 mg, have shown dextropropoxyphene to be a less effective

analgesic.<sup>(43)</sup> A more recent systematic review found that paracetamol alone is as effective as the combination of paracetamol with dextropropoxyphene,<sup>(44)</sup> though the studies included were again all single-dose studies. Single-dose studies may be misleading, as is the case with single-dose studies of oral morphine.

The extensive first-pass metabolism of dextropropoxyphene is dose dependent such that the systemic availability of the drug increases with increasing oral doses.<sup>(45)</sup> Thus, with regular administration, there is enhanced bioavailability and some degree of accumulation because of the long elimination half-lives of the parent drug and its main metabolite. Both dextropropoxyphene and norpropoxyphene reach plasma concentrations in the steady state which are five to seven times greater than those found after the first dose. Thus, there is a pharmacokinetic basis for believing that repeated doses of dextropropoxyphene are likely to be more effective than single doses. The usual starting dose of morphine for patients receiving dextropropoxyphene–paracetamol combinations every 4–6 h (representing 260–390 mg of dextropropoxyphene daily) is 60 mg per day.

### Toxicity of dextropropoxyphene

For a long time a combination of dextropropoxyphene and paracetamol was the most commonly prescribed analgesic in the United Kingdom and some Scandinavian countries, but it received much adverse publicity because of its lethal effects in overdose and fears about its addiction potential. Part of this concern was stimulated by its very widespread use. In addition to usual opioid adverse effects, propoxyphene may rarely induce a hepatotoxic reaction,<sup>(46)</sup> cardiac conduction disorder,<sup>(47)</sup> and potentially dangerous drug interactions have been reported when propoxyphene has been administered along with carbamazepine,<sup>(48)</sup> warfarin,<sup>(49)</sup> or alcohol.<sup>(50)</sup> At present, however, there is insufficient evidence to conclude that dextropropoxyphene is inherently more toxic than codeine or other opioids of similar efficacy, nor is there evidence that one is more effective than another.

### Oxycodone

Oxycodone is a semi-synthetic congener of morphine, which has been on the market for 80 years but until recently was only available in formulations which effectively circumscribed its use. In the United States, it has been prescribed in low-dose combination products with a non-opioid for oral administration (usually 5 mg of oxycodone with either aspirin or paracetamol) and has traditionally been used as a step 2 analgesic. In the United Kingdom and some other countries only a rectal suppository and no oral formulations have been available, so that it has been used only for patients unable to take oral medication.<sup>(51)</sup> Oxycodone has been more widely used by mouth as a first line step 3 opioid in Scandinavia where it has also been widely used as a post-operative opioid.<sup>(52)</sup> Recently, oxycodone has been produced as a single agent in new oral formulations, both normal release and sustained release, which has substantially improved the convenience of administration. In many countries sustained release oxycodone is available in 5, 10, 20, 40, and 80 mg formulations with a corresponding range of normal release formulations. Oxycodone is increasingly used as a step 3 opioid,<sup>(53–55)</sup> though the low-dose formulations allow it at step 2 also. Oxycodone probably provides the best example of the overlap in efficacy between opioids at steps 2 and 3.

### Tramadol

Tramadol is a centrally acting analgesic which possesses opioid agonist properties and may also activate monoaminergic spinal inhibition of pain.<sup>(56)</sup> It has modest affinity with  $\mu$  opioid receptors, with weak affinity to  $\delta$  and  $\kappa$  receptors, and its analgesic effect is reversed by naloxone. Unlike other opioids, it also inhibits the uptake of noradrenaline and serotonin, and in an animal model systemically administered yohimbine or ritanserin blocks tramadol-induced analgesia,<sup>(56)</sup> suggesting that this effect contributes significantly to the drug's analgesic action.

Tramadol can be administered orally, rectally, intravenously, subcutaneously, or intramuscularly. In many countries, it is available in both normal- and sustained-release formulations. Parenterally, 50–150 mg of tramadol is equianalgesic to 5–15 mg morphine.<sup>(57)</sup> There are insufficient data for a reliable assessment of its oral to parenteral relative analgesic potency and estimates range from 1 : 4<sup>(58)</sup> to 1 : 10.<sup>(59)</sup>

Recent studies have demonstrated the efficacy of oral tramadol in the management of chronic cancer pain of moderate severity.<sup>(58–60)</sup> Few patients with severe pain are adequately managed by tramadol.<sup>(59,61)</sup> Tramadol has a similar side-effect profile to morphine, but may cause less constipation and respiratory depression at equianalgesic doses.

## Opioids in combination with non-opioids

### The second step of the analgesic ladder

By convention, formulations combining aspirin or paracetamol with a low dose of codeine, oxycodone, or propoxyphene have been recommended for pain of moderate intensity (step 2 of the analgesic ladder). This recommendation was pragmatic rather than evidence based. It reflected the concern that in many parts of the world it would be unacceptable to use morphine or other potent opioids for moderate pain.

Overall, these combination preparations have frequently proved to be relatively ineffective because the dose of opioid was too low (e.g. codeine 8 or 16 mg). Indeed, in the validation studies of the WHO ladder few patients using these agents maintained adequate relief for more than a few weeks.<sup>(17)</sup> Additionally, these formulations all have a short duration of effect and require patients to use repeated doses every 3–4 h to achieve continuous analgesia in the setting of chronic pain.

The most frequently employed step 2 analgesics in cancer pain are combination preparations containing 300–500 mg paracetamol with 30 mg codeine, 32.5 mg dextropropoxyphene, or 5 mg oxycodone. The combination of dextropropoxyphene with paracetamol (coproxamol in the United Kingdom) has theoretical disadvantages of pharmacokinetic incompatibility (dextropropoxyphene has a much longer elimination half-life than paracetamol) and accumulation of dextropropoxyphene and its active metabolite norpropoxyphene. However, neither problem appears to have any clinical consequence in practice and this combination remains widely used. Codeine and paracetamol are pharmacokinetically more compatible, and at present either combination would be an appropriate choice.

Recent studies comparing single doses of opioid/non-opioid combinations with various NSAIDs in post-operative pain have shown advantages for the latter in terms of greater efficacy and less adverse effects.<sup>(62–64)</sup> Chronic use of NSAIDs may negate any advantage in terms of unwanted effects, although at present there are no comparative data for chronic cancer pain. NSAIDs are increasingly employed as step 2 analgesics.

Given the limitations of the conventional approach many clinicians now use a variety of single agent opioid agonists, some previously designated as 'step 3 opioids', in an appropriate dose, for moderate pain. Over recent years, sustained-release formulations of oxycodone, tramadol and morphine in dose formulations appropriate for pain of moderate severity have become widely available and are now often used in this setting. This practice is supported by evidence of efficacy.<sup>(54,60,65)</sup>

The partial agonist opioid buprenorphine also may be used in this setting since it has recently become available in a transdermal formulation. Preliminary experience has been reported in the management of moderate cancer pain.<sup>(66)</sup> A low-dose formulation of transdermal fentanyl is also under development and is designed for use in patients who may be opioid naive. There are potential dangers in the earlier use of the most potent opioids, particularly when administered in long acting formulations and more clinical trial data are required to clarify some of the issues surrounding these trends in opioid prescribing.

## Opioids for moderate to severe pain

### Morphine-like agonists

The morphine-like agonist drugs (Table 2) are widely used to manage cancer pain. Although they may differ from morphine in quantitative characteristics they qualitatively mimic the pharmacological profile of morphine, including both desirable and undesirable effects. Controversy has developed over the choice of an opioid drug, in part because of the dearth of well-controlled studies comparing the efficacy and side-effects of these drugs during chronic administration, and in part because of the large amount of survey data and anecdotal reports supporting one drug over another.

Clinicians in most countries have some choice when selecting which opioid drug(s) to prescribe, but the options can vary from country to country.

Morphine is still considered to be the opioid drug of choice by many practitioners<sup>(30)</sup> and has occupied this place throughout recorded history. However, some of the other potent  $\mu$  receptor agonists are gaining popularity for a variety of reasons. While greater choice is very important in analgesic therapy, it should not be forgotten that morphine is an excellent analgesic and maintains a key position and reference point for all opioids in our therapeutic armamentarium. Similarly, while there is theoretical evidence (on the basis of receptor binding profiles) that opioid combinations may give optimum analgesia with a more favourable side-effect profile, there is as yet no good clinical evidence to support such treatment strategies which are likely to be appropriate only in rare situations.

### Morphine

Morphine is a potent  $\mu$ -agonist drug that was first introduced into clinical use almost 200 years ago. It is the main naturally occurring alkaloid of opium derived from the poppy *Papaver somniferum* and is available for therapeutic use as the sulphate, hydrochloride, and tartrate. Recent evidence suggests that biosynthetic pathways for morphine exist in animal and human tissues such as liver, blood, and brain.<sup>(67)</sup> Its chemical structure is shown in Fig. 4. The WHO has placed oral morphine on the Essential Drug List, and preparations are available for oral, rectal, parenteral, and intraspinal administration.

### Bioavailability

Morphine is available in four oral formulations: an elixir, a normal-release tablet, a modified-release tablet or capsule (of which there are now several preparations using different sustained-release mechanisms), and sustained-release suspensions. Absorption of morphine after oral administration occurs predominantly in the alkaline medium of the upper small bowel (morphine is a weak base) and is more or less complete. After oral administration, extensive presystemic elimination of the drug occurs predominantly in the liver. In healthy volunteers and cancer patients, the average bioavailability for oral morphine is 20–30 per cent.<sup>(68–70)</sup> Like all other pharmacokinetic parameters, bioavailability demonstrates marked interindividual variability. In patients with normal renal function the plasma half-life (2–3 h) is somewhat shorter than the duration of analgesia (4–6 h). The pharmacokinetics remain linear with repetitive administration, and there does not appear to be autoinduction of biotransformation even following large chronic doses.<sup>(71)</sup>

Morphine is relatively hydrophilic and, when administered epidurally or intrathecally, it is not rapidly absorbed into the systemic circulation. This results in a long half-life in cerebrospinal fluid (90–120 min) and extensive rostral redistribution.<sup>(72)</sup>

### Metabolism

About 90 per cent of morphine is converted into metabolites (Fig. 5), principally the glucuronide conjugates morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G); minor metabolites include codeine, normorphine, and morphine ethereal sulphate. The liver appears to be the predominant site of metabolism in humans, although in animal models

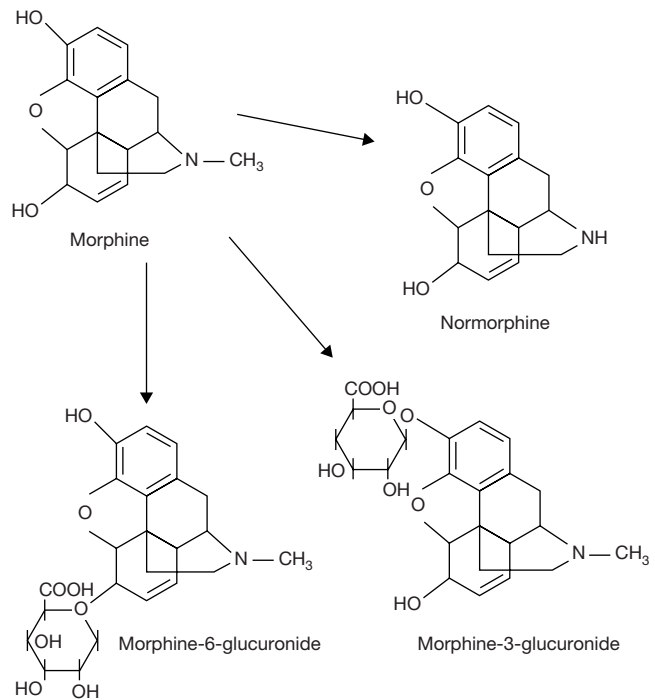


Fig. 5 The metabolites of morphine.

extrahepatic metabolism has been demonstrated in the small bowel and the proximal renal tubule of rodents. These sites may become important where liver function is impaired. M3G is the major metabolite and in recent years there has been some controversy about its possible role as an opioid antagonist or in mediating some of the adverse effects of morphine (vide infra).

### Morphine-6-glucuronide

M6G binds to opioid receptors<sup>(73)</sup> and produces potent opioid effects in animals<sup>(73–75)</sup> and humans.<sup>(73,76–78)</sup> M6G excretion by the kidney is directly related to creatinine clearance;<sup>(79)</sup> its elimination half-life is 2–3 h in patients with normal renal function (similar to that of morphine) but becomes progressively longer with deteriorating function, resulting in significant accumulation.<sup>(79)</sup> In patients with impaired renal function, M6G may accumulate in blood and cerebrospinal fluid,<sup>(80)</sup> and high concentrations of this metabolite have been associated with toxicity.<sup>(76,81)</sup> Although further studies are needed to clarify the clinical importance of M6G and other metabolites, the data available are sufficient to recommend caution when administering morphine to patients with renal impairment. Patients who are receiving regular morphine and develop acute renal failure in a previously stable situation (e.g. a rapidly developing obstructive uropathy in a patient with pelvic malignancy) may develop a sudden onset of signs and symptoms of opioid toxicity, necessitating temporary withdrawal of the morphine and subsequent dose reduction, and/or less frequent administration.

M6G is thought to be a potent analgesic and studies in acute post-operative pain are currently ongoing. It is not yet clear whether M6G will have fewer side-effects than morphine, though it has been suggested that M6G causes less respiratory depression than morphine.<sup>(82–84)</sup>

### Morphine-3-glucuronide

For many years, it has been assumed that M3G is inert as is the case with most glucuronide metabolites.<sup>(85)</sup> Recent behavioural studies in rodents, however, suggested that M3G produces a functional antagonism of the analgesic effects of morphine and its active metabolite M6G.<sup>(86,87)</sup> There is also some evidence in animal models that M3G may be responsible for the central nervous system excitatory adverse effects seen with morphine, such as myoclonus.<sup>(88,89)</sup>

It is now clear that M3G does not bind to opioid receptors. Data from electrophysiological animal models indicate no evidence of an antagonistic effect of M3G<sup>(90)</sup> and recent studies in human volunteers indicate that M3G appears to be devoid of significant activity.<sup>(83,91)</sup> In particular, there is no evidence of functional antagonism of morphine or M6G in humans and overall it seems that M3G plays no significant role in the pharmacodynamics of morphine.

### Oral to parenteral relative potency

Single-dose studies of morphine in post-operative cancer patients demonstrated an oral-to-intramuscular potency ratio of 1 : 6.<sup>(92)</sup> However, empirical clinical practice using chronically administered oral morphine in cancer patients has generated a different ratio of 1 : 3 or 1 : 2.<sup>(93,94)</sup> The reason for the discrepancy between relative potency estimates derived from single-dose versus chronic dosing studies is probably associated with both methodology<sup>(95)</sup> and the pharmacokinetics and pharmacodynamics of M6G.<sup>(93)</sup> It is possible that M6G accumulation relative to morphine may be greater with oral than with parenteral administration; this would lead to an increase in the relative potency of the orally administered drug when given on a chronic basis.

The important principle for clinical practice is that there is a difference in relative analgesic potency when the route of administration is changed, and that adjustment of dose is necessary in order to achieve an equivalent effect and to avoid either underdosing or toxicity. The usual practice when converting from oral morphine to subcutaneous morphine (or diamorphine) is to divide the oral dose by two or three.<sup>(30)</sup>

### Parenteral morphine

The inorganic salts of morphine (morphine sulphate and morphine hydrochloride) have limited solubility. Standard formulations are available up to 20 mg/ml, and morphine can be constituted from lyophilized powder up to 50 mg/ml. Morphine tartrate is substantially more soluble and, in some countries, is formulated in a concentration of 80 mg/ml.

### Sustained-release morphine preparations

The development of modified-release morphine preparations has had a major impact on clinical practice. These preparations, which are usually administered on a 12-h schedule, provide a much more convenient means of administering oral morphine.<sup>(96)</sup> Several preparations are available worldwide with a range of dose formulations (10, 15, 30, 60, 100, and 200 mg depending on the country), allowing considerable flexibility in their use. Some preparations allow once-daily administration and sustained-release suspensions are also available.<sup>(97)</sup>

In contrast with morphine solution or normal-release tablets, where peak plasma concentrations are achieved within the first hour followed by a rapid decline and an elimination half-life of 2–4 h, sustained-release morphine typically achieves peak plasma concentrations 3–6 h after administration, the peak is attenuated, and plasma concentrations are sustained over a 12- or 24-h period.<sup>(98–100)</sup> The type and incidence of adverse effects with sustained-release morphine and normal-release oral morphine appear to be similar with the currently available formulations.

Although some clinicians advocate the use of sustained-release morphine when initiating morphine therapy in cancer patients, a normal-release preparation is generally recommended in the dose titration period.<sup>(30)</sup> Initial dose titration using sustained-release morphine is difficult because of the delay in achieving peak plasma concentrations, the attenuation of peak concentrations, and the long duration of action. In this situation, dose finding is performed more efficiently with a short-acting morphine preparation. Once the effective dose is identified using a normal-release formulation, this may be changed to a sustained-release preparation using a milligram-to-milligram conversion. For the same reasons, sustained-release morphine is not appropriate for the treatment of acute pain or 'breakthrough' pain. A normal-release morphine preparation

should be provided to patients stabilized on sustained-release morphine to be used 'as required' for breakthrough pain.

### Diamorphine (heroin)

Diamorphine (diacetylmorphine) is a semi-synthetic analogue of morphine and has a long tradition of use for cancer pain in the United Kingdom. It is only available for legal medicinal use in the United Kingdom and Canada.

