

4. SYSTEMICALLY ADMINISTERED ANALGESIC DRUGS

4.1 OPIOIDS

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

4.1.1 Choice of opioid

All full opioid agonists given in appropriate doses produce the same analgesic effect and therapeutic index (McQuay, 1991), although accurate determination of equianalgesic doses is difficult due to interindividual variabilities in kinetics and dynamics (Gammaitoni et al, 2003). Equianalgesic conversion dose tables are often used to assist in the change from one opioid to another. However, such tables should be used as a guide only as they are based largely on single-dose studies in opioid-naive subjects and may not be as relevant when conversions are made after repeated doses of an opioid have been given (either in the acute pain or chronic pain setting) and do not take into account incomplete cross-tolerance (Weschules & Bain, 2008).

In general there is little evidence, on a population basis, to suggest that there are any major differences in efficacy or the incidence of side effects between any of the pure agonist opioids, although the results of individual studies are inconsistent. However, for pharmacokinetic and other reasons, some opioids may be better in some patients (Woodhouse et al, 1999 **Level II**). Comparisons of the different opioids are commonly done in patients using patient-controlled analgesia (PCA) (see Section 7.1.2 for these comparisons).

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

4.1.2 Specific opioids

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

Buprenorphine

Buprenorphine is a semi-synthetic derivative of thebaine, an alkaloid of opium, and a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist with high receptor affinity and slow dissociation from the mu-receptor (Johnson et al, 2005). Mean terminal half-lives are 24 hours following sublingual administration and 2 to 3 hours after parenteral injection; two-thirds of the drug is excreted unchanged, mainly in faeces, while the remaining one-third is metabolised predominantly in the liver and gut wall via glucuronidation to an inactive metabolite, buprenorphine-3-glucuronide, and via CYP3A4 to norbuprenorphine, which has 40 times less analgesic effect than buprenorphine (Kress, 2009). Maximum onset of effect is slower than for other opioids making acute titration difficult. In a study using experimental pain stimuli, the time to maximal peak effect after administration of an IV bolus dose of buprenorphine was between 70 and 100 minutes (Yassen et al, 2006 **Level III-3**).

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

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

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

Codeine

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

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

There are large inter-ethnic differences in the frequencies of the variant alleles. For example, the proportion of ultrarapid metabolisers is higher (up to 29%) in Middle Eastern and Northern African populations, and lower (0.5%) in Asians (Stamer & Stuber, 2007); the proportion of poor metabolisers is lower in Asians and African Americans (Holmquist, 2009).

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

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

Dextropropoxyphene

Dextropropoxyphene is often used in combination with paracetamol but this combination does not lead to better pain relief compared with paracetamol alone and increases the incidence of dizziness (Li Wan Po & Zhang, 1997 **Level I**). A later study comparing this combination with paracetamol alone in the treatment of pain after third molar surgery confirmed the lack of analgesic benefit (Sorich et al, 2004 **Level II**).

The use of this compound is discouraged, not only because of its low efficacy, but also because of a number of risks related to its use (Barkin et al, 2006). These include a euphorogenic component with risk of abuse and complex pharmacokinetics (particularly in the elderly), with the risk of accumulation and QT-interval prolongation and possibility of Torsades de Pointes (TdP) and cardiogenic death. For these reasons, it was announced that a phased withdrawal of dextropropoxyphene combination preparations would commence in the United Kingdom from January 2005 (Hawton et al, 2009). A marked decrease in prescribing of this combination was followed by a major reduction in deaths (accidental and suicide) related to its use, and while prescriptions of other analgesics increased significantly during this time, there was no evidence of a corresponding increase in deaths related to use of these other drugs (Hawton et al, 2009).

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

Diamorphine

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

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

Dihydrocodeine

Dihydrocodeine is a semi-synthetic derivative of codeine and has similar mu-opioid agonist activity. However, unlike codeine, inhibition of CYP2D6 by quinine does not alter its analgesic effect, even though the CYP2D6-dependant active metabolite, dihydromorphine, has a much higher mu-opioid receptor affinity than the parent drug (Lotsch, 2005).

Fentanyl

Fentanyl is a highly potent phenylpiperidine derivative, structurally related to pethidine. It is metabolised almost exclusively in the liver to minimally active metabolites. Less than 10% of unmetabolised fentanyl is renally excreted. Fentanyl is commonly used in the treatment of acute pain, especially when its lack of active metabolites and fast onset of action may be of clinical benefit (Peng & Sandler, 1999).

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

Hydromorphone

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

Methadone

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

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

Methadone is metabolised primarily by the cytochrome P450 group of enzymes including CYP2B6, CYP3A4 and, to a lesser extent, CYP2D6 (Weschules et al, 2008). Concurrent administration of other drugs that are cytochrome P450 inducers may increase methadone metabolism and lower methadone blood levels (eg carbamazepine, rifampicin, phenytoin, St John's Wort and some antiretroviral agents). Conversely, drugs that inhibit cytochrome P450 (eg other antiretroviral agents, some selective serotonin reuptake inhibitors, grapefruit juice, and antifungal agents) may lead to raised methadone levels and an increase in adverse effects (Fredheim et al, 2008). See Section 9.6.8 for interactions in patients with human immunodeficiency virus (HIV).