Following oral administration of diamorphine, only morphine can be measured in the patient's blood. The use of oral diamorphine is an inefficient way of delivering morphine to the systemic circulation. There is no good basis to believe that there is any difference between these two drugs when given by mouth. Sublingual administration of diamorphine has been advocated by some but, as discussed below, this route is not appropriate for either morphine or diamorphine because of poor absorption.

It has been thought that diamorphine does not itself bind to the  $\mu$  opioid receptor but must be biotransformed to 6-acetylmorphine and morphine to produce its analgesic effect.<sup>(101)</sup> However, recent studies with mor-knockout mice seem to indicate that it does not produce its effects through  $\mu$  receptor binding and may have effects at other receptors.<sup>(102)</sup> This may explain some of the pharmacodynamic differences between morphine and diamorphine when given parenterally.

Since diamorphine is more soluble and lipophilic than morphine, it does have some advantages for parenteral administration. When administered by subcutaneous or intramuscular injection, diamorphine is approximately twice as potent as morphine. There are also differences between diamorphine and morphine administered by intravenous injection: diamorphine has a marginally quicker onset of action, produces greater sedation, and possibly less vomiting.<sup>(103)</sup> This may be explained by different receptor binding. The greater solubility of diamorphine (shared also with hydromorphone and morphine tartrate) is of particular advantage for patients who require large doses of subcutaneous opioids.

### Methadone

Methadone is a synthetic opioid with an oral-to-parenteral potency ratio of 1 : 2 and an oral bioavailability greater than 85 per cent. In single-dose studies, methadone is only marginally more potent than morphine; however, with repeated administration it is several times more potent. Methadone has a very long plasma half-life, averaging approximately 24 h (with a range from 12 to over 150 h).<sup>(104,105)</sup> Whereas most patients can be well controlled on 8–12-h dosing, some patients require dosing at a 4–8-h interval to maintain analgesic effects.<sup>(106)</sup> Methadone may be a useful alternative to morphine, but its safe administration requires knowledge of its pharmacology and experience of its use.

After treatment is initiated or the dose is increased, plasma concentration rises over a prolonged period, and this may be associated with a delayed onset of side-effects. Consequently, patients must be followed closely until there is reasonable certainty that a steady state plasma concentration has been approached (approximately 1 week). Serious adverse effects can be avoided if the initial period of dosing is accomplished with 'as needed' administration.<sup>(107)</sup> When steady state has been achieved, scheduled dose frequency should be determined by the duration of analgesia following each dose.<sup>(108)</sup>

Oral and parenteral preparations of methadone are available. Subcutaneous infusion is possible<sup>(109)</sup> but caution is required since local skin toxicity may be a problem.<sup>(110)</sup>

The equianalgesic dose ratio of morphine to methadone has been a matter of confusion and controversy. Recent data from crossover studies with morphine and methadone and hydromorphone and methadone indicate that methadone is much more potent than previously described in literature, and that the ratio correlates with total opioid dose administered before switching to methadone.<sup>(111)</sup> Among patients receiving low doses of morphine, the ratio is 4 : 1. In contrast, for patients receiving more than 300 mg of oral morphine (or parenteral equivalent) the ratio is approximately 10 : 1 or 12 : 1.<sup>(111)</sup>

## Pethidine (meperidine)

Pethidine is a synthetic opioid with agonist effects similar to those of morphine but a profile of potential adverse effects that limits its utility as an analgesic for chronic cancer pain. Intramuscular pethidine 75 mg is equivalent to 10 mg of intramuscular morphine. Pethidine has an oral bioavailability of 40–60 per cent, and its oral-to-parenteral potency ratio is 1 : 4. It is more lipophilic than morphine, and produces a faster onset and shorter duration of analgesia of 2–3 h.

Pethidine is *N*-demethylated to norpethidine, which is an active metabolite that is twice as potent as a convulsant and half as potent as an analgesic compared with its parent compound. Accumulation of norpethidine after repetitive dosing of pethidine can result in central nervous system excitability characterized by subtle mood effects, tremors, multifocal myoclonus, and occasionally, seizures.<sup>(112,113)</sup> Naloxone does not reverse pethidine-induced seizures, and it is possible that its administration to patients receiving pethidine chronically could precipitate seizures by blocking the depressant action of pethidine and allowing the convulsant activity of norpethidine to become manifest.<sup>(114)</sup> If naloxone is necessary in this situation, it should be diluted and slowly titrated while appropriate seizure precautions are taken. Selective toxicity of pethidine can also occur following administration to patients receiving monoamine oxidase inhibitors. This combination may produce a syndrome characterized by hyperpyrexia, muscle rigidity, and seizures which may occasionally be fatal.<sup>(115)</sup> The pathophysiology of this syndrome is related to excess availability of serotonin at the 5HT<sub>1A</sub>-receptor in the central nervous system.

Although accumulation of norpethidine is most likely to affect patients with overt renal disease, toxicity is sometimes observed in patients with normal renal function. These potential adverse effects contraindicate pethidine for the management of chronic cancer pain. Given the availability of alternative drugs that lack these toxicities, its use in acute pain management is also not recommended.<sup>(117)</sup>

## Hydromorphone

Hydromorphone is another morphine congener. It is five times more potent than morphine and can be administered by the oral, rectal, parenteral, and intraspinal routes. Its oral bioavailability varies from 35 to 80 per cent, and its oral-to-parenteral potency ratio is 1 : 5.<sup>(118)</sup> Its half-life is 1.5–3 h and it has a short duration of action. Although it is largely excreted unchanged by the kidney, it is partially metabolized in the liver to a 3-glucuronide, which is excreted by the kidneys.<sup>(118,119)</sup>

Its solubility, the availability of a high-concentration preparation (10 mg/ml), and high bioavailability by the subcutaneous route (78 per cent) make it particularly suitable for subcutaneous infusion.<sup>(120)</sup> In the United States, it is routinely available in oral, rectal, and injectable formulations, and a sustained-release oral formulation.<sup>(121)</sup> For patients who require very high opioid doses via the subcutaneous route, hydromorphone can be constituted in concentrations of up to 50 mg/ml from lyophilized powder. It has also been administered via the epidural and intrathecal routes to manage acute and chronic pain. Hydromorphone is hydrophilic and, when administered via the epidural route, its pharmacokinetic profile, including its long half-life and extensive rostral distribution in cerebrospinal fluid, is similar to that of morphine.<sup>(122)</sup>

The equianalgesic ratio of parenteral morphine to hydromorphone has become a matter of controversy; recent data suggests that for chronic dosing it is less than the traditionally quoted ratio 1 : 7 and that it is probably closer to 1 : 4.<sup>(123,124)</sup>

## Levorphanol

Levorphanol is a morphine congener with a long half-life (12–16 h).<sup>(125)</sup> It is five times more potent than morphine and has an oral-to-parenteral potency ratio of 1 : 2.<sup>(126)</sup> Like methadone, the discrepancy between plasma half-life (12–16 h) and duration of analgesia (4–6 h) may predispose to drug accumulation following the initiation of therapy or dose escalation. Although dose titration needs to be done carefully in the opioid-naïve

patient, problems with drug accumulation appear to be less than those produced by methadone.

In the United States, levorphanol is generally used as a second-line agent in patients with chronic pain who cannot tolerate morphine. The possibility that this drug may be particularly useful in morphine-tolerant patients has been proposed on the basis of its affinity for receptors  $\kappa 3$  and  $\delta$  that are presumably not involved in morphine analgesia.<sup>(127)</sup> It is no longer available in the United Kingdom or Canada.

## Oxycodone

As previously described, oxycodone is a synthetic morphine congener that has a high oral bioavailability (60–90 per cent) and an analgesic potency 30–50 per cent greater than morphine.<sup>(128,129)</sup> Since the development of sustained release formulations in doses suitable for severe pain, it is now widely used for this indication. The sustained release formulation is available in a wide range of dose formulations (10, 20, 40, and 80 mg)<sup>(55)</sup> and has a duration of action of 8–12 h. The sustained-release formulation achieves effective therapeutic levels within an hour<sup>(130)</sup> and appears to be suitable for dose titration.<sup>(131)</sup> Oxycodone pectinate is available in the United Kingdom as a 30-mg rectal suppository which has a delayed absorption and prolonged duration of effect.<sup>(51)</sup>

There has been confusion about the relative efficacy of oxycodone. Until recently, it has been viewed primarily as a 'step 2' opioid because it has for long been available in low dose in combination products with non-opioid analgesics. It seems clear that the relative potency of oxycodone has been underestimated in early clinical studies in which it appeared to be less potent than morphine. As indicated above more recent studies indicate that it is more potent, in a ratio of about 1.5 : 1.<sup>(128)</sup>

There remains uncertainty also about the role of its active metabolite oxymorphone in mediating the effects of oxycodone. However, current evidence suggests that the metabolites of oxycodone do not contribute significantly to its pharmacological effects.<sup>(11)</sup>

## Oxymorphone

Oxymorphone is a lipophilic congener of morphine. It is currently most widely used in suppository form, infrequently used parenterally on a chronic basis, and is not available orally. The injectable formulation is 10 times more potent than morphine.<sup>(132)</sup> A rectal formulation that is approximately equipotent with parenteral morphine is also available in the United States. The plasma half-life of oxymorphone is 1.2–2 h, and its duration of action is 3–5 h. It is less likely to produce histamine release than morphine,<sup>(133)</sup> and may be particularly useful for patients who develop itch in response to other opioids.<sup>(134)</sup> Oxymorphone is currently not available in the United Kingdom.

## Fentanyl

Fentanyl is a semisynthetic opioid and is a highly selective  $\mu$  agonist<sup>(135)</sup> that is about 80 times as potent as parenteral morphine in the non-tolerant acute pain patient. It is also extremely lipophilic and is extensively taken up into fatty tissue.<sup>(136)</sup> Its elimination half-life ranges from 3 to 12 h and is influenced by the duration of prior administration and the extent of fat sequestration. Fentanyl has been used mainly as an intravenous anaesthetic agent and combines to be used parenterally as a pre-medication for painful procedures and in continuous infusions. When used intravenously, fentanyl has a very short duration of action of 0.5–1 h. This is related to the rapid redistribution of the drug into body tissues rather than to hepatic and renal elimination.<sup>(137)</sup> The development of a transdermal system and an oral transmucosal formulation has broadened the clinical utility of fentanyl for the management of cancer pain.

### Transdermal fentanyl

The low molecular weight and high lipid solubility of fentanyl facilitate absorption through the skin and a transdermal formulation that delivers 25, 50, 75, or 100  $\mu\text{g/h}$  is widely available.<sup>(138–140)</sup> The transdermal system

consists of a drug reservoir that is separated from the skin by a copolymer membrane that controls the rate of drug delivery to the skin surface. The drug is released at a nearly constant amount per unit time along a concentration gradient from the patch to the skin. After application of the transdermal system, serum fentanyl concentration increases gradually, usually levelling off after 12–24 h, and then remaining stable for a time before declining slowly. When the patch is removed, serum concentration falls 50 per cent in approximately 17 h (range 13–22 h).<sup>(141)</sup> The slow onset of effect after application and an equally slow decline in effect after removal are consistent with the development of a subcutaneous depot of drug that maintains the plasma concentration. There is significant interindividual variability in fentanyl bioavailability by this route and dose titration is necessary.<sup>(141)</sup> The dosing interval for each system is usually 72 h, but interindividual pharmacokinetic variability is large and some patients require a dosing interval of 48 h.<sup>(142)</sup>

Familiarity with the kinetics of the transdermal system is essential for optimal use. Since there is a delay of 8–12 h in achieving effective analgesia after initial application of the patch, it is essential to provide alternative analgesia for this initial period. It is prudent to apply the patch in the early hours of the day so that the patient can be observed as blood levels rise over the ensuing 12 h to minimize the risk of overdosing during sleep. Significant concentrations of fentanyl can remain in the plasma for up to 24 h after removal of the patch because of delayed release from tissue and subcutaneous depots. Neither age nor patch location appears to affect fentanyl absorption from the transdermal system.<sup>(140)</sup> There is a potential for temperature-dependent increases in fentanyl release from the system associated with increased skin permeability in patients with fever, who should be monitored for opioid side-effects. Patients should also avoid exposing the patch to direct external heat.

Empirically, the indications for the transdermal route include intolerance of oral medication, poor compliance with oral medication, and occasionally the desire to provide a trial of fentanyl to patients who have reacted unfavourably to other opioids. However, there are a number of limitations. The delay in onset of analgesia and in the establishment of steady state blood levels require the liberal use of an alternative short-acting opioid (usually morphine) for breakthrough pain during the early treatment period. Because of its 3-day duration of action, transdermal fentanyl is generally unsuitable for patients with unstable pain, and if a patient's pain goes out of control management may be complicated because of the delay in re-establishing steady state. If dose reductions are required or discontinuation is indicated, the continuing absorption following patch removal must be taken into account. Poor patch adhesion may be a problem in some patients. Set against these considerations are the advantages in terms of convenience and compliance and there is high patient acceptability of this mode of administration. Additionally there are experimental and clinical data to suggest that transdermal fentanyl is associated with less constipation than morphine.<sup>(143,144)</sup>

Empirical observations suggest that a 100- $\mu\text{g/h}$  fentanyl patch is approximately equianalgesic to 2–4 mg/h of intravenous morphine (or equivalent). The relative potency ratio that is applicable when converting patients from oral morphine to transdermal fentanyl has been the subject of some controversy, but the dosing recommendations of the manufacturer seem about right. The patch should be placed in an area where skin movement is limited, such as the upper anterior chest wall or either side of the midline on the back, preferably the lower back. Studies have shown that all areas of skin absorb the drug at roughly the same rate.<sup>(140)</sup> Since the adhesive strips on these patches are less than optimal, securing the patch with non-irritant tape is often necessary.

Transdermal fentanyl is best reserved for patients whose opioid requirements are stable<sup>(30)</sup> and in general it is likely to be a second-line choice. However, for suitable patients it works well and they like it.<sup>(145)</sup>

### Oral transmucosal fentanyl citrate (OTFC)

An oral transmucosal formulation of fentanyl (which incorporates the drug in a hardened lozenge on a stick) that is absorbed across the buccal mucosa,

has recently been introduced in many countries for the management of breakthrough pain. The lozenge is rubbed gently against the inside of the cheek until it has dissolved. The formulation is rapidly absorbed and achieves blood levels and time to peak effect that are comparable to parenterally administered fentanyl. Indeed, the time to onset of analgesia is 5–10 min<sup>(146–149)</sup> and studies in cancer patients suggest that it can provide rapid and very effective relief of breakthrough pain. Formulations incorporating 200, 400, 600, 800, and 1600  $\mu\text{g}$  are available. The most common adverse effects associated with this formulation are somnolence, nausea, and dizziness. One interesting observation which has emerged from the clinical trials and clinical use is that the successful dose of OTFC cannot be predicted and is not directly related to the daily dose of regular opioids being received for background pain. This raises some questions about the current management of breakthrough pain with conventional formulations of oral or parenteral opioids (see Chapter 8.2.10). The use of OTFC is still relatively limited but initial experience has been good.

## Other drugs

### Phenazocine

Phenazocine is a synthetic opioid structurally related to morphine with strong binding to the  $\sigma$  receptor. One 5-mg tablet is equivalent to 25 mg of oral morphine, which means that there is less flexibility in its use. Phenazocine may be given sublingually, although administration by this route is usually avoided because of its bitter taste and variable absorption. In the United Kingdom, it was often used for patients who are unable to tolerate oral morphine, but it is now largely replaced by the more recently available alternative opioids such as oxycodone, fentanyl, and hydromorphone.

### Dextromoramide

Dextromoramide is a  $\mu$  agonist and is approximately twice as potent as morphine when taken by mouth. Few data on its pharmacokinetics are available because of difficulties in accurately assaying the drug, but in clinical practice in cancer pain it has a rapid onset of action but a shorter duration than morphine. Tolerance to dextromoramide seems to develop rapidly in humans and, although the duration of analgesia may initially be 2–4 h, with repeated administration this may be reduced to only 1 or 2 h. For this reason, it is unsuitable for maintenance treatment in chronic cancer pain, although it has been used successfully as a short-acting strong analgesic for breakthrough pain in some patients. It does not have any particular advantages over morphine used in this way, and in general the use of dextromoramide in chronic cancer pain is not recommended.

### Dipipanone

Dipipanone is a diphenylpropylamine structurally related to both dextromoramide and methadone. As an analgesic, it is approximately half as potent as morphine, and in the United Kingdom it is only available in a combination tablet containing 10 mg dipipanone and 30 mg cyclizine. For many patients this results in excessive sedative and anticholinergic side-effects related to cyclizine when adequate analgesic doses are given, and thus it has only limited application in the management of chronic cancer pain.<sup>(150)</sup>

## Agonist–antagonist opioid analgesics

The agonist–antagonist opioid analgesics are a heterogeneous group of drugs with moderate to strong analgesic activity, comparable with that of the agonist opioids such as codeine and morphine. The group includes drugs which act as an agonist or partial agonist at one receptor and as an antagonist at another (pentazocine, dezocine, butorphanol, nalbuphine)—‘the mixed agonist–antagonists’—and drugs acting as a partial agonist at a single receptor (buprenorphine). These two groups of drugs can be also classified as nalorphine- or morphine-like. Meptazinol fits neither classification and occupies a separate category. The place of this group of drugs in

chronic cancer pain has been limited.<sup>(151)</sup> However, the recent development of a transdermal formulation of buprenorphine may allow its more widespread use in both chronic cancer and non-cancer pain.

### Mixed agonist–antagonist analgesics

The agonist–antagonists produce analgesia in the opioid-naïve patient but may precipitate withdrawal in patients who are physically dependent on morphine-like drugs. Therefore, when used for chronic pain, they should be tried before repeated administration of a morphine-like agonist drug.