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

Morphine

Morphine remains the most widely used opioid for the management of pain and the standard against which other opioids are compared. Morphine-6-glucuronide (M6G) and M3G, the main metabolites of morphine, are formed by morphine glucuronidation, primarily in the liver. M6G is a mu-opioid receptor agonist that crosses the blood-brain barrier more slowly than morphine, contributes to morphine analgesia in patients with both normal and impaired renal function, and has other morphine-like effects including respiratory depression; M3G has very low affinity for opioid receptors, has no analgesic activity, and animal studies have shown that it may be responsible for the neurotoxic symptoms (not mediated via opioid receptors), such as hyperalgesia, allodynia and myoclonus, sometimes associated with high doses of morphine (Lotsch, 2005; van Dorp, Romberg et al, 2006; Dahan, van Dorp et al, 2008).

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

Excellent pain relief was also obtained after intrathecal administration of 100 or 125 mcg M6G in patients after hip replacement surgery, but there was a high incidence (10%) of late respiratory depression (9 to 12 hours after the dose was given) requiring treatment with

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

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

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

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

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

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

Oxycodone

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

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

Pethidine

Pethidine (meperidine) is a synthetic opioid still widely used even though it has multiple disadvantages. Despite a common belief that it is the most effective opioid in the treatment of renal colic, it was no better than morphine (O'Connor et al, 2000 **Level II**) or hydromorphone (Jasani et al, 1994 **Level II**). Similarly, pethidine and morphine had similar effects on the sphincter of Oddi and biliary tract and there was no evidence that pethidine was better in the treatment of biliary colic (Latta et al, 2002 **Level IV**).

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

Accumulation of its active metabolite, norpethidine (normeperidine), is associated with neuroexcitatory effects that range from nervousness to tremors, twitches, multifocal myoclonus and seizures (Simopoulos et al, 2002 **Level IV**). As impaired renal function increases the half-life of norpethidine, patients with poor renal function are at increased risk of norpethidine toxicity. Naloxone does not reverse and may increase the problems related to norpethidine toxicity. Overall, the use of pethidine should be discouraged in favour of other opioids (Latta et al, 2002).

Tramadol

Tramadol is commonly referred to as an atypical centrally acting analgesic because of its combined effects as an opioid agonist and a serotonin and noradrenaline reuptake inhibitor (Lotsch, 2005). Although an effective analgesic, it may not provide adequate pain relief if used as the sole agent for the management of moderate to severe acute pain in the currently recommended doses (Thevenin et al, 2008 **Level II**). Tramadol is an effective treatment of neuropathic pain with an NNT of 3.8 (Hollingshead et al, 2006 **Level I**).

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

The (+) enantiomer of tramadol is the stronger inhibitor of serotonin reuptake and the (-) enantiomer the more potent inhibitor of noradrenaline reuptake; tramadol is metabolised by CYP2D6 and the resultant active metabolite, O-desmethyltramadol (or M1), is a more potent mu-opioid receptor agonist than the parent drug (Raffa et al, 1992; Lotsch, 2005). Patients who are poor metabolisers may get less analgesic effect from tramadol (Stamer et al, 2003). Conversely, carriers of a CYP2D6 gene duplication allele (ultrarapid metabolisers) may be more sensitive to the effects of tramadol (Kirchheiner et al, 2008).

Coadministration with other drugs that inhibit CYP2D6 may also influence the effectiveness of tramadol. For example, pretreatment with paroxetine in healthy extensive metabolisers reduced the hypoalgesic effect of tramadol in an experimental pain model (Laugesen et al, 2005 **Level II**).

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

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

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

4.1.3 Determinants of opioid dose

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

Patient age

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

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

Gender

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

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

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

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

Genetics

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

Psychological factors

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

4.1.4 Adverse effects of opioids

Common adverse effects of opioids are sedation, pruritus, nausea, vomiting, slowing of GI function and urinary retention. Meta-analyses have shown that the risk of side effects from opioids administered by PCA is similar to the risks from traditional methods of systemic opioid administration, with the exception of pruritus, which is increased in patients using PCA (Hudcova et al, 2005 **Level I**).

Results from a review of all trials (including cohort studies, case-controlled studies and audit reports as well as randomised-controlled trials) suggested that there may be differences in the clinical setting (Cashman & Dolin, 2004; Dolin & Cashman, 2005). The following incidences (means) were associated with the use of PCA opioids: respiratory depression 1.2% to 11.5% (using decreased respiratory rate and oxygen desaturation, respectively, as indicators), nausea 32%, vomiting 20.7%, pruritus 13.8% and excessive sedation 5.3%. The incidences reported for IM opioid analgesia were: respiratory depression 0.8% to 37% (using the same indicators), nausea 17%, vomiting 21.9%, pruritus 3.4%, and excessive sedation 5.2% (Cashman & Dolin, 2004 **Level IV**; Dolin & Cashman, 2005 **Level IV**).

Clinically meaningful adverse effects of opioids are dose-related. There was an increased risk of 0.9% for nausea and 0.3% for vomiting for every 1 mg increase in PCA morphine consumption after surgery (Marret et al, 2005 **Level I**³). In a later prospective evaluation of the incidence of nausea and vomiting in elderly surgical inpatients requiring a length of stay greater than 2 days and given no postoperative nausea and vomiting (PONV) prophylaxis, there was also a direct correlation between increasing opioid dose and the incidence of both nausea and vomiting (Roberts et al, 2005 **Level IV**). In patients after laparoscopic cholecystectomy performed on an ambulatory basis, once a threshold dose was reached, every 3 to 4 mg increase of morphine-equivalent dose per day was associated with one additional meaningful adverse event or patient-day with such an event (Zhao et al, 2004 **Level II**).