Pentazocine, butorphanol, and nalbuphine are  $\mu$  antagonists and  $\kappa$  agonists or partial agonists. All three drugs are strong analgesics when given by injection: pentazocine is one-sixth to one-third as potent as morphine, nalbuphine is roughly equipotent with morphine, and butorphanol is 3.5–7 times as potent. The duration of analgesia is similar to that of morphine (3–4 h). Oral pentazocine is closer in analgesic efficacy to aspirin and paracetamol than the weak opioid analgesics, such as codeine. Neither nalbuphine nor butorphanol is available as an oral formulation, and butorphanol is no longer available in any form in the United Kingdom.

At usual therapeutic doses, nalbuphine and butorphanol have respiratory depressant effects equivalent to that of morphine (although the duration of such effects may be longer with butorphanol). Unlike morphine, there appears to be a ceiling to both the respiratory depression and the analgesic action.

All three drugs have a lower abuse potential than the agonist opioid analgesics such as morphine. However, all have been subject to abuse and misuse, and pentazocine (but not the others) is subject to controlled drug restrictions. In North America, the oral preparation of pentazocine is marketed in combination with naloxone (but is available without naloxone elsewhere).

Meptazinol is a synthetic hexahydroazepine derivative with opioid agonist and antagonist properties, but is unlike either the nalorphine-type agonist–antagonists or buprenorphine. Meptazinol has central cholinergic properties which may account at least in part for its analgesic effects. Receptor binding studies show it to be a specific  $\mu 1$  agonist. Meptazinol is one-tenth as potent as morphine by intramuscular injection and has a duration of action of about 4 h. Some studies have shown adverse effects to be more frequent than with morphine, although respiratory depression and constipation appear to be less.

In therapeutic doses, the mixed agonists–antagonists may produce certain self-limiting psychotomimetic effects in some patients; pentazocine is the most common drug associated with these effects. These drugs play a very limited role in the management of chronic cancer pain because the incidence and severity of the psychotomimetic effects increase with dose escalation, and nalbuphine and butorphanol are only available for parenteral use.

A transnasal formulation of butorphanol is now on the market in the United States, but there is no reported experience of its use in the management of chronic cancer pain.

### Partial agonist analgesics

Buprenorphine (Table 2) is a semi-synthetic derivative of thebaine and chemically closely related to the strong agonist etorphine. Buprenorphine is a true partial agonist at the  $\mu$  receptor and exhibits a ceiling effect in dose response curves in various animal models. In some, a bell-shaped curve is seen, indicating that at doses above a certain level the pharmacological effect actually decreases with increasing dose.<sup>(152)</sup> Buprenorphine has until recently only been available by injection or for sublingual administration. A dose of 0.4 mg sublingually gives similar analgesia to 0.2–0.3 mg intramuscularly, with an onset of analgesia within 30–60 min of administration and a duration of 6–9 h.<sup>(153)</sup> In contrast, if taken orally, buprenorphine is a poor analgesic due to extensive presystemic elimination.<sup>(154)</sup> The long duration of analgesia with buprenorphine may be related to its affinity for the  $\mu$ -opioid receptor and an unusually slow dissociation constant for the drug–receptor complex.

Buprenorphine has been in clinical use for more than 25 years and has been evaluated in a variety of acute pain models. Direct single dose comparisons with other analgesics such as morphine is complicated by its long duration of action, but results from a number of studies in post-operative pain suggest that single doses of 0.3 mg buprenorphine parenterally or 0.4 mg sublingually give equivalent analgesia to 10–15 mg intramuscular morphine. A ceiling effect for analgesia in humans has not been clearly demonstrated.

Buprenorphine produces typical opioid adverse effects. Overall the available data (which is limited) suggest that the incidence of common adverse effects compared with morphine is similar. Naloxone appears to be relatively ineffective in reversing opioid effects due to buprenorphine.<sup>(155)</sup> Co-administration of buprenorphine to patients receiving high doses of a morphine-like agonist may precipitate withdrawal symptoms.

Buprenorphine was introduced in high-dose sublingual tablet formulations in 1999 for management of drug dependence. This potential use of the drug has long been recognized<sup>(156)</sup> and it has been suggested that there is less overdose risk compared with other opioids.<sup>(157)</sup>

Buprenorphine has been recently introduced in a patch for transdermal administration. The drug is incorporated in a polymer adhesive matrix (with no liquid reservoir). Three patch sizes are available delivering 35, 52.5, and 70  $\mu$ g buprenorphine per hour, and each lasts for 3 days. Therapeutic plasma concentrations are achieved within 11–21 h and steady state between the second and third applications of the patch. At usual clinical doses of 3–4 mg per 24 h buprenorphine functions as a pure  $\mu$  agonist.

Transdermal buprenorphine has been licensed for use in both cancer pain and non-cancer pain but clinical experience with this formulation is limited.

## Principles of opioid administration

The effective clinical use of opioid drugs requires familiarity with the different drugs available, routes of administration, dosing guidelines, and potential adverse effects.

### Indications

A trial of opioid therapy should be given to all patients with pain of moderate or greater severity, irrespective of the underlying pathophysiological mechanism. As discussed in Chapter 8.2.10, the suggestion that some forms of pain, such as neuropathic pain, are intrinsically refractory to opioid analgesia has been refuted by several studies that demonstrate that pain mechanisms do not accurately predict analgesic outcome from opioid therapy.<sup>(158)</sup> Given the variability of response, all opioid trials in the clinical setting should include dose titration until adequate analgesia occurs or intolerable adverse effects supervene. This approach will identify those responders who can gain substantial clinical benefit from opioid therapy.

Patients whose pain is not easily controlled with an opioid analgesic because of troublesome adverse effects may benefit from alternative strategies and these are discussed below.

### Drug selection

The factors that influence opioid selection include pain intensity, pharmacokinetic considerations and available formulations, previous adverse effects, and the presence of co-existing disease.

### Pain intensity

Patients who present with severe pain are usually treated with a 'step 3' opioid (morphine, hydromorphone, oxycodone, oxymorphone, fentanyl, methadone, or levorphanol). Patients with moderate pain are conventionally treated with a combination product containing paracetamol or aspirin plus a conventional step 2 opioid [codeine, dihydrocodeine, hydrocodone, oxycodone (low dose), and propoxyphene].

### Pharmacokinetic considerations and type of formulation

Any of the available agonist opioids can be selected for the opioid-naïve patient without major organ failure. Short-half-life opioids (morphine, hydromorphone, oxycodone, or oxymorphone) are generally favoured because they are easier to titrate than the long-half-life drugs, which require a longer period to approach steady state plasma concentrations. Among the short-half-life opioids, the range of available formulations often influences specific drug selection. For ambulatory patients who are able to tolerate oral opioids, morphine sulphate is generally preferred since it has a short half-life and is easy to titrate in its normal-release form; it is also available as sustained-release preparations that allow 12- and 24-h dosing intervals. The long-half-life opioids methadone and levorphanol are not usually considered for first-line therapy because they can be difficult to titrate and present challenging management problems if delayed toxicity develops as plasma concentrations gradually rise following dose increments. For the reasons previously described, the use of pethidine, dextromoramide, and dipipanone for the management of cancer pain is discouraged.

When the oral route of opioid administration is contraindicated, the available routes of administration may become an important consideration in opioid selection. Fentanyl and buprenorphine are available for administration by the transdermal route. Although most of the full agonist drugs are well absorbed by subcutaneous infusion, some (like morphine tartrate, hydromorphone, and diamorphine) are more suitable by virtue of their high solubility and low irritability. Methadone and fentanyl may produce significant local irritation when administered by the subcutaneous route. For cultural and aesthetic reasons, the subcutaneous route is often preferred to rectal administration. Subcutaneous infusion may be also preferable in patients at the end of life because it is less disruptive than using intermittent analgesic suppositories when nursing a sick patient.

### Response to previous trials of opioid therapy

It is always important to review the response to previous trials of opioid therapy. If the current opioid is well tolerated, it is usually continued unless difficulties in dose titration occur or the required dose cannot be administered conventionally. If dose-limiting side-effects develop, a trial of an alternative opioid should be considered as discussed in the section on adverse effects.

### Co-existing disease

Pharmacokinetic studies of pethidine, pentazocine, and propoxyphene have revealed that liver disease may decrease the clearance and increase the bioavailability and half-lives of these drugs.<sup>(159,160)</sup> These changes may result in above-normal plasma concentrations. Mild or moderate hepatic impairment has only a minor impact on morphine clearance;<sup>(161)</sup> however, advanced disease may be associated with reduced elimination.<sup>(162)</sup>

Patients with renal impairment may accumulate the active metabolites of propoxyphene (norpropoxyphene), pethidine (norpethidine), and morphine (M6G). Particular caution is required in the administration of these drugs to such patients.<sup>(76,79,163,164)</sup> Until more data are available, it may be wise to assume that other opioids with active metabolites may produce similar problems of toxicity in patients with impaired renal function.

Morphine remains the standard step 3 opioid analgesic against which others are measured and is the most widely available in a variety of oral formulations.<sup>(30)</sup> It has limitations; the systemic availability of morphine by the oral route is poor (20–30 per cent) and this contributes to the sometimes unpredictable onset of action and great interindividual variability in dose requirements and response. Active metabolites may contribute to toxicity particularly in patients with renal impairment.<sup>(164)</sup> Sometimes the pain does not respond well or completely to morphine, notably neuropathic pain. However, none of the alternatives to morphine has so far demonstrated advantages which would make it preferable in routine use as the first-line oral opioid for cancer pain. Morphine remains the standard but for reasons of familiarity, availability and cost rather than proven superiority.

### Routes of administration

Opioids should be administered by the least invasive and safest route capable of providing adequate analgesia. In a survey of patients with advanced cancer, more than half required two or more routes of administration prior to death, and almost a quarter required three or more.<sup>(165)</sup>

#### Oral administration

The oral route of opioid administration remains the most important and appropriate in routine practice. Orally administered drugs have a slower onset of action, a delayed peak time, and a longer duration of effect compared with parenterally administered drugs. The time to peak effect depends on the drug and the nature of the formulation. For most normal-release oral formulations, peak effect is typically achieved within 60 min. The oral route of drug administration is inappropriate for patients who have impaired swallowing or gastrointestinal obstruction, and for some patients who require a rapid onset of analgesia. For patients who require very high doses, the inability to prescribe a manageable oral opioid regimen may be an indication for the use of a non-oral route.

When given orally, the opioids differ substantially with respect to their relative analgesic potency compared with parenteral administration. To some extent, this reflects differences in presystemic metabolism, that is, the degree to which they are inactivated as they are absorbed from the gastrointestinal tract and pass through the liver into the systemic circulation. As indicated in Table 3, morphine, diamorphine, pethidine, hydromorphone and oxymorphone, have ratios of oral to parenteral potency ranging from 1 : 3 to 1 : 12. Methadone, levorphanol, and oxycodone are subject to less presystemic elimination and also demonstrate a lower oral-to-parenteral potency ratio of at least 1 : 2. Failure to recognize these differences may result in a substantial reduction in analgesia when a change from parenteral to oral administration is attempted without upward titration of the dose, or toxic effects when changing in the opposite direction.

#### Rectal administration

The rectal route is a non-invasive alternative to parenteral routes for patients unable to use oral opioids. Rectal suppositories containing morphine, hydromorphone, oxymorphone, and oxycodone are available. The pharmacokinetics and bioavailability of drugs given rectally may differ from that of oral administration because of delayed or limited absorption and partial bypassing of presystemic hepatic metabolism. In practice, however, the potency of opioids administered rectally is approximately equal to that achieved by oral dosing.<sup>(166)</sup> In contrast with morphine, rectal oxycodone appears to have a delayed absorption and prolonged duration of action.

For many patients, the rectal route is not used because it is more convenient to convert directly to a subcutaneous infusion of opioid using a portable syringe driver or similar device.

#### Parenteral administration

##### Bolus injections

Parenteral routes of administration are considered for patients who have impaired swallowing or gastrointestinal obstruction, those who require a rapid onset of analgesia, and those who require very high doses that cannot be conveniently administered by other methods. Repeated parenteral bolus injections, which can be delivered by the intravenous, intramuscular, or subcutaneous routes, may be complicated by the occurrence of untoward 'bolus' effects (toxicity at peak concentration and/or pain breakthrough at the trough). Intravenous bolus provides the most rapid onset; the time to peak effect correlates with the lipid solubility of the opioid, ranging from 2 to 5 min for methadone and from 10 to 15 min for morphine. Although repetitive intramuscular injections are commonplace in some countries, they are painful and offer no pharmacokinetic advantage, and their use is not recommended.<sup>(30,31)</sup> Repeated bolus doses, if required, can be accomplished without frequent skin punctures by using an indwelling intravenous

or subcutaneous infusion device. To deliver repeated subcutaneous injections, a 25–27 gauge ‘butterfly’ can be left under the skin for up to a week.<sup>(167)</sup> The discomfort associated with this technique is partially related to the volume to be injected; it can be minimized by the use of concentrated formulations.

### Continuous infusions

Continuous infusions avoid the problems associated with the ‘bolus effect’ and can be administered intravenously or subcutaneously.<sup>(168,169)</sup> Continuous subcutaneous infusion using a portable battery-operated syringe driver or other similar device was originally devised to administer infusions of desferrioxamine to patients with thalassemia, but was subsequently used to deliver diamorphine to patients with advanced cancer who were unable to take oral drugs.<sup>(170)</sup> This technique is now well established in palliative care and is used to administer analgesics, antiemetics, anxiolytic sedatives, and dexamethasone.

Ambulatory infusion devices vary in complexity, cost, and ability to provide patient-controlled ‘rescue doses’ as an adjunct to a continuous basal infusion. A variety of devices have been employed, all designed to be lightweight and portable, and in one case disposable. Opioids suitable for continuous subcutaneous infusion must be soluble, well absorbed and non-irritant. Extensive experience has been reported with morphine, diamorphine, hydromorphone, fentanyl, and oxymorphone.<sup>(120,168,171)</sup> Methadone<sup>(110)</sup> and fentanyl appear to be relative irritants and are best avoided by this route.

Studies suggest that dosing with subcutaneous administration can proceed in a manner identical to continuous intravenous infusion: a post-operative study comparing patients who received an identical dose of morphine by either intravenous or subcutaneous infusion found no difference in blood levels,<sup>(172)</sup> and a controlled study of hydromorphone calculated a bioavailability of 78 per cent for the subcutaneous route and observed that analgesic outcome was identical during intravenous or subcutaneous infusion. To maintain the comfort of an infusion site, the subcutaneous infusion rate should not exceed 5 ml/h. Subcutaneous infusion has become the first choice when parenteral analgesia is required in palliative care patients.

Continuous intravenous infusion may be the most appropriate way of delivering an opioid for patients with a pre-existing implanted central line, when there is a need for infusion of a large volume of solution, or when using methadone. If continuous intravenous infusion must be continued on a long-term basis, a permanent central venous port is recommended.

Continuous infusions of drug combinations may be indicated when pain is accompanied by nausea, anxiety, or agitation. In such cases an antiemetic, neuroleptic, or anxiolytic may be combined with an opioid provided that it is non-irritant, miscible, and stable in combined solution. As noted later in the text, a variety of different combinations of drugs are commonly given by continuous infusion.<sup>(173)</sup> However, the stability/compatibility of many of these combinations is not known. The compatibility of drug combinations is dependent on a number of factors, including the types of drugs, the concentrations of drugs, the diluent and temperature, and UV light. A database of compatible drug combinations is now available on the internet (<http://www.pallmed.net/>). Generally infusions should contain as few drugs as possible, preferably no more than three. The absence of precipitation within a drug mixture is not synonymous with compatibility between the drugs in that mixture.<sup>(174)</sup>

### Epidural, intrathecal, and intraventricular administration (see also Chapter 8.2.6)

The discovery of opioid receptors in the dorsal horn of the spinal cord led to the development of intraspinal opioid delivery techniques. In general, they provide a longer duration of analgesia at doses lower than required by systemic administration. The delivery of low opioid doses near the sites of action in the spinal cord may decrease supraspinally mediated adverse effects. Opioid selection for intraspinal delivery is influenced by several

factors. Hydrophilic drugs, such as morphine and hydromorphone, have a prolonged half-life in cerebrospinal fluid and significant rostral redistribution.<sup>(175)</sup> Lipophilic opioids, such as fentanyl and sufentanil, have less rostral redistribution and therefore less prolonged adverse effects if these become a problem.

The addition of local anaesthetic such as bupivacaine to an epidural or intrathecal opioid has been demonstrated to improve analgesia without increasing toxicity.<sup>(176,177)</sup> Unlike in acute post-operative pain, where a large volume of low concentration local anaesthetic is used, in chronic cancer pain, a small volume of high concentration of local anaesthetic is preferred and can be mixed with an appropriate dose of a small volume of opioid.

The initial conversion of opioid dose from systemic subcutaneous diamorphine or morphine is:

- ◆ epidural—1/10 of systemic dose;
- ◆ intrathecal—1/10 of epidural dose.

Thus, if a patient were on 100 mg of subcutaneous morphine or diamorphine/day, the equivalent epidural dose would be 10 mg, and the equivalent intrathecal dose would be 1 mg/day.

The initial solution used for epidural infusion is usually:

- ◆ 9 ml 0.5 per cent bupivacaine;
- ◆ 150 µg clonidine;
- ◆ morphine or diamorphine dose according to individual patient requirements (as calculated above).

This gives a total volume of 10 ml infused over 24 h.

The initial solution used for intrathecal infusion is normally around 1/10 of the above, that is:

- ◆ 1 ml 0.5 per cent bupivacaine;
- ◆ 15 µg clonidine;
- ◆ morphine or diamorphine according to individual patient requirements.

Should there be a major problem with pump malfunction, and the whole dose is delivered as a bolus, this should *not* result in a major, life-threatening overdose.

There are no trials comparing the intrathecal and epidural routes in cancer pain. The epidural route is generally preferred because the techniques to accomplish long-term administration are simpler. A combined analysis of adverse effects observed in numerous trials of epidural or intrathecal administration suggests that the risks associated with these techniques are similar (see Chapter 8.2.6). The potential morbidity associated with these procedures emphasizes the need for a well-trained clinician and long-term monitoring.

Limited experience suggests that the administration of an opioid into the cerebral ventricles can provide long-term analgesia in selected patients. This technique has been used for patients with upper-body or head pain or with severe diffuse pain. Schedules have included both intermittent injection via an Ommaya reservoir and continual infusion using an implanted pump.

The indication for the spinal routes of administration of opioid analgesics in palliative care patients is discussed in more detail in Chapter 8.2.6.

## Other routes and modes of administration

### Transdermal

As previously described, fentanyl and buprenorphine are available in a transdermal formulation and their use is discussed above.

### Sublingual

Sublingual absorption could potentially occur with any opioid, but bioavailability is very poor with drugs that are not highly lipophilic.<sup>(178,179)</sup> A sublingual preparation of buprenorphine is available in some countries, although not in the United States. Anecdotally, sublingual morphine has also been reported to be effective; given the poor sublingual absorption of

this drug, this efficacy may be related in part to swallowing of the dose. Both fentanyl and methadone are well absorbed sublingually, but no preparations are currently available for clinical use. Thus the sublingual approach has limited value owing to the lack of true sublingual formulations, poor absorption of most drugs, and the inability to deliver high doses or to prevent swallowing of the dose. Sublingual administration of an injectable formulation is occasionally used in patients requiring low doses of opioids who temporarily lose the option of oral dosing. Sublingual administration of fentanyl and related drugs (alfentanyl) has also been reported to be effective in the management of breakthrough pain.<sup>(180)</sup> The injectable formulation is used and is much cheaper than the oral transmucosal formulation of fentanyl (OTFC). However, it is not really a practical option for patients who are still mobile and at home for whom OTFC may work well and is more convenient to use.

### Oral transmucosal and nasal

The management of 'breakthrough' pain has been a topic of considerable recent interest<sup>(181)</sup> partly stimulated by the development of OTFC and other novel approaches to the administration of potent opioids. The nasal route may be effective for a number of opioids<sup>(182)</sup> and nasal diamorphine spray has been shown to provide effective pain relief for children and teenagers presenting to emergency departments in acute pain with clinical fractures.<sup>(183)</sup> This approach is also currently being investigated in adult cancer patients with troublesome acute episodic pain.

### Topical

There are several case series and one very small randomized controlled trial (in press) that examine the role of topical morphine for local analgesia. The small amount of existing evidence seems to point to a role in some situations, for example, cutaneous ulcers or tumour with cutaneous inflammation. Doses of 10–40 mg of morphine are used in simple gel, saline soaks, or local anaesthetic gel.<sup>(184–186)</sup>

## Changing the route of administration

As described above, when changing from the oral to parenteral routes, or vice versa, an adjustment in dose is required to avoid either toxic effects or a reduction in analgesia. The ratios of oral to parenteral relative potency given in Table 3 are estimates and should not be taken as precise figures but used as guidelines to achieve a roughly equianalgesic effect. There is considerable variation between patients, and upward or downward adjustment may then be required for individual patients. The slower onset of analgesia after oral administration often requires some adaptation on the part of a patient who is accustomed to the more rapid onset seen after parenteral opioid. In some patients, the problems associated with switching from the parenteral to the oral route of opioid administration may need to be minimized by slowly reducing the parenteral dose and increasing the oral dose over a 2–3-day period.

Usually, no dose adjustment is required when patients are switched from the subcutaneous to the intravenous route or vice versa.

## Scheduling opioid administration

### 'Around-the-clock' dosing

To provide the patient with continuous relief by preventing the pain from recurring, patients with continuous or frequent pain are usually scheduled for 'around-the-clock' dosing. However, clinical vigilance is required in patients with no previous opioid exposure and those administered drugs with long half-lives. With methadone, for example, delayed toxicity may develop as plasma concentration rises slowly toward steady state levels.

### Rescue doses

All patients who receive an around-the-clock opioid regimen should also be offered a 'rescue dose', that is, a supplemental dose given on an as-needed basis to treat pain that breaks through the regular schedule.<sup>(30)</sup> The integration of scheduled dosing with rescue doses provides a method for safe and

rational stepwise dose escalation and is applicable to all routes of opioid administration. The rescue drug is typically identical to that administered on a continuous basis, with the exception of transdermal fentanyl and methadone; the use of an alternative short-half-life opioid is recommended for the rescue dose when these drugs are used. The frequency with which the rescue dose can be administered depends on the time to peak effect for the drug and the route of administration. Oral rescue doses can be offered up to every 60–90 min, and parenteral rescue doses can be offered up to every 15–30 min. Clinical experience suggests that the size of the rescue dose should be equivalent to one-sixth of the 24-h baseline dose, that is, the same as the 4-hourly dose of opioid. The magnitude of the rescue dose should be individualized and some patients with low baseline pain but severe exacerbations may require rescue doses that are substantially larger.

### Scheduling with sustained-release formulations

Sustained-release formulations can reduce the inconvenience associated with around-the-clock administration. These formulations should not be used for rapid titration of the dose in patients with severe pain. Sustained-release oral morphine sulphate, oxycodone, and transdermal fentanyl are now widely used, and sustained-release formulations of codeine, tramadol, and hydromorphone have been introduced in various countries.

A normal-release formulation of a short-half-life opioid (usually the same drug) is generally used as the rescue medication. Sustained- and normal-release formulations of oral morphine are dose equivalent; switching from one to the other is done on a milligram-for-milligram basis after the daily dose requirement is identified using a normal-release formulation.

### As-needed dosing

In some limited situations, an as-needed dosing regimen alone can be recommended. This type of dosing provides additional safety during the initiation of opioid therapy in the opioid-naïve patient, particularly when rapid dose escalation is needed or a long-half-life drug is administered. This technique is strongly recommended when starting methadone therapy and for patients with acute renal failure.

### Patient-controlled analgesia

Patient-controlled analgesia is a technique of parenteral drug administration in which the patient controls a pump that delivers bolus doses of an analgesic according to parameters set by the physician. Use of a patient-controlled analgesia device allows the patient to titrate the opioid dose carefully to his or her individual analgesic needs. Long-term patient-controlled analgesia in cancer patients is accomplished via subcutaneous or intravenous routes using an ambulatory infusion device.<sup>(187)</sup> The more technologically advanced of these devices have programmable variables, including infusion rate, rescue dose, and lock-out interval. The option for bolus dosing is typically used in conjunction with continuous opioid infusion. There is relatively little experience of patient-controlled analgesia in chronic cancer pain; it is a technique largely confined to the management of acute post-operative pain.

## Dose selection and adjustment

### Initial dose selection

A patient with severe pain that is not controlled with a step 2 opioid–non-opioid combination in full dose should begin one of the opioid agonists at a dose equivalent to 10 mg oral morphine sulphate every 4 h.

### Dose titration

Inadequate pain relief should be addressed by gradual escalation of the opioid dose until adequate analgesia is reported or intolerable side-effects (that cannot be managed by simple interventions) supervene. Because analgesic response to opioids increases linearly with the logarithm of the dose, dose escalations of less than 30–50 per cent are not likely to improve analgesia significantly. Clinical experience indicates that a dose increment of this order of magnitude is safe and is large enough to observe a meaningful

change in effects. In most cases, gradual dose escalation identifies a favourable balance between analgesia and side-effects which remains stable for a prolonged period. While doses can become extremely large during this process, the absolute dose is immaterial as long as the balance between analgesia and side-effects remains favourable. In a retrospective study of 100 patients with advanced cancer, the average daily opioid requirement was equivalent to 400–600 mg of intramuscular morphine, but approximately 10 per cent of patients required more than 2000 mg and one patient required over 30 000 mg every 24 h. Other centres have generally reported lower doses. A median dose of 60 mg/day in one centre<sup>(188)</sup> and 120 mg/day in another.<sup>(189)</sup>

A simple method of dose titration using oral morphine is to prescribe a dose of immediate-release morphine every 4 h and the same dose for rescue (for breakthrough pain).<sup>(30)</sup> The rescue dose can be given as often as required (e.g. every hour) and the total dose of morphine can be reviewed daily. The regular dose can then be adjusted according to how many rescue doses have been given.

### Rate of dose titration

The severity of the pain should determine the rate of dose titration. Patients with very severe pain can be managed by repeated parenteral dosing every 15–30 min until pain is partially relieved when an oral dosing regimen should be started.

### Tolerance

Patients vary greatly in the opioid dose required to manage their pain. The need for escalating doses is a complex phenomenon. Most patients reach a dose that remains constant for prolonged periods. When the need for dose escalation arises, any of a variety of distinct processes may be involved. Clinical experience suggests that true pharmacological tolerance is a much less common reason than disease progression or increasing psychological distress. Changes in the pharmacokinetics of an analgesic drug could also be implicated.

True pharmacological tolerance probably involves changes at the receptor level, and in this situation continued drug administration itself induces an attenuation of effect. Clinically, tolerance to the non-analgesic effects of opioids appears to occur commonly albeit at varying rates for different effects. For example, tolerance to respiratory depression, somnolence, and nausea generally develops rapidly, whereas tolerance to opioid-induced constipation develops very slowly, if at all. Tolerance to these opioid side-effects is not a clinical problem, and indeed is a desirable outcome that allows effective dose titration to proceed.

From the clinical perspective, the concern is that tolerance to the analgesic effect of the drug will develop and that this will necessitate rapid dose escalation which may continue until the drug is no longer useful. Induction of true analgesic tolerance which could compromise the utility of treatment can only be said to occur if a patient manifests a need for increasing opioid doses in the absence of other factors (e.g. progressive disease) that would be capable of explaining the increase in pain. Extensive clinical experience suggests that most patients who require an escalation in dose to manage increasing pain have demonstrable progression of disease.

This conclusion has two important implications: concern about tolerance should not impede the use of opioids early in the course of the disease, and worsening pain in a patient receiving a stable dose of opioid should not be attributed to tolerance but taken as presumptive evidence of disease progression or, less commonly, increasing psychological distress.

## Opioid pharmacokinetic factors that may influence drug dosing

### Hepatic and renal impairment

The impact of hepatic and renal impairment on opioid metabolism and excretion has been described previously. Neither hepatic nor renal dysfunction is a contra-indication to the use of opioid analgesics in cancer pain. Care is required, particularly in patients with renal impairment, but most

situations can be managed without complex or exceptional measures. Opioids may exacerbate the central nervous system signs and symptoms in patients with very severe hepatic or renal dysfunction. A high level of vigilance is required, and clinical signs and symptoms are more important than biochemical data in indicating appropriate intervention.

### Drug interactions

The tricyclic antidepressants clomipramine and amitriptyline may increase plasma morphine levels as measured by an increase in bioavailability and the half-life of morphine in cancer patients.<sup>(190)</sup> The concurrent administration of drugs that induce the hepatic mixed function oxidase system can alter the disposition of certain opioids. The metabolism of pethidine is increased by phenobarbitone and phenytoin, and that of methadone is increased by phenytoin and rifampicin. Methadone has also been reported to induce its own metabolism.

The potential for additive side-effects and serious toxicity from drug combinations must be recognized. The sedative effect of an opioid may add to that produced by numerous other centrally acting drugs such as anxiolytics, neuroleptics, and antidepressants. Likewise, the constipating effects of opioids are probably worsened by drugs with anticholinergic effects. A severe adverse reaction, including excitation, hyperpyrexia, convulsions, and death, has been reported after the administration of pethidine to patients treated with a monoamine oxidase inhibitor.

### Advanced age

It appears that all phases of pharmacokinetics are affected by the ageing process. Absorption may be influenced by decreases in gastric acid, intestinal blood flow, mucosal cell mass, and intestinal motility. The clearance of morphine, fentanyl, and nalbuphine is decreased in the elderly, and this age-related difference in pharmacokinetics may partially explain the greater sensitivity of older patients to therapeutic opioid doses compared with younger patients. Pharmacodynamic responses may also be altered in older patients. Increased receptor sensitivity and concurrent alterations in mental status may account in part for the increased response shown by elderly patients to opioid analgesics. In practice, reducing the dose or lengthening the time interval between doses for the elderly patient will minimize the development of serious adverse effects.

### Children

The management of pain in children with opioid analgesics follows the same principles as described for the adult patient (see Chapter 9.1). The oral and intravenous routes are commonly used to avoid repetitive needle injections. Continuous subcutaneous infusion has also been used in the terminally ill child. Individualization of doses and titration to the needs of the child are essential.

## Management of opioid adverse effects

Successful opioid therapy requires that the benefits of analgesia clearly outweigh treatment-related adverse effects. This requires understanding of adverse opioid effects and the strategies used to prevent and manage them are essential skills for all involved in cancer pain management.<sup>(191)</sup> The adverse effects that are frequently observed in patients receiving oral morphine and other opioids are summarized in Table 4. The most common are sedation, constipation, and nausea and vomiting, but there are other adverse effects including confusion, hallucinations, nightmares, urinary retention, multifocal myoclonus, dizziness, and dysphoria. The mechanisms that underlie these various adverse effects, even the most common, are only partly understood and, as discussed above, appear to depend upon a number of factors including age, extent of disease and organ dysfunction, concurrent administration of certain drugs, prior opioid exposure, and the route of drug administration. Studies comparing the adverse effects of one opioid analgesic with another in this population are lacking. Similarly, controlled studies comparing the adverse effects produced by the same opioid given by various routes of administration are also lacking.

As a general rule, caution is required when using opioids in patients in acute pain with impaired ventilation, bronchial asthma, or raised intracranial pressure; the same caveats do not usually limit dose titration in chronic cancer pain management.

## Factors predictive of opioid adverse effects

### Drug related

Overall, there is very little reproducible evidence suggesting that any one opioid agonist has a substantially better adverse effect profile than any other. Pethidine is not recommended in the management of chronic cancer pain because of concerns regarding its side-effect profile. Recent data from controlled studies indicate that the transdermal administration of fentanyl is associated with a lesser incidence of constipation than oral morphine.<sup>(145,192)</sup>

### Route related

There is very limited evidence to suggest differences in adverse effects associated with specific routes of systemic administration. Compared to oral

administration of morphine, small studies have demonstrated less nausea and vomiting with rectal<sup>(193)</sup> and subcutaneous administration.<sup>(194)</sup> As noted above, transdermal fentanyl appears to be associated with less constipation than oral morphine. It is not clear whether this is a route- or drug-related effect.

### Patient related

For reasons that are not well explained, there is striking interindividual variability in the sensitivity to adverse effects from morphine and other opioid drugs. Genetic variability may be at least part of the explanation in that it may influence both therapeutic and unwanted effects.

Some of this variability is related to co-morbidity. Ageing is associated with altered pharmacokinetics particularly characterized by diminished clearance and volume of distribution. This has been well described for morphine<sup>(195)</sup> and fentanyl.<sup>(196,197)</sup> In a study of morphine in chronic cancer pain, overall elderly patients required lower doses than their younger counterparts without exhibiting an enhanced risk for opioid induced adverse effects.<sup>(198)</sup> In patients with impaired renal function there is delayed clearance of the metabolite M6G.<sup>(199)</sup> Anecdotally, high concentrations of M6G have been associated with toxicity,<sup>(76,200,201)</sup> however, in a prospective study of patients with opioid-induced delirium or myoclonus no relationship to renal function was observed.<sup>(202)</sup>

Other patient-related factors that may enhance the risk of adverse effects include the co-administration of drugs which may have cumulative toxicity or other concurrent co-morbidity (Table 5).

### Opioid initiation and dose escalation

Some adverse effects appear transiently, after the initiation of an opioid or after dose escalation and spontaneously abate. This phenomenon has been well demonstrated in a prospective study of morphine dose escalation and its effects on cognitive function.<sup>(203)</sup> This study demonstrated that cognitive impairment which was evident at the start of treatment with morphine or when the dose was increased commonly improved after 7 days. This phenomenon, though often described, has not been formally studied with other adverse effects.

There is substantial variability in the dose response of opioid adverse effects. A dose-response relationship is most commonly evident with

**Table 4** Common opioid-induced adverse effects

Gastrointestinal	Nausea
	Vomiting
	Constipation
Autonomic	Xerostomia
	Urinary retention
	Postural hypotension
Central nervous system	Drowsiness
	Cognitive impairment
	Hallucinations
	Delirium
	Respiratory depression
	Myoclonus
	Seizure disorder
Hyperalgesia	
Cutaneous	Itch
	Sweating

**Table 5** Co-morbidity that may mimic opioid-induced adverse effects

Cause		Adverse effects
Central nervous system	Cerebral metastases	Drowsiness, cognitive impairment, nausea, vomiting
	Leptomeningeal metastases	Drowsiness, cognitive impairment, nausea, vomiting
	Cerebrovascular event	Drowsiness, cognitive impairment
	Extradural haemorrhage	Drowsiness, cognitive impairment
Metabolic	Dehydration	Drowsiness, cognitive impairment
	Hypercalcaemia	Drowsiness, cognitive impairment, nausea, vomiting
	Hyponatraemia	Drowsiness, cognitive impairment
	Renal failure	Drowsiness, cognitive impairment, nausea, vomiting, myoclonus
	Liver failure	Drowsiness, cognitive impairment, nausea, vomiting, myoclonus
	Hypoxaemia	Drowsiness, cognitive impairment
Sepsis/infection		Drowsiness, cognitive impairment, nausea, vomiting
Mechanical	Bowel obstruction	Nausea, vomiting
Iatrogenic	Tricyclic antidepressants	Drowsiness, cognitive impairment, constipation
	Benzodiazepines	Drowsiness, cognitive impairment
	Antibiotics	Nausea and vomiting
	Vinca alkaloids	Constipation
	Flutamide	Constipation
	Corticosteroids	Agitated delirium
	Non-steroidal anti-inflammatory drugs	Nausea, drowsiness
	Chemotherapy	Nausea, vomiting, drowsiness, cognitive impairment
	Radiotherapy	Nausea, vomiting, drowsiness

central nervous system effects of sedation, cognitive impairment, hallucinations, myoclonus, and respiratory depression. Even among these, however, there is very substantial interindividual variability. Additionally, as tolerance develops to some effects, the spectrum of adverse effects changes over time. Commonly, patients who have had prolonged opioid exposure have a lesser tendency to develop sedation or respiratory depression, and the predominant central nervous system effects become the neuroexcitatory ones of delirium and myoclonus. Gastrointestinal adverse effects generally have a weaker dose–response relationship. Some, like nausea and vomiting, are common with the initiation of therapy but are subsequently unpredictable with resolution among some patients and persistence among others. Constipation is virtually universal and demonstrates no consistent dose relationship.