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

Opioid-related adverse effects in surgical patients were associated with increased length of stay in hospital and total hospital costs; the use of opioid-sparing techniques can be cost-effective (Philip et al, 2002; Oderda et al, 2007 **Level IV**).

Respiratory depression

Respiratory depression (decreased central CO₂ responsiveness resulting in hypoventilation and elevated PaCO₂ levels), the most feared side effect of opioids, can usually be avoided by careful titration of the dose against effect. However, a variety of clinical indicators have been used to indicate respiratory depression, and not all may be appropriate or accurate.

A number of studies investigating hypoxia in the postoperative period, in patients receiving opioids for pain relief, have found that measurement of respiratory rate as an indicator of respiratory depression may be of little value and that hypoxaemic episodes often occur in the absence of a low respiratory rate (Catley et al, 1985 **Level IV**; Jones et al, 1990; Wheatley et al, 1990 **Level IV**; Kluger et al, 1992 **Level IV**). As respiratory depression is almost always preceded by sedation, the best early clinical indicator is increasing sedation (Ready et al, 1988; Vila et al, 2005; Macintyre & Schug, 2007).

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

In a review of PCA, case reports of respiratory depression in patients with obstructive sleep apnoea were examined (Macintyre & Coldrey, 2008). It would appear that the development of respiratory depression may have been missed because of an apparent over-reliance on the use of respiratory rate as an indicator of respiratory depression; the significance of excessive sedation was not recognised (see Section 11.5).

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

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

Checking a patient's level of alertness was considered by the American Society of Anesthesiologists (ASA) Task Force on Neuraxial Opioids to be important in the detection of respiratory depression in patients given neuraxial opioids, as well as assessments of adequacy of ventilation and oxygenation (Horlocker et al, 2009). However, it was noted only that 'in cases with other concerning signs, it is acceptable to awaken a sleeping patient to assess level of consciousness'. In this situation it would be possible for increasing sedation and respiratory depression to be missed if no attempt is made to rouse the patient.

A workshop convened by the Anesthesia Patient Safety Foundation to discuss this issue in response to concerns about the safety of IV PCA, recommended 'the use of continuous monitoring of oxygenation (generally pulse oximetry) and ventilation in nonventilated patients'

(Weinger, 2007). This was despite recognising the limitations of currently available monitors, and despite the low sensitivity of continuous pulse oximetry in patients given supplemental oxygen (common in many countries). In contrast, the ASA publication (Horlocker et al, 2009) stated that both the Task Force members and consultants 'disagree that pulse oximetry is more likely to detect respiratory depression than are clinical signs'.

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

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

Cardiac effects

The use of methadone has been linked to the development of prolonged QT interval with a risk of TdP and cardiac arrest (Gupta et al, 2007). Most case reports of TdP in patients taking methadone have identified the presence of at least one other risk factor in addition to methadone (Justo et al, 2006; Fredheim et al, 2008). Risk factors include female sex, heart disease, other drugs with effects on QT interval (eg tricyclic antidepressants, antipsychotics, diuretics) or methadone metabolism, congenital or acquired prolonged QT syndromes, liver impairment and hypokalaemia (Fredheim et al, 2008).

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

There is as yet no consensus regarding the benefits or otherwise of obtaining an electrocardiogram (ECG) in patients prior to starting methadone, although it may be that the threshold for doing so should be lower in patients with other concomitant risk factors, including those receiving higher doses of methadone (Cruciani, 2008).

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

Nausea and vomiting

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

The risk of PONV is significantly reduced by the use of droperidol, dexamethasone and ondansetron, which are equally effective (Tramer, 2001 **Level I**; Apfel et al, 2004 **Level II**); propofol and omission of nitrous oxide (N₂O) are less effective (Apfel et al, 2004 **Level II**).

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

Combinations of antiemetics may be more effective than one drug given alone. Prophylaxis with the combination of a 5HT₃-receptor antagonist and dexamethasone was associated with lower use of rescue antiemetics than 5HT₃-receptor antagonist or dexamethasone alone (Kovac, 2006 **Level I**). Similarly, the combination of droperidol and ondansetron was additive (Chan et al, 2006 **Level I**). Other combinations that were more effective than either drug given alone were cyclizine and granisetron (Johns et al, 2006 **Level II**), dexamethasone and haloperidol (Rusch et al, 2007 **Level II**; Chu CC et al, 2008 **Level II**), and dexamethasone and dolasetron (Rusch et al, 2007 **Level II**). The addition of metoclopramide to dexamethasone also led to better PONV prophylaxis but, compared with dexamethasone 8 mg alone, only if doses of 25 mg and 50 mg metoclopramide were used and not 10 mg (Wallenborn et al, 2006 **Level II**).

Droperidol, and to a lesser extent, ondansetron, may lead to prolonged QT intervals. Concerns about the potential for serious cardiac arrhythmias secondary to QT prolongation associated with administration of droperidol led to a 'black box' warning by the United States Food and Drug Administration (FDA) in 2001. Following this there has been a significant reduction in the use of this drug, even though the warning was felt by many to be unwarranted (Habib & Gan, 2008a).

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

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

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

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

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

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

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

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

P6 acupoint stimulation in patients with no antiemetic prophylaxis resulted in significant reductions in the risks of nausea, vomiting and the need for rescue antiemetics; compared with antiemetic prophylaxis, P6 acupoint stimulation seems to reduce the risk of nausea but not vomiting (Lee & Done, 2004 **Level I**).

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

Impairment of gastrointestinal motility

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

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

Urinary retention

Opioids cause urinary retention due to presumed central and peripheral mechanisms. Opioid antagonists reverse this effect; naloxone reversed opioid-induced urinary retention in 100% of patients, while the peripheral opioid antagonist methylnaltrexone was effective in 42% of study participants (Rosow et al, 2007 **Level II**). These data suggest that at least part of the bladder dysfunction caused by opioids is peripherally mediated.

Premedication with gabapentin reduced urinary retention caused by opioids (NNT 7) (Tiippana et al, 2007 **Level I**). This effect is most likely related to the opioid-sparing effect of gabapentin.

Pruritus

The mechanism of opioid-induced pruritus, which is particularly common after neuraxial opioid administration, is not fully understood, but central mu-opioid receptor-mediated mechanisms are thought to be the primary cause (Ganesh & Maxwell, 2007). Naloxone, naltrexone, nalbuphine and droperidol are effective in the treatment of opioid-induced pruritus, although minimum effective doses remain unknown (Kjellberg & Tramer, 2001 **Level I**).

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

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

Cognitive function and confusion

The risk of delirium and/or changes in cognitive function has been compared in patients receiving different PCA opioids. There was no statistically significant difference in the rates of confusion between morphine and fentanyl but the rates were 4.3% for patients given fentanyl and 14.3% for those receiving morphine; there was less depression of cognitive function with fentanyl (Herrick et al, 1996 **Level II**). Compared with morphine, no differences in cognitive function were reported in patients receiving tramadol (Silvasti et al, 2000 **Level II**; Ng et al, 2006 **Level II**), but cognitive function was poorer in patients given hydromorphone (Rapp et al, 1996 **Level II**). Studies of lower quality reported a significantly greater incidence of delirium with pethidine compared with morphine (Adunsky et al, 2002 **Level III-3**) and a variety of other opioids

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

Tolerance and hyperalgesia

In the absence of disease progression, a decrease in the effectiveness of opioid analgesia has traditionally been attributed to opioid tolerance. It is now known that administration of opioids can lead to both opioid-tolerance (a desensitisation of antinociceptive pathways to opioids) and, paradoxically, to opioid-induced hyperalgesia (OIH) (a sensitisation of pronociceptive pathways leading to pain hypersensitivity), and that both these phenomena can significantly reduce the analgesic effect of opioids (Angst & Clark, 2006; Chu LF et al, 2008). The mechanisms underlying the development of tolerance and OIH are still not fully understood but, as with neuropathic pain, are thought to include activation of the glutaminergic system via the NMDA receptor, as well as other transmitter and receptor systems (Angst & Clark, 2006; Mao, 2008).

Mao (Chang et al, 2007; Mao, 2008) distinguishes between ‘pharmacological tolerance’ (ie tolerance, as defined in Section 11.7 — the predictable and physiological decrease in the effect of a drug over time) and ‘apparent tolerance’, where both tolerance and OIH contribute to a decrease in the effectiveness of opioids. The clinical significance of this mix, and the relevant contribution of pharmacological tolerance and OIH to ‘apparent tolerance’ in any particular patient, is difficult if not impossible to determine (Angst & Clark, 2006). Inadequate pain relief because of pharmacological tolerance may improve with opioid dose escalation, while improvements in analgesia in the presence of OIH may follow a reduction in opioid dose (Chang et al, 2007; Mao, 2008; Chu LF et al, 2008).

It is probable that the degree of OIH varies between opioids. Morphine, in high doses, may be more likely to result in OIH than other opioids; experimental data and a very limited number of case reports have shown an improvement when morphine doses were reduced or a change to methadone, fentanyl or sufentanil was made (Angst & Clark, 2006). Similarly, it appears that opioids differ in their ability to induce tolerance and, at least in part, this may reflect their varying ability to promote receptor internalisation and recycling. While drugs such as methadone, fentanyl and sufentanil promote receptor internalisation and thereby recycling, activation of opioid receptors by morphine leads to little or no receptor internalisation and an increased risk of development of tolerance (Joo, 2007).

The difference between opioids is one reason why opioid-rotation may be a useful strategy in the clinical setting in attempts to improve pain relief (see Section 11.7.3).

Studies using experimental pain stimuli

Many animal studies have shown that opioid administration can lead to OIH (Angst & Clark, 2006). A number of human studies have also investigated changes in pain sensitivity following long-term opioid use and reported increases in sensitivity to certain pain stimuli.

Patients taking methadone as part of a drug-dependence treatment program have been shown to have an increased sensitivity to cold pressor pain stimuli (Compton et al, 2000 **Level IV**; Doherty et al, 2001 **Level III-2**; Athanasos et al, 2006 **Level III-2**). Similarly, pain sensitivity to cold pressor but not heat stimuli was noted in patients 1 month after starting oral morphine therapy (Chu et al, 2006 **Level III-2**), and to cold pressor but not electrical pain stimuli in patients with chronic non-cancer pain taking either methadone or morphine (Hay et al, 2009 **Level III-2**). In a comparison of methadone-maintained and buprenorphine-maintained patients, pain sensitivity to cold pressor pain stimuli was increased in both groups and overall there was no difference between

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

Angst and Clark (Angst & Clark, 2006 **Level I**) summarised studies that investigated the effects of a short-duration remifentanil infusion in volunteer subjects with pre-existing experimentally induced mechanical hyperalgesia; the use of remifentanil was shown to aggravate hyperalgesia, the magnitude of the effect was directly related to the dose given, and coadministration of ketamine abolished the effect of remifentanil. Methadone-maintained subjects were shown to have a significant tolerance to remifentanil given by short-duration infusion, suggesting that opioid-tolerant patients may require significantly higher doses for the treatment of acute pain compared with opioid-naïve patients; dose-dependent increases in cold pressor tolerance were found (Hay et al, 2009 **Level III-2**).