## Differential diagnosis

Adverse symptoms in patients taking opioids are not always caused by the opioid. Drug induced effects must be differentiated from other causes and from drug interactions (Table 2). Indeed, the appearance of a new adverse change in patient well-being that occurs in the setting of stable opioid dosing is rarely caused by the opioid, and an alternative explanation should be vigorously sought.

## Strategies for management of opioid adverse effects

In general, four different approaches to the management of opioid adverse effects have been described:

1. dose reduction of systemic opioid;
2. specific therapy to reduce the adverse effect;
3. opioid switch (or rotation);
4. change in the route of administration.

### Dose reduction of systemic opioid

Reducing the dose of administered opioid usually results in a reduction in dose-related adverse effects. When patients have well-controlled pain, gradual reduction in the opioid dose will often result in the resolution of dose-related adverse effects whilst preserving adequate pain relief.<sup>(204)</sup>

When opioid doses cannot be reduced without the loss of pain control, reduction in dose must be accompanied by the addition of an accompanying synergistic approach.

#### *The addition of a non-opioid co-analgesic*

The analgesia achieved from NSAIDs is additive and often synergistic with that achieved by opioids.<sup>(205–208)</sup>

#### *The addition of an adjuvant analgesic that is appropriate to the pain syndrome and mechanism (see Chapter 8.2.5)*

Adjuvant analgesics (see below) may be combined with primary analgesics to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side-effects.<sup>(209)</sup> There is great interindividual variability in the response to all adjuvant analgesics and, for many only limited benefit. Many of the adjuvant analgesics have the potential to cause side-effects that may be additive to the opioid-induced adverse effects that are already problematic. In evaluating the utility of an adjuvant agent in a particular patient setting, one must consider the likelihood of benefit, the risk of adverse effects, the ease of administration, and patient convenience.

#### *The application of a therapy targeting the cause of the pain*

Specific antitumour therapies, such as radiotherapy, chemotherapy, or surgery targeting the cause of cancer related pain can provide substantial relief and thus reduce the need for opioid analgesia. Radiotherapy is of proven benefit in the treatment of painful bone metastases, epidural neoplasm and headache due to cerebral metastases (see Chapter 8.1.2). In other

settings, there is a lack of well established supportive data, and the use of radiotherapy is largely anecdotal. Despite a paucity of evidence concerning the specific analgesic benefits of chemotherapy,<sup>(210,211)</sup> there is a strong clinical impression that tumour shrinkage is generally associated with relief of pain. Surgery may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bony structures and compression of neural tissues (Chapter 8.1.3).

#### *The application of a regional anaesthetic or neuroablative intervention (see Chapter 8.2.6)*

The results of the WHO analgesic ladder validation studies suggest that 10–30 per cent of patients with cancer pain do not achieve a satisfactory balance between relief and side-effects using systemic pharmacotherapy alone without unacceptable drug toxicity. Anaesthetic and neurosurgical techniques may reduce or eliminate the requirement for systemically administered opioids to achieve adequate analgesia. In general, regional analgesic techniques such as intraspinal opioid and local anaesthetic administration or intrapleural local anaesthetic administration are usually considered first because they can achieve this end without compromising neurological integrity. Neurodestructive procedures, however, are valuable in a small subset of patients; and some of these procedures, such as coeliac plexus blockade in patients with pancreatic cancer, may have a favourable enough risk : benefit ratio that early treatment is warranted.

### Symptomatic therapy to reduce the adverse effects

Symptomatic drugs used to prevent or control opioid adverse effects are commonly employed. With few exceptions, the literature describing these approaches is anecdotal. Very few studies have prospectively evaluated efficacy and no studies have evaluated the toxicity of these approaches over the long term. In general, this approach involves the addition of a new medication, adding to medication burden and with the associated risks of additional or different adverse effects or drug interactions.

### Opioid switch (or rotation)

It has long been observed anecdotally that patients who develop intolerable adverse effects with morphine while achieving inadequate analgesia may sometimes benefit from switching to an alternative oral opioid agonist.<sup>(212,213)</sup> In recent years, the practice has focused particularly on the problems of cognitive impairment and the possible relationship with toxic metabolites of morphine and other opioids. The frequency with which this is a problem and the suggested pathophysiology has been the subject of some controversy<sup>(214,215)</sup> and some have advocated multiple switches if the first change in drug does not achieve or maintain the desired effect.<sup>(216–219)</sup> Improvements in cognitive impairment, sedation, hallucinations, nausea, vomiting, and myoclonus have been commonly reported. This approach requires familiarity with a range of opioid agonists and with the use of equianalgesic tables to convert doses when switching between opioids. While this approach has the practical advantage of minimizing polypharmacy, outcomes are variable and unpredictable. When switching between opioids, even with prudent use of equianalgesic tables, patients are at risk for under or over dosing by virtue of individual sensitivities.

#### *Dose adjustments when switching opioids*

When patients are switched from one opioid analgesic to another, lack of attention to the drug-dependent differences in opioid dose may result in undermedication or overdose. In this setting familiarity with the use of the equianalgesic dose table (Table 3) is essential. For patients with good pain control, the starting dose of the new drug should be reduced to 50–75 per cent of the equianalgesic dose to account for incomplete cross-tolerance. However, if the patient had inadequate pain control on the previous opioid, a smaller dose reduction is used and the starting dose of the new drug can be usually 75–100 per cent of the equianalgesic dose. Clinical experience suggests that additional caution is needed when the change is to methadone; a reduction to 25–33 per cent of the equianalgesic dose is prudent. After any change from one opioid to another, patients must be

monitored to assess the adequacy of analgesia and to detect the development of side-effects. Subsequent dose adjustments are usually necessary.

This information has been gained empirically but is based upon the concept that cross-tolerance is not complete among opioids and conforms to our recognition that the relative potency of some of the opioid analgesics may change with repetitive dosing, particularly those opioids with a long plasma half-life.

The biological basis for the observed intraindividual variability in sensitivity to opioid analgesia and adverse effects is multifactorial. Preclinical studies show that opioids can act on different receptors or sub-type receptors<sup>(220)</sup> and individual receptor profiles may influence the analgesia as well as the side-effects. The genetic makeup of the individual plays an important role in analgesia for some opioids<sup>(221)</sup> and similar phenomena may contribute to variability in adverse effect sensitivity.

#### Change in the route of systemic administration

There is no good evidence that efficacy is dependent on route of administration: in general, morphine has equal efficacy if given in appropriate dosage by oral, parenteral, or spinal routes. However, there are limited data that indicate that some adverse side-effects among patients receiving oral morphine can be relieved by switching the route of admission to the subcutaneous route. In one small study, this phenomenon was reported for nausea and vomiting,<sup>(194)</sup> in another there was less constipation, drowsiness, and nausea.<sup>(222)</sup>

#### Initial management of the patient receiving opioids who presents with adverse effects

Among patients receiving opioid analgesic therapy, there are two key steps in the initial management of adverse effects. First, the clinician must distinguish between morphine adverse effects and co-morbidity or drug interactions, and deal with the latter appropriately. In patients with advanced cancer, side-effects due to drug combinations are common. The potential for additive side-effects and serious toxicity from drug combinations must be recognized. The sedative effect of an opioid may add to that produced by numerous other centrally acting drugs, such as anxiolytics, neuroleptics, and antidepressants.<sup>(223)</sup> Likewise, drugs with anticholinergic effects probably worsen the constipatory effects of opioids.

If it seems that there is a true adverse effect of the opioid, consideration should be given to reducing the opioid dose. If the patient has good pain control, the morphine dose should be reduced by 25 per cent.

#### Gastrointestinal side-effects

The gastrointestinal adverse effects of opioids are common. In general, they are characterized by having a weak dose–response relationship.

##### Constipation

Constipation is the most common adverse effect of chronic opioid therapy.<sup>(224)</sup> Laxative medications should be routinely prescribed prophylactically to most patients.

##### Nausea and vomiting

Opioids may produce nausea and vomiting through both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity, and have effects on the gastrointestinal tract (including increased gastric antral tone, diminished motility, and delayed gastric emptying). With the initiation of opioid therapy, patients should be informed that nausea can occur and that it is usually transitory and controllable. Routine prophylactic administration of an antiemetic is not necessary, except in patients with a history of severe opioid-induced nausea and vomiting, but patients should have access to an antiemetic at the start of therapy if the need for one arises. Anecdotally, the use of prochlorperazine, metoclopramide, or haloperidol in low dose has usually been sufficient.

#### Central nervous system side-effects

The central nervous system side-effects of opioids are generally dose related. The specific pattern of central nervous system adverse effects is influenced by individual patient factors, duration of opioid exposure and dose.

##### Sedation

Initiation of opioid therapy or significant dose escalation commonly induces sedation that persists until tolerance to this effect develops, usually in days to weeks. It is useful to forewarn patients of this potential, and thereby reduce anxiety and encourage avoidance of activities, such as driving, that may be dangerous if sedation occurs.<sup>(225)</sup> Some patients have a persistent problem with sedation, particularly if other confounding factors exist. These factors include the use of other sedating drugs or co-existent diseases such as dementia, metabolic encephalopathy, or brain metastases. Both dextroamphetamine and methylphenidate have been used in the treatment of opioid-induced sedation.<sup>(226)</sup> Treatment with methylphenidate or dextroamphetamine is typically begun at 2.5–5 mg in the morning, which is repeated at midday if necessary to maintain effects until evening. Doses are then increased gradually if needed. Few patients require more than 40 mg per day in divided doses. This approach is relatively contra-indicated among patients with cardiac arrhythmias, agitated delirium, paranoid personality, and past amphetamine abuse.

##### Confusion and delirium

Mild cognitive impairment is common following the initiation of opioid therapy or dose increases. Similar to sedation, however, pure opioid-induced encephalopathy appears to be transient in most patients, persisting from days to a week or two. Although persistent confusion attributable to the opioid alone occurs, the aetiology of persistent delirium is usually related to the combined effect of the opioid and other contributing factors, including electrolyte disorders, neoplastic involvement of the central nervous system, sepsis, vital organ failure, and hypoxaemia.<sup>(226)</sup> A stepwise approach to management (Table 6) often culminates in a trial of a neuroleptic drug. Haloperidol in low doses (0.5–1.0 mg PO or 0.25–0.5 mg intravenously or intramuscularly) is most commonly recommended because of its efficacy and low incidence of cardiovascular and anticholinergic effects.

##### Respiratory depression

When sedation is used as a clinical indicator of central nervous system toxicity and appropriate steps are taken, respiratory depression is rare. When, however, it does occur it is always accompanied by other signs of central nervous system depression, including sedation and mental clouding. Respiratory compromise accompanied by tachypnoea and anxiety is never a primary opioid event.

With repeated opioid administration, tolerance appears to develop rapidly to the respiratory depressant effects of opioid drugs and consequently clinically important respiratory depression is a very rare event in the cancer patient whose opioid dose has been titrated against pain.

The ability to tolerate high doses of opioids is also related to the stimulus related effect of pain on respiration in a manner that is balanced against the

**Table 6** A stepwise approach to the management of confusion and delirium

- |   |
|---|
| 1. Discontinue non-essential centrally acting medications                   |
| 2. If analgesia is satisfactory, reduce opioid dose by 25%                  |
| 3. Exclude sepsis or metabolic derangement                                  |
| 4. Exclude CNS involvement by tumour  |
| 5. If delirium persists, consider:  |
| —trial of neuroleptic (e.g. haloperidol)                                    |
| —change to an alternative opioid drug                                       |
| —a change in opioid route to the intraspinal route<br>(± local anaesthetic) |
| —a trial of other anaesthetic or neurosurgical options                      |

depressant opioid effect. Opioid-induced respiratory depression can occur, however, if pain is suddenly eliminated (such as may occur following neurolytic procedures) and the opioid dose is not reduced.<sup>(227)</sup>

When respiratory depression occurs in patients on chronic opioid therapy, administration of the specific opioid antagonist, naloxone, usually improves ventilation. This is true even if the primary cause of the respiratory event was not the opioid itself, but rather, an intercurrent cardiac or pulmonary process. A response to naloxone, therefore, should not be taken as proof that the event was due to the opioid alone and an evaluation for these other processes should ensue.

Naloxone can precipitate a severe abstinence syndrome and should be administered only if strongly indicated. If the patient is bradypnoeic but readily arousable, and the peak plasma level of the last opioid dose has already been reached, the opioid should be withheld and the patient monitored until improved. If severe hypoventilation occurs (regardless of the associated factors that may be contributing to respiratory compromise), or the patient is bradypnoeic and unrousable, naloxone should be administered. To reduce the risk of severe withdrawal following a period of opioid administration, dilute naloxone (1 : 10) should be used in doses titrated to respiratory rate and level of consciousness. In the comatose patient, it may be prudent to place an endotracheal tube to prevent aspiration following administration of naloxone.

#### *Multifocal myoclonus*

All opioid analgesics can produce myoclonus. Mild and infrequent myoclonus is common. In occasional patients, however, myoclonus can be distressing or contribute to breakthrough pain that occurs with the involuntary movement. If the dose cannot be reduced due to persistent pain, consideration should be given to either switching to an alternative opioid<sup>(216)</sup> or to symptomatic treatment with a benzodiazepine (particularly clonazepam or midazolam), dantrolene or an anticonvulsant.<sup>(226)</sup>

#### **Other effects**

##### *Urinary retention*

Opioid analgesics increase smooth muscle tone and can occasionally cause bladder spasm or urinary retention (due to an increase in sphincter tone). This is an infrequent problem that is usually observed in elderly male patients. Tolerance can develop rapidly but catheterization may be necessary to manage transient problems.

#### **Opioids and driving**

The ability to continue driving is very important to maintaining the quality of life of many patients with advanced cancer. Many assume that they must stop driving whilst taking regular potent opioid analgesics, but this is not necessarily so. The usual advice to patients is that they should not drive or engage in other skilled activities such as operating machinery when they first start on morphine or a similar opioid, or when they increase the dose. However, once the initial sedative effects have resolved and both the patient and physician are confident that cognitive and psychomotor performance are no longer impaired, driving and other similar activities may restart.

This advice is based to a large extent on empirical experience and there have been few objective data to substantiate it. However, recent studies confirm, perhaps surprisingly, that morphine produces little measurable impairment of cognitive and psychomotor function,<sup>(228)</sup> particularly in patients receiving continuous treatment with stable doses.<sup>(229)</sup> In one study, which used a battery of performance tests designed specifically to assess functions related to driving ability, chronic morphine use was associated with slower reaction times, more mistakes, and a slowing in ability to process visual information and perform motor sequences, but these changes were not statistically significant compared with a control group of cancer patients not taking morphine.<sup>(225)</sup> These data support the clinical impression that stable doses of morphine are unlikely to cause substantial impairment of the psychomotor skills required for driving, and allow us to continue to advise patients to this effect.

#### **'Allergy' and intolerance to morphine**

Morphine and other opioids cause histamine release, and this is said to contribute to asthma or urticaria in allergic patients.<sup>(133,230,231)</sup> There is no published information on the incidence of this phenomenon and, in our experience, it is very rare.

However, it is not uncommon for patients to claim that they are 'allergic' to morphine. This usually means that they have had a bad experience with the drug but, on investigation, what they describe are its common side-effects. There is no doubt that most patients experience some adverse effects when they first start regular morphine treatment. Most commonly this is sedation, nausea, and, less often, vomiting. All patients must be warned about this and appropriate measures must be taken, as described above. If patients are not warned and experience unpleasant adverse effects they will be discouraged from continuing with the drug, and if they do not understand what is going on they may assume they that are 'allergic' to it.

#### **The opioid-dependent patient: definitions and misconceptions**

Addiction and substance abuse are social and medical problems of pandemic proportions which are associated with major social and human costs. Commonly, opioid drugs are the preferred substances of abuse. This association, combined with the principle of non-maleficence is the basis for concern regarding risk of addiction caused by the medical use of opioids. In recent years, the relationship between the medical use of opioids and the risk of addiction has been the focus of policy makers, medical sociologists, and pain clinicians. Overall, this body of research has demonstrated: (i) the risk of developing addictive behaviours or substance abuse as a consequence of the medical use of opioids is low; (ii) patient, family members, members of the health care professions, and regulators commonly overestimate the risk of addiction; (iii) patient, family members, members of the health care professions, and regulators often confuse physical dependence and addiction and; (iv) together, these concerns contribute substantially to physician reluctance to prescribe opioids and patient reluctance to use them.<sup>(232–234)</sup>

To understand these phenomena as they relate to opioid treatment of cancer pain, it is useful first to present a concept that might be called 'therapeutic dependence'. Patients who require a specific drug therapy to control a symptom or disease process are clearly dependent on the therapeutic efficacy of the drugs in question. Examples of this 'therapeutic dependence' include the requirements of patients with congestive cardiac failure for cardiotonic and diuretic medication or the reliance of insulin-dependent diabetics on insulin therapy. In these patients, undermedication or withdrawal of treatment would result in serious untoward consequences. Patients with chronic cancer pain have an analogous relationship to their analgesic therapy. This relationship may or may not be associated with the development of physical dependence, but is virtually never associated with addiction.