Clinical studies

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

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

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

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

There are case reports of patients with cancer and chronic non-cancer pain and taking high doses of opioid, who developed OIH and whose pain relief improved following reduction of

their opioid dose or after a change was made to another opioid (Angst & Clark, 2006; Chu LF et al, 2008), however there have been no similar reports from an acute pain setting.

Clinical implications and possible attenuation of tolerance and OIH

See Section 11.7.1.

Tolerance to adverse effects of opioids

Tolerance to the side effects of opioids also occurs; tolerance to sedation, cognitive effects, nausea and respiratory depression can occur reasonably rapidly, but there is little if any change in miosis or constipation (Chang et al, 2007).

Key messages

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

18. In clinically relevant doses, there is a ceiling effect for respiratory depression with buprenorphine but not for analgesia (**N**) (**Level III-2**).
19. Assessment of sedation is a more reliable way of detecting early opioid-induced respiratory depression than a decreased respiratory rate (**S**) (**Level III-3**).
20. The evidence for risk of cardiac arrhythmias following low-dose droperidol is poor (**N**) (**Level III-3**).
21. In adults, patient age rather than weight is a better predictor of opioid requirements, although there is a large interpatient variation (**U**) (**Level IV**).
22. Impaired renal function and the oral route of administration result in higher levels of the morphine metabolites morphine-3-glucuronide and morphine-6-glucuronide with increased risk of sedation and respiratory depression (**S**) (**Level IV**).

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

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

4.2 PARACETAMOL, NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND COXIBS

4.2.1 Paracetamol

Paracetamol (acetaminophen) is the only remaining para-aminophenol used in clinical practice and is an effective analgesic (see below) and antipyretic. It is absorbed rapidly and well from the small intestine after oral administration with a bioavailability of between 63% and 89% (Oscier & Milner, 2009). It can also be given rectally and intravenously (see below and Section 6).

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

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

Efficacy

Single doses of paracetamol are effective in the treatment of postoperative pain. The NNTs for a variety of doses as well as combinations of paracetamol with other analgesic drugs such as codeine are discussed and listed in Section 6 and Table 6.1.

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

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

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

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

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

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

Adverse effects

Paracetamol has fewer side effects than NSAIDs and can be used when the latter are contraindicated (eg patients with a history of asthma or peptic ulcers). It is commonly recommended that paracetamol should be used with caution or in reduced doses in patients with active liver disease, history of heavy alcohol intake and glucose-6-phosphate dehydrogenase deficiency. However, others report that it can be used safely in patients with liver disease and is preferred to NSAIDs, and that therapeutic doses of paracetamol, at least for short-term use, are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol (Benson et al, 2005; Graham et al, 2005; Oscier & Milner, 2009). There is no evidence that patients who have depleted glutathione stores (eg patients who are malnourished, or who have cirrhosis, hepatitis C or human immunodeficiency virus [HIV]) are at increased risk of liver dysfunction when exposed to therapeutic doses of paracetamol (Benson et al, 2005; Graham et al, 2005; Oscier & Milner, 2009).

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

4.2.2 Non-selective non-steroidal anti-inflammatory drugs

The term NSAIDs is used to refer to both nsNSAIDs and coxibs (COX-2 selective inhibitors). NSAIDs have a spectrum of analgesic, anti-inflammatory and antipyretic effects and are effective analgesics in a variety of acute pain states. Many effects of NSAIDs can be explained by inhibition of prostaglandin synthesis in peripheral tissues, nerves, and the CNS (Botting, 2006). However, NSAIDs and aspirin may have other mechanisms of action independent of any effect on prostaglandins, including effects on basic cellular and neuronal processes. Prostaglandins are produced by the enzyme prostaglandin endoperoxide (PGH) synthase, which has both cyclo-oxygenase and hydroperoxidase sites. Two subtypes of cyclo-oxygenase enzyme have been identified – the ‘constitutive’ COX-1, the ‘inducible’ COX-2: a COX-3 is also being investigated (Simmons et al, 2004; Gajraj & Joshi, 2005; Botting, 2006; Kam & So, 2009).

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

Efficacy

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

nsNSAIDs are integral components of multimodal analgesia (Kehlet, 1997; Brodner et al, 2001; Barratt et al, 2002). However, while useful analgesic adjuncts, they are inadequate as the sole analgesic agent in the treatment of severe postoperative pain. When given in combination with opioids after surgery, nsNSAIDs resulted in better analgesia, reduced opioid consumption and a lower incidence of PONV and sedation (Elia et al, 2005 **Level I⁵**; Marret et al, 2005 **Level I⁵**). There was no effect on pruritus, urinary retention and respiratory depression (Marret et al, 2005 **Level I⁵**). Similarly, in patients less than 70 years of age undergoing cardiothoracic surgery, the use of nsNSAIDs reduced pain scores and opioid requirements (Bainbridge et al, 2006 **Level I**) although the use of these drugs in patients following coronary artery bypass surgery is controversial (see below).

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

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

Adverse effects

NsNSAID side effects are more common with long-term use — and there are concerns relating to prothrombotic effects. In the perioperative period the main concerns are renal impairment, interference with platelet function, wound and bone healing, and peptic ulceration or bronchospasm in individuals at risk. Certain risks are accentuated in the perioperative period because of haemodynamic disturbances, fluid shifts, activation of the neurohumoral stress response and deficient enteral feeding. In general, the risk and severity of nsNSAID-associated side effects is increased in elderly people (Pilotto et al, 2003; Juhlin et al, 2005).

Renal function

Renal prostaglandins regulate tubular electrolyte handling, modulate the actions of renal hormones, and maintain renal blood flow and glomerular filtration rate in the presence of circulating vasoconstrictors. The adverse renal effects of chronic nsNSAID use are common and well-recognised. In some clinical conditions, including hypovolaemia, dehydration and major surgery, high circulating concentrations of the vasoconstrictors angiotensin II, noradrenaline and vasopressin increase production of intrarenal vasodilators including prostacyclin — maintenance of renal function may then depend on prostaglandin synthesis and thus can be sensitive to brief nsNSAID administration.

In patients with normal preoperative renal function, nsNSAIDs caused a clinically insignificant and transient decrease in creatinine clearance the first day after surgery, and there were no differences between patients given diclofenac, ketorolac, indomethacin (indometacin) or ketoprofen (Lee A et al, 2007 **Level I**). The risk of adverse renal effects of nsNSAIDs and coxibs is increased in the presence of factors such as pre-existing renal impairment, hypovolaemia, hypotension, use of other nephrotoxic agents and angiotensin-converting enzyme (ACE) inhibitors (RCA, 1998 **Level IV**).

With proper selection and monitoring, the incidence of NSAID-induced perioperative renal impairment is low and NSAIDs need not be withheld in patients with normal preoperative renal function (Lee A et al, 2007 **Level I**).

Platelet function

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

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

Peptic ulceration

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

Acute gastroduodenal damage and bleeding can also occur with short-term nsNSAID use — the risk is increased with higher doses, a history of peptic ulceration, use for more than 5 days and in elderly people (Strom et al, 1996 **Level IV**). After 5 days of naproxen and ketorolac use in healthy elderly subjects, ulcers were found on gastroscopy in 20% and 31% of cases respectively (Harris et al, 2001 **Level II**; Stoltz et al, 2002 **Level II**; Goldstein et al, 2003 **Level II**).

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

Aspirin-exacerbated respiratory disease

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

Bone healing

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

Cardiovascular

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

4.2.3 Cyclo-oxygenase-2 selective inhibitors (coxibs)

Coxibs selectively inhibit the inducible cyclo-oxygenase enzyme, COX-2, and spare constitutive COX-1 (see above). The coxibs available at present include celecoxib, etoricoxib and parecoxib, the injectable precursor of valdecoxib. By sparing physiological tissue prostaglandin production while inhibiting inflammatory prostaglandin release, coxibs offer the potential for effective analgesia with fewer side effects than nsNSAIDs.

Efficacy

Coxibs were as effective as nsNSAIDs in the management of postoperative pain (Romsing & Moiniche, 2004 **Level I⁶**). They were also as effective as nsNSAIDs for the treatment of low back pain (although effect sizes were small) but the incidence of side effects was lower with coxibs (Roelofs et al, 2008 **Level I**). NNTs are comparable with those for nsNSAIDs for the treatment of moderate to severe acute pain. For a list of NNTs for each drug see Table 6.1.

Preoperative coxibs reduced postoperative pain and opioid consumption and increased patient satisfaction (Straube et al, 2005 **Level I⁶**). When given in combination with opioids after surgery, coxibs were opioid-sparing (Hubbard et al, 2003 **Level II**; Malan et al, 2003 **Level II**; Ng et al, 2003 **Level II**; Reynolds et al, 2003 **Level II**; Gan et al, 2004 **Level II**; Celik et al, 2005 **Level II**; Nussmeier et al, 2006 **Level II**; Snabes et al, 2007 **Level II**; White PF et al, 2007 **Level II**), but both a decrease in the incidence of opioid-related side effects (Malan et al, 2003 **Level II**; Gan et al, 2004 **Level II**) and no difference (Hubbard et al, 2003 **Level II**; Ng et al, 2003 **Level II**; Celik et al, 2005 **Level II**; Snabes et al, 2007 **Level II**; White PF et al, 2007 **Level II**) has been reported. A meta-analysis concluded that there was no evidence for a decrease in adverse effects (Romsing et al, 2005 **Level I**) as did a meta-analysis that included trials of coxibs given to patients receiving PCA morphine; it showed reduced opioid consumption but no significant reductions in pain scores or opioid-related adverse effects (Elia et al, 2005 **Level I⁷**).

Timing of administration may not be critical. A comparison of celecoxib, started preoperatively or postoperatively and continued for 3 days after surgery, showed opioid-sparing and improved patient satisfaction in both patient groups compared with placebo, but there was no advantage for administration before surgery (Sun et al, 2008 **Level II**). Similarly, in patients undergoing hip arthroplasty, preoperative administration of parecoxib offered no advantage compared with postoperative use; opioid-sparing was again seen in both groups compared with placebo (Martinez et al, 2007 **Level II**). Pain relief was also no better when parecoxib was given before incision compared with administration at the end of surgery in patients undergoing colorectal surgery (Lee et al, 2008 **Level II**).

Adverse effects

Renal function

COX-2 is constitutively expressed in the kidney and is highly regulated in response to alterations in intravascular volume. COX-2 has been implicated in maintenance of renal blood flow, mediation of renin release and regulation of sodium excretion (Cheng & Harris, 2004 **Level IV**; Kramer et al, 2004 **Level IV**).