#### **Psychological dependence and 'addiction'**

The properties of the opioid analgesics that are most likely to lead to their being misused are effects mediated in the central nervous system. The term addiction refers to a psychological and behavioural syndrome characterized by a continued craving for an opioid drug to achieve a psychic effect (psychological dependence) and associated aberrant drug-related behaviours, such as compulsive drug-seeking, unsanctioned use or dose escalation, and use despite harm to self or others. Addiction should be suspected if patients demonstrate compulsive use, loss of control over drug use, and continuing use despite harm. The term addiction should not be used to describe physical dependence.

There is a common perception that opioid use, for any reason, is associated with a high risk of iatrogenic psychological dependence and that it is best avoided or minimized.<sup>(235)</sup> This bias is largely derived from experience with patients suffering from substance abuse disorder who use opioids in settings other than pain. Many health care professionals and laypersons fail to distinguish between patients with substance abuse disorder and psychologically well patients with pain, and consequently overestimate the risk

of iatrogenic addiction. This skews evaluation of the therapeutic index of opioids, and impacts adversely on the likelihood of a clinician to prescribe opioids and on the patients' compliance with an opioid prescription.

Despite very extensive use of opioids in the management of acute pain and cancer pain, and a growing experience in the use of opioids in recurrent acute pain and chronic non-cancer pain, there have been relatively few studies that have specifically addressed the risk of iatrogenic addiction.

In the only reported prospective study among cancer patients treated with morphine, Schug et al. identified one case of substance abuse among 550 cancer patients who were treated for a total of 22 525 treatment days.<sup>(236)</sup> In a national survey of burn centres, no cases of addiction were identified among more than 10 000 patients who were administered opioids for pain.<sup>(237)</sup> The largest prospective study involved a mixed population of 11 882 patients treated with acute or chronic cancer pain in the hospital setting. In this study only four cases of addiction could be identified among patients with no history of addiction who received at least one dose of an opioid for strong pain.<sup>(238)</sup> Finally, among 2369 headache patients, most of whom had access to opioid therapy, only three cases of addiction were identified.<sup>(239)</sup>

### Physical dependence

Physical dependence is the term used to describe the phenomenon of withdrawal when an opioid is abruptly discontinued or an opioid antagonist is administered.<sup>(240)</sup> The severity of withdrawal is a function of the dose and duration of administration of the opioid just discontinued (i.e. the patient's prior opioid exposure). The administration of an opioid antagonist to a physically dependent individual produces an immediate precipitation of the withdrawal syndrome. Patients who have received repeated doses of a morphine-like agonist to the point where they are physically dependent may experience an opioid withdrawal reaction when given a mixed agonist-antagonist. It can be shown that prior exposure to a morphine-like drug greatly increases a patient's sensitivity to the antagonist component of a mixed agonist-antagonist. Therefore, when used for chronic pain, the mixed agonist-antagonists should be tried before prolonged administration of a morphine-like agonist is initiated.

The abrupt discontinuation of an opioid analgesic in a patient with significant prior opioid experience will result in signs and symptoms characteristic of the opioid withdrawal or abstinence syndrome.<sup>(241)</sup> The onset of withdrawal is characterized by the patient's report of feelings of anxiety, nervousness and irritability, and alternating chills and hot flushes. A prominent withdrawal sign is 'wetness' including salivation, lacrimation, rhinorrhoea, sneezing, and sweating, as well as gooseflesh. At the peak intensity of withdrawal patients may experience nausea and vomiting, abdominal cramps, insomnia, and, rarely, multifocal myoclonus. The time course of the withdrawal syndrome is a function of the elimination half-life of the opioid on which the patient has become dependent. Abstinence symptoms generally appear within 6–12 h and reach a peak at 24–72 h following cessation of a short-half-life drug such as morphine, while onset may be delayed for 36–48 h with methadone, which has a long half-life. Therefore, it is important to emphasize that, even in a patient in whom pain has been completely relieved by a procedure (e.g. a cordotomy), it is necessary to decrease the opioid dose slowly to prevent withdrawal.

Experience indicates that the usual daily dose required to prevent withdrawal is equal to 75 per cent of the previous daily dose. Following this rule of thumb, doses can be gradually titrated down until the drug is discontinued.

### 'Pseudoaddiction'

Some cancer patients who continue to experience unrelieved pain manifest intense concern about opioid availability and drug-seeking behaviour that is reminiscent of addiction but ceases once pain is relieved, often through opioid dose escalation. This behaviour has been termed 'pseudoaddiction'.<sup>(242)</sup> Pain relief usually produced by dose escalation eliminates this aberrant behaviour and distinguishes the patient from the true addict. Misunderstanding of this phenomenon may lead the clinician inappropriately to stigmatize the patient with the label 'addict', which may compromise care and erode the doctor-patient relationship. In the setting of

unrelieved pain, the request for increases in drug doses requires careful assessment, renewed efforts to manage pain, and avoidance of stigmatizing labels.

## Management of cancer pain in patients with a history of drug abuse

Patients with a history of abuse of opioid analgesics may develop cancer and severe pain.<sup>(243,244)</sup> The management of such patients is, in principle, exactly the same as that outlined in this chapter. Our approach is to maintain such patients on oral medication if possible, even though they may require very much larger doses than normal. If parenteral medication is required, continuous subcutaneous infusion remains the mode of administration of choice.

For patients receiving therapy for drug abuse, with or without opioid maintenance therapy (e.g. methadone maintenance), it is essential that the issues relating to the use of opioid analgesics for pain management are discussed not only with the patient but also with his or her family and drug abuse counsellors, so that the patient's support group reaches a consensus on the utility and appropriateness of analgesic therapy. An open and supportive approach, and the use of concomitant psychotropic medication as appropriate, will aid the effective management of these patients.<sup>(244)</sup>

In managing such patients, clinicians should be aware of several common issues that may confound therapy. Mental clouding, either as an effect of disease progression or as an iatrogenic adverse effect, commonly raises concerns about the relapse or recurrence of psychological dependence. A request for escalation of their opioid dose may be generated by increased psychological stress rather than pain alone. Aberrant drug-seeking behaviour such as acquisition of opioids from multiple sources, 'loss' of prescribed drugs or prescriptions, unsanctioned dose escalation, and prescription fraud must be recognized as suggestive of true addiction and addressed openly as such. In all cases, one clinician should be identified as responsible for pain management, and these patients should be reviewed frequently.<sup>(244,245)</sup>

## Conclusions

There have been many development in our understanding of opioid pharmacology, particularly at a molecular level, in the 10 years since the first edition of this textbook. Genomic research promises further major advances in allowing us to understand many of the clinical dilemmas surrounding the use of these drugs in patients with pain. New formulations and increased availability of a wide range of drugs have resulted in much greater sophistication in their use. But the overarching advice remains the same. That optimal therapy for the cancer patient with pain depends on a comprehensive assessment of his or her pain, medical condition, and psychosocial status as well as an understanding of the clinical pharmacology of analgesic drugs. Cancer patients with pain very greatly in their response to analgesics. Genetic, pharmacokinetic and pharmacodynamic factors, as well as psychological factors, will influence the effectiveness of an analgesic in an individual patient. Through a process of repeated evaluation and continuous review, analgesic therapy with opioids, non-opioids, and adjuvant analgesics is individualized so that a favourable balance between pain relief and adverse pharmacological effects is maintained.

## References

1. **World Health Organization.** *Cancer Pain Relief*, 2nd edn. Geneva: WHO, 1996.
2. **Portenoy, R.K. and Lesage, P.** (1999). Management of cancer pain. *Lancet* **353**, 1695–1700.
3. **Lötsch, J. et al.** (2002). The polymorphism A118G of the human mu-opioid receptor gene decreases the pupil constrictory effect of morphine-6-glucuronide but not that of morphine. *Pharmacogenetics* **12**, 3–9.

4. Hughes, J. and Kosterlitz, H.W. (1983). Introduction (to opioid peptides). *British Medical Bulletin* **39**, 1–3.
5. Pasternak, G. (2001). The pharmacology of mu analgesics: from patients to genes. *Neuroscientist* **7**, 220–31.
6. Reisine, T. and Pasternak, G. (1996). Opioid analgesics and antagonists. In *Goodman and Gilman's Pharmacological Basis of Therapeutics* 9th edn, (ed. J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon, and A.G. Gilman), pp. 521–55. New York: McGraw-Hill.
7. Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., and Gilbert, P.E. (1976). The effects of morphine and nalorphine-like drugs in the non-dependent and morphine-dependent spinal dog. *Journal of Pharmacology and Experimental Therapeutics* **197**, 517–32.
8. Pasternak, G.W. (1993). Pharmacological mechanisms of opioid analgesics. *Clinical Neuropharmacology* **16**, 1–18.
9. Sindrup, S.H. et al. (1991). Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolisers of sparteine. *Clinical Pharmacology and Therapeutics* **49**, 686–93.
10. Inturrisi, C.E. et al. (1983). Evidence from opiate binding studies that heroin acts through its metabolites. *Life Sciences* **33**, 773–6.
11. Heiskanen, T., Olkkola, K.T., and Kalso, K. (1998). Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clinical Pharmacology and Therapeutics* **64**, 603–11.
12. Christensen, C.B. (1993). The opioid receptor binding profiles of ketobemidone and morphine. *Pharmacology and Toxicology* **73**, 344–5.
13. Raynor, K. et al. (1995). Characterization of the cloned human mu opioid receptor. *Journal of Pharmacology and Experimental Therapeutics* **272**, 423–8.
14. Traynor, J.R. (1996). The mu-opioid receptor. *Pain Reviews* **3**, 221–48.
15. Johnson, R.E. (1997). Review of US clinical trials of buprenorphine. *Research and Clinical Forums* **19**, 17–23.
16. World Health Organization. *Cancer Pain Relief*. Geneva: WHO, 1986.
17. Ventafridda, V., Tamburini, M., Caraceni, A., DeConno, F., and Naldi, F. (1987). A validation study of the WHO method for cancer pain relief. *Cancer* **59**, 851–6.
18. Takeda, F. (1990). Japan's WHO cancer pain relief program. In *Advances in Pain Research and Therapy* Vol. 16 (ed. K.M. Foley, J.J. Bonica, V. Ventafridda, and M. V. Callaway), pp. 475–83. New York: Raven Press.
19. Walker, V.A. et al. (1988). Evaluation of WHO analgesic guidelines for cancer pain in a hospital-based palliative care unit. *Journal of Pain and Symptom Management* **3**, 145–9.
20. Goisis, A. et al. (1989). Application of a WHO protocol on medical therapy for oncologic pain in an internal medicine hospital. *Tumori* **75**, 470–2.
21. Schug, S.A. et al. (1990). Cancer pain management according to WHO analgesic guidelines. *Journal of Pain and Symptom Management* **5**, 27–32.
22. Zech, D.F.J., Grond, S., Lynch, J., Hertel, D., and Lehman, K.A. (1995). Validation of World Health Organization guidelines for cancer pain relief. A 10-year prospective study. *Pain* **63**, 65–76.
23. Mercadante, S. (1999). Pain treatment and outcomes for patients with advanced cancer who receive follow-up care at home. *Cancer* **85**, 1849–58.
24. McQuay, H.J. and Moore, R.A. (1997). Antidepressants and chronic pain. *British Medical Journal* **314**, 763–4.
25. Kalso, E. et al. (1998). Systemic local-anaesthetic-type drugs in chronic pain: a systematic review. *European Journal of Pain* **2**, 3–14.
26. Jadad, A.R. and Browman, G.P. (1995). The WHO analgesic ladder for cancer pain management. *Journal of the American Medical Association* **274**, 1870–3.
27. Benedetti, C. et al. (2000). NCCN Practice Guidelines for cancer pain. *Oncology* **14**, 135–50.
28. Cleary, J.F. (2000). Cancer pain management. *Cancer Control* **7**, 120–31.
29. Walsh, D. (2000). Pharmacological management of cancer pain. *Seminars in Oncology* **27**, 45–63.
30. Hanks, G.W. et al. (2001). Morphine and alternative opioids in cancer pain: the EAPC recommendations. *British Journal of Cancer* **84**, 587–93.
31. Agency for Health Care Policy and Research: **Cancer Pain Management Panel**. *Management of Cancer Pain. Clinical Practice Guideline 9*. Washington DC: US Department of Health and Human Services, 1994.
32. Sindrup, S.H. and Brosen, K. (1995). The pharmacogenetics of codeine hypoalgesia. *Pharmacogenetics* **5**, 335–46.
33. Poulsen, L. et al. (1996). Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. *European Journal of Clinical Pharmacology* **51**, 289–95.
34. Persson, K., Hammarlund-Udenaes, M., Mortimer, O., and Rane, A. (1992). The postoperative pharmacokinetics of codeine. *European Journal of Clinical Pharmacology*.
35. Vree, T.B. and Verwey-van Wissen, C.P. (1992). Pharmacokinetics and metabolism of codeine in humans. *Biopharmaceutics and Drug Disposition* **13**, 445–60.
36. de Crean, A.J.M., Di Guiulio, G., Lampe-Schoenmaeckers, A.J.E.M., Kessels, A.G.H., and Kleijnen, J. (1996). Analgesic efficacy and safety of paracetamol–codeine combinations versus paracetamol alone: a systematic review. *British Medical Journal* **313**, 321–5.
37. Moore, A., Collins, S., Carroll, D., and McQuay, H. (1997). Paracetamol with and without codeine in acute pain: a quantitative systematic review. *Pain* **70**, 193–201.
38. Rowell, F.J., Seymour, R.A., and Rawlins, M.D. (1983). Pharmacokinetics of intravenous and oral dihydrocodeine and its acid metabolites. *European Journal of Clinical Pharmacology* **25**, 419–24.
39. Barnes, J.N. and Goodwin, F.J. (1983). Dihydrocodeine narcosis in renal failure. *British Medical Journal* **286**, 438–9.
40. Barnes, J.N., Williams, A.J., Tomson, M.J.F., Toseland, P.A., and Goodwin, F.J. (1985). Dihydrocodeine in renal failure: further evidence for an important role of the kidney in the handling of opioid drugs. *British Medical Journal* **290**, 740–2.
41. Crome, P., Gain, R., Ghurye, R., and Flanagan, R.J. (1984). Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in elderly hospital patients after single and multiple doses of Distalgesic. Preliminary analysis of results. *Human Toxicology* **3**, 41S–8S.
42. Inturrisi, C.E., Colburn, W.A., Vereby, K., Dayton, H.E., Woody, G.E., and O'Brien, C.P. (1982). Propoxyphene and norpropoxyphene kinetics after single and repeated doses of propoxyphene. *Clinical Pharmacology and Therapeutics* **31**, 157–67.
43. Beaver, W.T. (1984). Analgesic efficacy of dextropropoxyphene and dextropropoxyphene-containing combinations: a review. *Human Toxicology* **3**, 191S–220S.
44. Li Wan Po, A. and Zhang, W.Y. (1997). Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *British Medical Journal* **315**, 1565–71.
45. Perrier, D. and Gibaldi, M. (1972). Influence of first-pass effect on the systemic availability of propoxyphene. *Journal of Clinical Pharmacology* **12**, 449–52.
46. Rosenberg, W.M. et al. (1993). Dextropropoxyphene induced hepatotoxicity: a report of nine cases. *Journal of Hepatology* **19**, 470–4.
47. Hantson, P. et al. (1995). Adverse cardiac manifestations following dextropropoxyphene overdose: can naloxone be helpful? *Annals of Emergency Medicine* **25**, 263–6.
48. Pippenger, C.E. (1987). Clinically significant carbamazepine drug interactions: an overview. *Epilepsia* **28** (Suppl. 3), S71–6.
49. Justice, J.L. and Kline, S.S. (1988). Analgesics and warfarin. A case that brings up questions and cautions. *Postgraduate Medicine* **83**, 217–18, 220.
50. Whittington, R.M. (1984). Dextropropoxyphene deaths: coroner's report. *Human Toxicology* **3** (Suppl.), 175S–85S.
51. Leow, K.P. et al. (1995). Pharmacokinetics and pharmacodynamics of oxycodone when given intravenously and rectally to adult patients with cancer pain. *Anesthesia and Analgesia* **80**, 296–302.
52. Kalso, E., Poyhia, R., Onnela, P., Linko, K., Tigerstedt, I., and Tammisto, T. (1991). Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anaesthesiologica Scandinavica* **35**, 642–6.
53. Glare, P.A. and Walsh, T.D. (1993). Dose-ranging study of oxycodone for chronic pain in advanced cancer. *Journal of Clinical Oncology* **11**, 973–8.
54. Heiskanen, T. and Kalso, E. (1997). Controlled-release oxycodone and morphine in cancer related pain. *Pain* **73**, 37–45.
55. Hanks, G.W. and Hawkins, C. (2000). Agreeing a gold standard in the management of cancer pain: the role of opioids. In *The Effective Management*

- of *Cancer Pain* (ed. R. Hillier, I. Finlay, J. Welsh, and A. Miles), pp. 57–77. London: Aesculapius Medical Press.
56. Raffa, R.B., Friderichs, E., Reimann, W., Shank, R.P., Codd, E.E., and Vaught, J.L. (1992). Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *Journal of Pharmacology and Experimental Therapeutics* **260**, 275–85.
  57. Lee, C.R. et al. (1993). Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs* **46**, 313–40.
  58. Wilder Smith, C.H., Schimke, J., Osterwalder, B., and Senn, H.J. (1994). Oral tramadol, a mu-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Annals of Oncology* **5**, 141–6.
  59. Grond, S. et al. (1999). High-dose tramadol in comparison to low-dose morphine for cancer pain relief. *Journal of Pain and Symptom Management* **18**, 174–9.
  60. Petzke, F. et al. (2001). Slow-release tramadol for treatment of chronic malignant pain—an open multicenter trial. *Supportive Care in Cancer* **9**, 48–54.
  61. Radbruch, L. et al. (1996). A risk–benefit assessment of tramadol in the management of pain. *Drug Safety* **15**, 8–29.
  62. McEvoy, A. et al. (1996). Comparison of diclofenac sodium and morphine sulphate for postoperative analgesia after day case inguinal hernia surgery. *Annals of the Royal College of Surgeons of England* **78**, 363–6.
  63. St Charles, C.S. et al. (1997). A comparison of ibuprofen versus acetaminophen with codeine in the young tonsillectomy patient. *Otolaryngology—Head and Neck Surgery* **117**, 76–82.
  64. Innes, G. D. et al. (1998). Ketorolac versus acetaminophen-codeine in the emergency department treatment of acute low back pain. *Journal of Emergency Medicine* **16**, 549–56.
  65. De Conno, F. et al. (1991). A clinical study on the use of codeine, oxycodone, dextropropoxyphene, buprenorphine, and pentazocine in cancer pain. *Journal of Pain and Symptom Management* **6**, 423–7.
  66. Kopp, M. (1994). Buprenorphine transdermal system (TTS) delivery rate 35 mcg/h in an open long-term study with chronic patients. In *3rd Congress of the European Federation of IASP Chapter Nice, France. September 2000. Abstracts*.
  67. Benyhe, S. (1994). Morphine: new aspects in the study of an ancient compound. *Life Sciences* **55**, 969–79.
  68. Sawe, J., Dahlstrom, B., Paalzow, L., and Rane, A. (1981). Morphine kinetics in cancer patients. *Clinical Pharmacology and Therapeutics* **30**, 629–35.
  69. Hoskin, P.J., Hanks, G.W., Aherne, G.W., Chapman, D., Littleton, P., and Filshie, J. (1989). The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *British Journal of Clinical Pharmacology* **27**, 499–505.
  70. Gourlay, G.K., Plummer, J.L., Cherry, D.A., and Purser, T. (1991). The reproducibility of bioavailability of oral morphine from solution under fed and fasted conditions. *Journal of Pain and Symptom Management* **6**, 431–6.
  71. Sawe, J., Svensson, J.O., and Rane, A. (1983). Morphine metabolism in cancer patients on increasing oral doses—no evidence for autoinduction or dose dependence. *British Journal of Clinical Pharmacology* **16**, 85–93.
  72. Max, M.B., Inturrisi, C.E., Kaiko, R.F., Grabinski, P.Y., Li, C.H., and Foley, K.M. (1985). Epidural and intrathecal opiates: cerebrospinal fluid and plasma profiles in patients with chronic cancer pain. *Clinical Pharmacology and Therapeutics* **38**, 631–41.
  73. Paul, D., Standifer, K.M., Inturrisi, C.E., and Pasternak, G.W. (1989). Pharmacological characterization of morphine-6-beta-glucuronide, a very potent morphine metabolite. *Journal of Pharmacology and Experimental Therapeutics* **251**, 477–83.
  74. Shimomura, K. et al. (1971). Analgesic effect of morphine glucuronides. *Tohoku Journal of Experimental Medicine* **105**, 45–52.
  75. Pasternak, G.W., Bodnar, R.J., Clark, J.A., and Inturrisi, C.E. (1987). Morphine-6-glucuronide, a potent mu agonist. *Life Sciences* **41**, 2845–9.
  76. Osborne, J.R., Joel, S.P., and Slevin, M.L. (1986). Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *British Medical Journal* **292**, 1548–9.
  77. Osborne, R., Thompson, P., Joel, S., Trew, D., Patel, N., and Slevin, M.L. (1992). The analgesic activity of morphine-6-glucuronide. *British Journal of Clinical Pharmacology* **34**, 130–8.
  78. Portenoy, R.K., Thaler, H.T., Inturrisi, C.E., Friedlander-Klar, H., and Foley, K.M. (1992). The metabolite, morphine-6-glucuronide, contributes to the analgesia produced by morphine infusion in pain patients with normal renal function. *Clinical Pharmacology and Therapeutics* **51**, 422–31.
  79. Portenoy, R.K. et al. (1991). Plasma morphine and morphine-6-glucuronide during chronic morphine therapy for cancer pain: plasma profiles, steady state concentrations and the consequences of renal failure. *Pain* **47**, 13–19.
  80. D'Honneur, G., Gilton, A., Sandouk, P., Scherrmann, J.M., and Duvaldestin, P. (1994). Plasma and cerebrospinal fluid concentrations of morphine and morphine glucuronides after oral morphine. The influence of renal failure. *Anesthesiology* **81**, 87–93.
  81. Lehmann, K.A. and Zech, D. (1993). Morphine-6-glucuronide a pharmacologically active morphine metabolite: a review of the literature. *European Journal of Pain* **12**, 28–35.
  82. Peat, S.J., Hanna, M.H., Woodham, M., Knibb, A.A., and Ponte, J. (1991). Morphine-6-glucuronide: effects on ventilation in normal volunteers. *Pain* **45**, 101–4.
  83. Penson, R.T., Joel, S.P., Bakhshi, K., Clark, S.J., Langford, R.M., and Slevin, M.L. (2000). Randomised placebo-controlled trial of the activity of the morphine glucuronides. *Clinical Pharmacology and Therapeutics* **68**, 667–76.
  84. Penson, R.T., Joel, S.P., Roberts, M., Gloyne, A., Beckwith, S., and Slevin, M.L. (2000). The bioavailability and pharmacokinetics of subcutaneous, nebulized and oral morphine-6-glucuronide. *British Journal of Clinical Pharmacology* **53**, 347–54.
  85. Hanks, G.W. (1991). Morphine pharmacokinetics and analgesia after oral administration. *Postgraduate Medical Journal* **67** (Suppl. 2), S60–3.
  86. Smith, M.T., Watt, J.A., and Cramond, T. (1990). Morphine-3-glucuronide—a potent antagonist of morphine analgesia. *Life Sciences* **47**, 579–85.
  87. Gong, Q.-L., Hedner, J., Bjorkman, R., and Hedner, T. (1992). Morphine-3-glucuronide may functionally antagonise morphine-6-glucuronide induced antinociception and ventilatory depression in the rat. *Pain* **48**, 249–55.
  88. Yaksh, T.L. and Harty, G.J. (1987). Pharmacology of the allodynia in rats evoked by high dose intrathecal morphine. *Journal of Pharmacology and Experimental Therapeutics* **244**, 501–7.
  89. Labella, F.S., Pinsky, C., and Havlicek, V. (1979). Morphine derivatives with diminished opiate receptor potency show enhanced central excitatory activity. *Brain Research* **174**, 263–71.
  90. Hewett, K., Dickenson, A.H., and McQuay, H.J. (1993). Lack of effect of morphine-3-glucuronide on the spinal antinociceptive action of morphine in the rat: an electrophysiological study. *Pain* **53**, 59–63.
  91. Penson, R.T., Joel, S.P., Clark, S., Gloyne, A., and Slevin, M.L. (2001). Limited phase I study of morphine-3-glucuronide. *Journal of Pharmaceutical Sciences* **90**, 1810–16.
  92. Houde, R.W., Wallenstein, S., and Beaver, W.T. (1965). Clinical measurement of pain. In *Analgetics* (ed. G. Stevens), pp. 75–122. New York: Academic Press.
  93. Hanks, G.W., Hoskin, P.J., Aherne, G.W., Turner, P., and Poulain, P. (1987). Explanation for potency of repeated oral doses of morphine? *Lancet* **ii**, 723–5.
  94. Twycross, R.G. (1988). The therapeutic equivalence of oral and subcutaneous/intramuscular morphine sulphate in cancer patients. *Journal of Palliative Care* **2**, 67–8.
  95. Kaiko, R.F. (1986). Commentary: equianalgesic dose ratio of intramuscular/oral morphine, 1 : 6 versus 1 : 3. In *Advances in Pain Research and Therapy* Vol. 8 (ed. K.M. Foley and C.E. Inturrisi), pp. 87–93. New York: Raven Press.
  96. Hanks, G.W. (1989). Controlled-release morphine (MST Contin) in advanced cancer: the European experience. *Cancer* **623**, 2378–82.
  97. Forman, W.B., Portenoy, R.K., Yanagihara, R.H., Hunt, C., Kush, R., and Shepard, K. (1993). A novel morphine sulphate preparation: clinical trial of a controlled-release morphine suspension in cancer pain. *Palliative Medicine* **7**, 301–6.

98. Savarese, J.J., Goldenheim, P.D., Thomas, G.B., and Kaiko, R.F. (1986). Steady-state pharmacokinetics of controlled release oral morphine sulphate in healthy subjects. *Clinical Pharmacokinetics* **11**, 505–10.
99. Poulain, P. et al. (1988). Relative bioavailability of controlled release morphine tablets (MST Continus) in cancer patients. *British Journal of Anaesthesia* **61**, 569–74.
100. Gourlay, G.K., Cherry, D.A., Onley, M.M., Tordoff, S.G., Conn, D.A., Hood, G.M., and Plummer, J.L. (1997). Pharmacokinetics and pharmacodynamics of 24 hourly Kapanol compared to 12 hourly MST Contin in the treatment of severe cancer pain. *Pain* **69**, 295–302.
101. Inturrisi, C.E., Max, M.B., Foley, K.M., Schultz, M., Shin, S.-U., and Houde, R.W. (1984). The pharmacokinetics of heroin in patients with chronic pain. *New England Journal of Medicine* **210**, 1213–17.
102. Pasternak, G.W. and Standifer, K.M. (1995). Mapping of opioid receptors using antisense oligodeoxynucleotides: correlating their molecular biology and pharmacology. *Trends in Pharmacological Sciences* **16**, 334–50.
103. Kaiko, R.F., Wallenstein, S.L., Rogers, A.G., Grabinski, P.Y., and Houde, R.W. (1981). Analgesic and mood effects of heroin and morphine in cancer patients with postoperative pain. *New England Journal of Medicine* **304**, 1501–5.
104. Ripamonti, C. et al. (1997). An update on the clinical use of methadone for cancer pain. *Pain* **70**, 109–15.
105. Davis, M.P. and Walsh, D. (2001). Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. *Supportive Care in Cancer* **9**, 73–83.
106. Grochow, L., Sheidler, V., Grossman, S., Green, L., and Enterline, J. (1989). Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized double-blind study. *Pain* **38**, 151–7.
107. Sawe, J. et al. (1981). Patient-controlled dose regimen of methadone for chronic cancer pain. *British Medical Journal* **282**, 771–3.
108. Mercadante, S. et al. (1996). Patient-controlled analgesia with oral methadone in cancer pain: preliminary report. *Annals of Oncology* **7**, 613–17.
109. Mathew, P. and Storey, P. (1999). Subcutaneous methadone in terminally ill patients: manageable local toxicity. *Journal of Pain and Symptom Management* **18**, 49–52.
110. Bruera, E., Fainsinger, R., Moore, M., Thibault, R., Spoldi, E., and Ventafridda, V. (1991). Local toxicity with subcutaneous methadone. Experience of two centers. *Pain* **45**, 141–5.
111. Ripamonti, C. et al. (1998). Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: comparison of two clinical experiences. *Annals of Oncology* **9**, 79–83.
112. Szeto, H.H., Inturrisi, C.E., Houde, R., Saal, R., Cheigh, J., and Reidenberg, M.M. (1977). Accumulation of normeperidine an active metabolite of meperidine, in patients with renal failure or cancer. *Annals of Internal Medicine* **86**, 738–41.
113. Eisendrath, S.J., Goldman, B., Douglas, J., Dimatteo, L., and Van, D.C. (1987). Meperidine-induced delirium. *American Journal of Psychiatry* **144**, 1062–5.
114. Umans, J.G. and Inturrisi, C.E. (1982). Antinociceptive activity and toxicity of meperidine and normeperidine in mice. *Journal of Pharmacology and Experimental Therapeutics* **223**, 203–6.
115. Sporer, K.A. (1995). The serotonin syndrome. Implicated drugs, pathophysiology and management. *Drug Safety* **13**, 94–104.
116. Kaiko, R.F. et al. (1983). Central nervous system excitatory effects of meperidine in cancer patients. *Annals of Neurology* **13**, 180–5.
117. Agency for Health Care Policy and Research: Acute Pain Management Panel. *Acute Pain Management: Operative or Medical Procedures and Trauma*. Washington DC: US Department of Health and Human Services, 1992.
118. Houde, R.W. (1986). Clinical analgesic studies of hydromorphone. In *Advances in Pain Research and Therapy* Vol. 8 (ed. K.M. Foley and C.E. Inturrisi), pp. 129–36. New York: Raven Press.
119. Sarhill, N. et al. (2001). Hydromorphone: pharmacology and clinical applications in cancer patients. *Supportive Care in Cancer* **9**, 84–96.
120. Moulin, D.E., Kreeft, J.H., Murray, P.N., and Bouquillon, A.I. (1991). Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet* **337**, 465–8.
121. Hays, H. et al. (1994). Comparative clinical efficacy and safety of immediate release and controlled release hydromorphone for chronic severe pain. *Cancer* **74**, 1808–16.
122. Brose, W.G., Tanalian, D.L., Brodsky, J.B., Mark, J.B.D., and Cousins, M.J. (1991). CSF and blood pharmacokinetics of hydromorphone and morphine following lumbar epidural administration. *Pain* **45**, 11–17.
123. Collins, J.J. et al. (1996). Patient-controlled analgesia for mucositis pain in children: a three- period crossover study comparing morphine and hydromorphone. *Journal of Pediatrics* **129**, 722–8.
124. Lawlor, P. et al. (1997). Dose ratio between morphine and hydromorphone in patients with cancer pain: a retrospective study. *Pain* **72**, 79–85.
125. Dixon, R., Crews, T., Inturrisi, C.E., and Foley, K.M. (1983). Levorphanol: pharmacokinetics and steady-state plasma concentrations in patients with pain. *Research Communications in Chemistry, Pathology and Pharmacology* **41**, 3–17.
126. Wallenstein, S.L., Rogers, A.G., Kaiko, R.F., and Houde, R.W. (1986). Clinical analgesic studies of levorphanol in acute and chronic cancer pain. In *Advances in Pain Research and Therapy* Vol 8 (ed. K.M. Foley and C.E. Inturrisi), pp. 211–15. New York: Raven Press.
127. Moulin, D.E., Ling, G.S., and Pasternak, G.W. (1988). Unidirectional cross tolerance between morphine and levorphanol in the rat. *Pain* **33**, 233–9.
128. Kalso, E. and Vainio, A. (1990). Morphine and oxycodone hydrochloride in the management of cancer pain. *Clinical Pharmacology and Therapeutics* **47**, 639–46.
129. Poyhia, R., Vainio, A., and Kalso, E. (1993). A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. *Journal of Pain and Symptom Management* **8**, 63–7.
130. Kaiko, R.F. et al. (1996). Pharmacokinetic–pharmacodynamic relationships of controlled-release oxycodone. *Clinical Pharmacology and Therapeutics* **59**, 52–61.
131. Salzman, R.T. et al. (1999). Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? *Journal of Pain and Symptom Management* **18**, 271–9.
132. Eddy, N.B. and Lee, L.E. (1959). The analgesic equivalence and relative side action liability of oxymorphone. *Journal of Pharmacology and Experimental Therapeutics* **125**, 116–21.
133. Hermens, J.M., Hanifin, J.M., and Hirshman, C.A. (1985). Comparison of histamine release in human skin mast cells by morphine, fentanyl and oxymorphone. *Anesthesiology* **62**, 124–9.
134. Rogers, A. (1991). Considering histamine release in prescribing opioid analgesics. *Journal of Pain and Symptom Management* **6**, 44–5.
135. Yeadon, M. and Kitchen, I. (1988). Comparative binding of mu and delta selective ligands in whole brain and pons/medulla homogenates from rat: affinity profiles of fentanyl derivatives. *Neuropharmacology* **27**, 345–8.
136. Hess, R., Steibler, G., and Herz, A. (1972). Pharmacokinetics of fentanyl in man and the rabbit. *European Journal of Clinical Pharmacology* **4**, 135–41.
137. Mather, L.E. (1983). Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clinical Pharmacokinetics* **8**, 422–46.
138. Lehmann, K.A. and Zech, D. (1992). Transdermal fentanyl: clinical pharmacology. *Journal of Pain and Symptom Management* **7** (Suppl.), S8–16.
139. Varvel, J.R., Shafer, S.L., Hwang, S.S., Coen, P.A., and Stanski, D.R. (1989). Absorption characteristics of transdermally administered fentanyl. *Anesthesiology* **70**, 928–34.
140. Southam, M.A. (1995). Transdermal fentanyl therapy: system design, pharmacokinetics and efficacy. *Anti-Cancer Drugs* **6** (Suppl. 3), 26–34.
141. Portenoy, R.K. et al. (1993). Transdermal fentanyl for cancer pain: repeated doses pharmacokinetics. *Anesthesiology* **78**, 36–43.
142. Jeal, W. and Benfield, P. (1997). Transdermal fentanyl. A review of its pharmacological properties and therapeutic efficacy in pain control. *Drugs* **53**, 109–38.
143. Megens, A., Artois, K., and Vermeire, J. (1998). Comparison of the analgesic and intestinal effects of fentanyl and morphine in rats. *Journal of Pain and Symptom Management* **15**, 253–7.
144. Haazen, L., Noorduin, H., and Megens, A. (1999). The constipation-inducing potential of morphine and transdermal fentanyl. *European Journal of Pain* **3** (Suppl.), 9–15.