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

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

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

Platelet function

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

Cardiovascular effects

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

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

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

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

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

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

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

Gastrointestinal

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

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

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

Aspirin-exacerbated respiratory disease

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

Bone healing

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

Key messages

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

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

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

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

4.3 ADJUVANT DRUGS

4.3.1 Inhalational agents

Nitrous oxide

Nitrous oxide (N_2O) has been used since the inception of anaesthesia for its modest analgesic and sedative properties, with minimal respiratory and cardiovascular depression. In many countries it is available as a 50% N_2O /50% oxygen mixture called Entonox[®]. While it has a long history of use, there is a paucity of good studies examining its effectiveness in comparison with other analgesics.

In adults, N_2O in oxygen has some analgesic efficacy in labour (Rosen, 2002 **Level I**) and is effective during painful procedures such as bone marrow aspiration (Gudgin et al, 2008 **Level III-3**), venous cannulation (Gerhardt et al, 2001 **Level II**), sigmoidoscopy (Harding & Gibson, 2000 **Level II**) and liver biopsy (Castera et al, 2001 **Level II**), and in relieving acute ischaemic chest

pain (O'Leary et al, 1987 **Level II**). In elderly patients (median age 84 years), N₂O provided better analgesia than morphine during bed sore and ulcer care (Paris et al, 2008 **Level II**).

In children, N₂O was effective in reducing pain associated with IV cannulation (Henderson et al, 1990 **Level II**; Hee et al, 2003 **Level III-2**; Ekblom et al, 2005 **Level III-2**), urethral catheterisation (Zier et al, 2007 **Level III-2**), and laceration repair (Burton et al, 1998 **Level II**; Luhmann et al, 2006 **Level II**). It has been reported to provide analgesia for the pain associated with fracture manipulation in children (Gregory & Sullivan, 1996 **Level III-1**; Evans et al, 1995 **Level III-1**), although its efficacy as an analgesic during very painful procedures may be limited (Babl et al, 2008 **Level IV**).

In the experimental setting, a study measuring changes in detection and pain thresholds to electrical tooth stimulation, reported the development of acute and chronic tolerance in response to single and repeated administration of N₂O (38% or 35%) for 30 minutes (Ramsay et al, 2005 **Level II**). The significance of this finding in the clinical setting is unknown.

N₂O diffuses more rapidly than nitrogen and can expand enclosed air-containing spaces within the body. Its use is therefore contraindicated in the presence of a pneumothorax, obstruction of middle ear and sinus cavities, recent vitreoretinal surgery, pneumocephalus, bowel obstruction and gas embolism (Shaw & Morgan, 1998).

Toxicity

N₂O oxidises the cobalt ion of cobalamin (vitamin B12) preventing it from acting as a coenzyme for methionine synthetase (MS); MS also requires 5-methyltetrahydrofolate as a coenzyme (Sanders et al, 2008). MS is required for the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), and therefore the production of rapidly dividing tissues such as bone marrow and GI mucosa, as well as the synthesis of myelin (Sanders et al, 2008).

Bone marrow and neurological complications have been reported in patients exposed to N₂O. The risk may be greater in critically ill patients with increased metabolic demands or poor nutrition (Amos et al, 1982 **Level IV**).

N₂O-induced bone marrow toxicity leading to megaloblastic anaemia is usually progressive but reversible. The bone marrow changes are almost completely prevented by administration of folic acid (Amos et al, 1982).

Neurotoxicity associated with N₂O use is rare but can be rapid and may be irreversible. Patients deficient in vitamin B12, including those with a subclinical deficiency (ie without an associated anaemia), may develop a severe and progressive myeloneuropathy even after brief exposure to N₂O. There are many examples of such case reports (Schilling, 1986; Holloway & Alberico, 1990; Flippo & Holder, 1993; Kinsella & Green, 1995; Nestor & Stark, 1996; Rosener & Dichgans, 1996; Sesso et al, 1999; Marie et al, 2000; Waters et al, 2005; Cartner et al, 2007; Wu et al, 2007; Meyers & Judge, 2008; Singer et al, 2008; Somyreddy & Kothari, 2008). Those at risk of vitamin B12 deficiency include some vegetarians (in particular vegans), the newborn of vegetarian mothers, patients with GI pathology, elderly people or patients taking PPIs and H₂ blockers, and alcoholics (Schilling, 1986; Rosener & Dichgans, 1996; Nilsson-Ehle, 1998; Schenk et al, 1999; Carmel, 2000; McNeely et al, 2000; Sanders et al, 2008). In individuals who are not vitamin B12 deficient, larger quantities or more prolonged use of N₂O seems to be required before neurotoxicity is seen. Examples have been reported in those abusing the drug (Sanders et al, 2008).

The neuropathy appears to be the result of decreased methionine and subsequent defective myelin formation. The clinical and radiological (magnetic resonance imaging [MRI]) picture is that of a vitamin B12 deficiency where subacute combined degeneration (SACD) of the spinal cord causes numbness, tingling, paresthesiae, ataxia and spasticity (Weimann, 2003). Involvement of peripheral, autonomic and central nervous systems may also lead to incontinence, diplopia, confusion or impaired cognitive function (Weimann, 2003). In patients with pernicious anaemia, SACD usually responds well to treatment with vitamin B12,

although it may take many months and response to treatment may be incomplete (Toh et al, 1997). Patients with SACD related to N₂O exposure may sometimes show improvement after administration of vitamin B12 +/- methionine (Wu et al, 2007; Meyers & Judge, 2008; Singer et al, 2008) although this is not always the case.