145. Payne, R. et al. (1998). Quality of life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. *Journal of Clinical Oncology* **16**, 1588–93.
146. Fine, P.G. et al. (1991). An open label study of oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough cancer pain. *Pain* **45**, 149–53.
147. Farrar, J.T. et al. (1998). Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *Journal of the National Cancer Institute* **90**, 611–16.
148. Christie, J.M. et al. (1998). Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *Journal of Clinical Oncology* **16**, 3238–45.
149. Egan, T.D. et al. (2000). Multiple dose pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers. *Anesthesiology* **92**, 665–73.
150. Faull, C., McKechnie, E., Riley, J., and Ahmedzai, S. (1994). Experience with dipipanone elixir in the management of cancer related pain: case study. *Palliative Medicine* **8**, 63–5.
151. Hoskin, P.J. and Hanks, G.W. (1991). Opioid agonist antagonist drugs in acute and chronic pain states. *Drugs* **41**, 326–44.
152. Rance, M.J. (1979). Animal and molecular pharmacology of mixed agonist–antagonist analgesic drugs. *British Journal of Clinical Pharmacology* **7**, 281–6.
153. Bullingham, R.E.S., McQuay, H.J., and Moore, R.A. (1983). Clinical pharmacokinetics of narcotic agonist-antagonist drugs. *Clinical Pharmacology* **8**, 332–43.
154. Bullingham, R.E.S., McQuay, H.J., Dwyer, D., Allen, M.C., and Moore, R.A. (1981). Sublingual buprenorphine used post-operatively: clinical observations and preliminary pharmacokinetic analysis. *British Journal of Clinical Pharmacology* **12**, 117–22.
155. Gal, T.J. (1989). Naloxone reversal of buprenorphine-induced respiratory depression. *Clinical Pharmacology and Therapeutics* **45**, 6–71.
156. Mello, N.K. and Mendelson, J.H. (1980). Buprenorphine suppresses heroin use by heroin addicts. *Science* **207**, 657–9.
157. Hammersley, R., Cassidy, M.T., and Oliver, J. (1995). Drugs associated with drug related deaths in Edinburgh and Glasgow, November 1990–October 1992. *Addiction* **90**, 959–65.
158. Portenoy, R.K., Foley, K.M., and Inturrisi, C.E. (1990). The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. *Pain* **43**, 273–86.
159. Neal, E.A., Meffin, P.J., Gregory, P.B., and Blaschke, T.F. (1979). Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. *Gastroenterology* **77**, 96–102.
160. Giacomini, K.M., Giacomini, J.C., Gibson, T.P., and Levy, G. (1980). Propoxyphene and norpropoxyphene plasma concentrations after oral propoxyphene in cirrhotic patients with and without surgically constructed portacaval shunt. *Clinical Pharmacology and Therapeutics* **28**, 417–24.
161. Patwardhan, R. V. et al. (1981). Normal metabolism of morphine in cirrhosis. *Gastroenterology* **81**, 1006–11.
162. Hasselstrom, J., Eriksson, L.S., Persson, A., Rane, A., Svensson, J., and Sawe, J. (1990). The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. *British Journal of Clinical Pharmacology* **29**, 289–97.
163. Chan, G.L. and Matzke, G.R. (1987). Effects of renal insufficiency on the pharmacokinetics and pharmacodynamics of opioid analgesics. *Drug Intelligence in Clinical Pharmacology* **21**, 773–83.
164. McQuay, H.J. and Moore, R.A. (1997). Opioid problems, and morphine metabolism and excretion. In *Handbook of Experimental Pharmacology* (ed. A.H. Dickenson and J.-M. Besson), pp. 335–60. Berlin: Springer-Verlag.
165. Coyle, N., Adelhardt, J., Foley, K.M., and Portenoy, R.K. (1990). Character of terminal illness in the advanced cancer patient: pain and other symptoms during last four weeks of life. *Journal of Pain and Symptom Management* **5**, 83–9.
166. Hanning, C.D. (1990). The rectal absorption of opioids. In *Advances in Pain Research and Therapy* Vol. 14 (ed. C. Benedetti, C.R. Chapman, and G. Giron), pp. 259–69. New York: Raven Press.
167. Coyle, N., Cherny, N.I., and Portenoy, R.K. (1994). Subcutaneous opioid infusions in the home. *Oncology* **8**, 21–7.
168. Oliver, D.J. (1985). The use of the syringe driver in terminal care. *British Journal of Clinical Pharmacology* **20**, 515–16.
169. Portenoy, R.K. (1987). Continuous intravenous infusions of opioid drugs. *Medical Clinics of North America* **71**, 233–41.
170. Russell, P.S.B. (1979). Analgesia in terminal malignant disease. *British Medical Journal* **i**, 1561.
171. Bruera, E., Brenneis, C., Michaud, M., MacMillan, K., Hanson, J., and MacDonald, R.N. (1988). Patient-controlled subcutaneous hydromorphone versus continuous subcutaneous infusion for the treatment of cancer pain. *Journal of the National Cancer Institute* **80**, 1152–4.
172. Waldmann, C.S., Eason, J.R., Rambohul, E., and Hanson, G.C. (1984). Serum morphine levels. A comparison between continuous subcutaneous infusions and intravenous infusions in post-operative patients. *Anaesthesia* **39**, 768–71.
173. O'Doherty, C.A., Hall, E.J., Schofield, L., and Zeppetella, G. (2001). Drugs and syringe drivers: a survey of adult specialist palliative care practice in the United Kingdom and Eire. *Palliative Medicine* **15**, 149–54.
174. Grassby, P.F. and Hutchings, L. (1997). Drug combinations in syringe drivers: the compatibility and stability of diamorphine with cyclizine and haloperidol. *Palliative Medicine* **11**, 217–24.
175. Moulin, D.E., Inturrisi, C.E., and Foley, K.M. (1986). Epidural and intrathecal opioids: cerebrospinal fluid and plasma pharmacokinetics in cancer pain patients. In *Pain Research and Therapy* Vol. 8 (ed. K.M. Foley and C.E. Inturrisi), pp. 369–84. New York: Raven Press.
176. Du Pen, S. and Williams, A.R. (1992). Management of patients receiving combined epidural morphine and bupivacaine for the treatment of cancer pain. *Journal of Pain and Symptom Management* **7**, 125–7.
177. Hogan, Q., Haddox, J.D., Abram, S., Weissman, D., Taylor, M.L., and Janjan, N. (1991). Epidural opiates and local anesthetics for the management of cancer pain. *Pain* **46**, 271–9.
178. Weinberg, D. S. et al. (1988). Sublingual absorption of selected opioid analgesics. *Clinical Pharmacology and Therapeutics* **44**, 335–42.
179. Ripamonti, C. and Bruera, E. (1991). Rectal, buccal and sublingual narcotics for the management of cancer pain. *Journal of Palliative Care* **7**, 30–5.
180. Zeppetella, G. (2001). Sublingual fentanyl citrate for cancer-related breakthrough pain: a pilot study. *Palliative Medicine* **15**, 323–8.
181. Mercadante, S. et al. (2002). Episodic (breakthrough) pain. *Cancer* **94**, 832–9.
182. Dale, O., Hjortkjaer, R., and Kharasch (2002). Nasal administration of opioids for pain management in adults. *Acta Anaesthesiologica Scandinavica* **46**, 759–70.
183. Kendall, J.M., Reeves, B.C., and Latter, V.S. (2001). Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures. *British Medical Journal* **322**, 261–5.
184. Stein, C. (1995). The control of pain in peripheral tissues by opioids. *New England Journal of Medicine* **332**, 1685–90.
185. Back, I.N. and Finlay, I. (1995). Analgesic effect of topical opioids on painful skin ulcers. *Journal of Pain and Symptom Management* **10**, 493.
186. Krajnik, M. et al. (1999). Potential uses of topical opioids in palliative care—reports of 6 cases. *Pain* **80**, 121–5.
187. Citron, M.L., Kalra, J.M., Seltzer, V.L., Chen, S., Hoffman, M., and Walczak, M.B. (1992). Patient-controlled analgesia for cancer pain: a long-term study of inpatient and outpatient use. *Cancer Investigation* **10**, 335–41.
188. Walsh, T.D. and Cheater, F.M. (1983). Use of morphine for cancer pain. *Pharmaceutical Journal* **231**, 525–8.
189. Brooks, D.J., Gamble, W., and Ahmedzai, S. (1995). A regional survey of opioid use by patients receiving specialist palliative care. *Palliative Medicine* **9**, 229–38.
190. Ventafridda, V., Ripamonti, C., DeConno, F., Bianchi, M., Pazzuconi, F., and Panerai, A.E. (1987). Antidepressants increase bioavailability of morphine in cancer patients. *Lancet* **i**, 1204.
191. Cherny, N. et al. (2001). Strategies to manage the adverse effects of oral morphine: an evidence-based report. *Journal of Clinical Oncology* **19**, 2542–54.

192. Donner, B. et al. (1996). Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. *Pain* **64**, 527–34.
193. Babul, N., Provencher, L., Laberge, F., Harsanyi, Z., and Moulin, D. (1998). Comparative efficacy and safety of controlled-release morphine suppositories and tablets in cancer pain. *Journal of Clinical Pharmacology* **38**, 74–81.
194. McDonald, P. et al. (1991). Regular subcutaneous bolus morphine via an indwelling cannula for pain from advanced cancer. *Palliative Medicine* **5**, 323–9.
195. Baillie, S.P. et al. (1989). Age and the pharmacokinetics of morphine. *Age and Ageing* **18**, 258–62.
196. Bentley, J.B. et al. (1982). Age and fentanyl pharmacokinetics. *Anesthesia and Analgesia* **61**, 968–71.
197. Holdsworth, M.T. et al. (1994). Transdermal fentanyl disposition in elderly subjects. *Gerontology* **40**, 32–7.
198. Rapin, C.H. (1989). The treatment of pain in the elderly patient. The use of oral morphine in the treatment of pain. *Journal of Palliative Care* **5**, 54–5.
199. Osborne, R. et al. (1993). The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clinical Pharmacology and Therapeutics* **54**, 158–67.
200. Hagen, N.A. et al. (1991). Chronic nausea and morphine-6-glucuronide. *Journal of Pain and Symptom Management* **6**, 125–8.
201. Sjogren, P. et al. (1993). Myoclonic spasms during treatment with high doses of intravenous morphine in renal failure. *Acta Anaesthesiologica Scandinavica* **37**, 780–2.
202. Tiseo, P.J. et al. (1995). Morphine-6-glucuronide concentrations and opioid-related side effects: a survey in cancer patients. *Pain* **61**, 47–54.
203. Bruera, E. et al. (1989). The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain* **39**, 13–16.
204. Fallon, M.T. and O'Neill, W.M. (1998). Substitution of another opioid for morphine. Opioid toxicity should be managed initially by decreasing the opioid dose. *British Medical Journal* **317**, 81.
205. Sevarino, F.B. et al. (1992). The efficacy of intramuscular ketorolac in combination with intravenous PCA morphine for postoperative pain relief. *Journal of Clinical Anesthesia* **4**, 285–8.
206. Bjorkman, R. et al. (1993). Morphine-sparing effect of diclofenac in cancer pain. *European Journal of Clinical Pharmacology* **44**, 1–5.
207. Joishy, S.K. and Walsh, D. (1998). The opioid-sparing effects of intravenous ketorolac as an adjuvant analgesic in cancer pain: application in bone metastases and the opioid bowel syndrome. *Journal of Pain and Symptom Management* **16**, 334–9.
208. Minotti, V. et al. (1998). Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. *Pain* **74**, 133–7.
209. Portenoy, R.K. (1996). Adjuvant analgesic agents. *Hematology/Oncology Clinics of North America* **10**, 103–19.
210. Queisser, W. (1984). Chemotherapy for the treatment of cancer pain. *Recent Results in Cancer Research* **89**, 171–7.
211. Rubens, R.D. et al. (1992). Appropriate chemotherapy for palliating advanced cancer. *British Medical Journal* **304**, 35–40.
212. Twycross, R.G. and Lack, S.A. *Symptom Control in Far-Advanced Cancer: Pain Relief*. London: Pitman Books, 1983.
213. Hanks, G.W. (1991). Opioid-responsive and opioid-non-responsive pain in cancer. *British Medical Bulletin* **47**, 718–31.
214. de Stoutz, N.D. et al. (1995). Opioid rotation for toxicity reduction in terminal cancer patients. *Journal of Pain and Symptom Management* **10**, 378–84.
215. Fallon, M. (1997). Opioid rotation: does it have a role? *Palliative Medicine* **11**, 177–8.
216. Cherny, N.J. et al. (1995). Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer* **76**, 1283–93.
217. Bruera, E. et al. (1995). Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration, and opioid rotation. *Journal of Pain and Symptom Management* **10**, 287–91.
218. Bruera, E. et al. (1996). Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer* **78**, 852–7.
219. Ashby, M.A. et al. (1999). Opioid substitution to reduce adverse effects in cancer pain management. *Medical Journal of Australia* **170**, 68–71.
220. Pasternak, G.W. and Standifer, K.M. (1995). Mapping of opioid receptors using antisense oligodeoxynucleotides: correlating their molecular biology and pharmacology. *Trends in Pharmacological Sciences* **16**, 344–50.
221. Brosen, K. et al. (1993). Role of genetic polymorphism in psychopharmacology—an update. *Psychopharmacology Series* **10**, 199–211.
222. Drexel, H. et al. (1989). Treatment of severe cancer pain by low-dose continuous subcutaneous morphine. *Pain* **36**, 169–76.
223. Pies, R. (1996). Psychotropic medications and the oncology patient. *Cancer Practice* **4**, 164–6.
224. Fallon, M. and O'Neill, B. (1997). ABC of palliative care. Constipation and diarrhoea. *British Medical Journal* **315**, 1293–6.
225. Vainio, A. et al. (1995). Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet* **346**, 667–70.
226. Portenoy, R.K. (1994). Management of common opioid side effects during long-term therapy of cancer pain. *Annals of the Academy of Medicine Singapore* **23**, 160–70.
227. Hanks, G.W., Twycross, R.G., and Lloyd, J.W. (1981). Unexpected complication of successful nerve block. Morphine-induced respiratory depression precipitated by removal of severe pain. *Anaesthesia* **36**, 37–9.
228. O'Neill, W.M., Hanks, G.W., Simpson, P., Fallon, M.T., Jenkins, E., and Wesnes, K. (2000). The cognitive and psychomotor effects of morphine in healthy subjects: a randomised controlled trial of repeated (four) oral doses of dextropropoxyphene, morphine, lorazepam and placebo. *Pain* **85**, 209–15.
229. Zacny, J.P. (1996). Should people taking opioids for medical reasons be allowed to work and drive? *Addiction* **91**, 1581–4.
230. Warner, M.A. et al. (1991). Narcotic-induced histamine release: a comparison of morphine, oxymorphone, and fentanyl infusions. *Journal of Cardiothoracic and Vascular Anesthesia* **5**, 481–4.
231. Katcher, J. and Walsh, D. (1999). Opioid-induced itching: morphine sulfate and hydromorphone hydrochloride. *Journal of Pain and Symptom Management* **17**, 70–2.
232. McCaffery, M. (1992). Pain control. Barriers to the use of available information. World Health Organization Expert Committee on Cancer Pain Relief and Active. *Supportive Care in Cancer* **70** (Suppl. 5), 1438–49.
233. Ward, S. E. et al. (1993). Patient-related barriers to management of cancer pain. *Pain* **52**, 319–24.
234. Mortimer, J.E. and Bartlett, N.L. (1997). Assessment of knowledge about cancer pain management by physicians in training. *Journal of Pain and Symptom Management* **14**, 21–8.
235. Sees, K.L. and Clark, H.W. (1993). Opioid use in the treatment of chronic pain: assessment of addiction. *Journal of Pain and Symptom Management* **8**, 257–64.
236. Schug, S.A. et al. (1992). A long-term survey of morphine in cancer pain patients. *Journal of Pain and Symptom Management* **7**, 259–66.
237. Perry, S. and Heidrich, G. (1982). Management of pain during debridement: a survey of US burn units. *Pain* **13**, 267–80.
238. Porter, J. and Jick, H. (1980). Addiction rare in patients treated with narcotics. *New England Journal of Medicine* **302**, 123.
239. Medina, J.L. and Diamond, S. (1977). Drug dependency in patients with chronic headaches. *Headache* **17**, 12–14.
240. Jasinski, D.R. (1981). Opiate withdrawal syndrome: acute and protracted aspects. *Annals of the New York Academy of Sciences* **362**, 183–6.
241. Rogers, A.G. (1991). Prevention of the withdrawal syndrome in an opioid-dependent one-year-old child with decreasing pain. *Journal of Pain and Symptom Management* **6**, 129.
242. Weissman, D.E. and Haddox, J.D. (1989). Opioid pseudoaddiction—an iatrogenic syndrome. *Pain* **36**, 363–6.
243. Passik, S.D. et al. (1998). Substance abuse issues in cancer patients. Part 1: Prevalence and diagnosis (in process Citation). *Oncology (Huntington)* **12** (4), 517–21, 524.
244. Passik, S.D. et al. (1998). Substance abuse issues in cancer patients. Part 2: Evaluation and treatment. *Clinical Techniques in Small Animal Practice* **13**, 65–9.
245. Passik, S.D. and Theobald, D.E. (2000). Managing addiction in advanced cancer patients. Why bother? *Journal of Pain and Symptom Management* **19**, 229–34.