In monkeys exposed continuously to N₂O, SACD is prevented by a diet supplemented with methionine (Scott et al, 1981) and in cultured human fibroblasts, a methionine-rich media diminished the rate of MS activation (Christensen & Ueland, 1993). Despite the lack of any good data assessing efficacy in humans, and even though the bone marrow changes are usually reversible, it may be reasonable to give patients repeatedly exposed to N₂O, vitamin B12 and folic or folinic acid supplements (Weimann, 2003).

Another consequence of N₂O-induced inactivation of MS is elevation of plasma homocysteine (a known risk factor for coronary artery and cerebrovascular disease), the levels of which rise after anaesthesia using N₂O (Badner et al, 1998 **Level II**; Myles, Chan, Leslie et al, 2008 **Level II**; Nagele et al, 2008 **Level III-3**). Patients who are homozygous for polymorphisms in the gene encoding the enzyme that is an antecedent to MS are at a higher risk of developing abnormal plasma homocysteine concentrations after N₂O anaesthesia (Nagele et al, 2008 **Level III-3**). A subset analysis of data from a large trial of 2050 patients — the ENIGMA trial (Myles et al, 2007) — found a relationship between increased plasma homocysteine levels and all major postoperative complications (Myles, Chan, Leslie et al, 2008 **Level II**) as well as marked impairment of endothelial function (Myles, Chan, Kaye et al, 2008 **Level II**). However, the ENIGMA study looked at patients who were undergoing major surgery that lasted for 2 hours or longer and were given N₂O in a concentration of 70% (compared with a nitrous-free anaesthetic), and not at N₂O used as an analgesic agent in a non-operative setting. The significance of this in respect to N₂O use in this group of patients is unknown.

Methionine given preoperatively to patients undergoing N₂O anaesthesia improved the rate of recovery of MS and prevented the prolonged postoperative rise in plasma homocysteine concentrations (Christensen et al, 1994 **Level IV**). Preoperative administration of oral B vitamins (folate, B6 and B12) also prevent the postoperative increase in homocysteine following N₂O anaesthesia (Badner et al, 2001 **Level II**).

The information about the complications of N₂O comes from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to N₂O in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to N₂O. Nevertheless, the severity of the potential problems requires highlighting. The suggestions for the use of N₂O outlined below are extrapolations only from the information above.

Suggestions for the use of nitrous oxide as an analgesic

When N₂O is to be used repeatedly for painful short procedures, it may be reasonable to:

- exclude patients with a known vitamin B12 deficiency;
- screen patients at risk of B12 deficiency by examination of the blood picture and serum B12 concentrations before using N₂O;
- exclude asymptomatic patients with macrocytic anaemia or hypersegmentation of neutrophils until it is established that vitamin B12 or folate deficiency is not the cause;
- exclude females who may be in the early stages of pregnancy, although this will depend on the relative harm of any alternative methods;
- limit exposure to N₂O to the briefest possible time — restricting the duration of exposure may require strict supervision and limited access to the gas;

- administer methionine, vitamin B12 (both inexpensive and with a good safety profile) and possibly folic or folinic acid to patients repeatedly exposed to N₂O. The doses that may prevent the complications of exposure to N₂O have not been established; and
- monitor for clinical signs and symptoms of neuropathy on a regular basis.

Methoxyflurane

Methoxyflurane is a volatile anaesthetic agent with analgesic properties. It was first marketed in 1962 and later withdrawn from sale in 2001. The FDA withdrew the drug because of the risk of nephrotoxicity and hepatotoxicity and stated that it would not consider reintroduction into the market until new clinical trials were undertaken (FDA-Penthrane, 2005). Methoxyflurane is also not licensed in the United Kingdom. Although no longer used as an anaesthetic, methoxyflurane has been reintroduced into the health-care market in Australia and New Zealand for use as an analgesic, and is available as a self-administered 'Penthrox[®]' inhaler, which dispenses 0.2% to 0.4% methoxyflurane (Medical Devices International, 2009).

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

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

Methoxyflurane causes a dose-dependent renal toxicity and, as noted above, renal failure was a key reason behind the withdrawal of the drug from use. Use of an analgesic device delivering higher concentrations of methoxyflurane was reported to have led to two fatalities from renal toxicity (Toomath & Morrison, 1987). However, the amount of methoxyflurane delivered using the Penthrox[®] inhaler is said to be significantly less than the dose that has been associated with subclinical nephrotoxicity (Grindlay & Babl, 2009).

Key messages

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

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

- Neuropathy and bone marrow suppression are rare but potentially serious complications of nitrous oxide use, particularly in at-risk patients (**U**).
- The information about the complications of nitrous oxide is from case reports only. There are no controlled studies that evaluate the safety of repeated intermittent exposure to nitrous oxide in humans and no data to guide the appropriate maximum duration or number of times a patient can safely be exposed to nitrous oxide. The suggestions for the use of nitrous oxide are extrapolations only from the information above. Consideration should be given to duration of exposure and supplementation with vitamin B12, methionine, and folic or folinic acid (**U**).
- If nitrous oxide is used with other sedative or analgesic agents, appropriate clinical monitoring should be used (**U**).

4.3.2 NMDA-receptor antagonists

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

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

Ketamine

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

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

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

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

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

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

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

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

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

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

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

Low-dose parenteral ketamine may also improve analgesia in patients with opioid-induced tolerance or hyperalgesia. In patients taking opioids on a long-term basis, the administration of ketamine has been reported to lead to improved pain relief and reduced opioid requirements (Bell, 1999; Eilers et al, 2001; Mitra, 2008). After spinal fusion in opioid-tolerant patients, use of a continuous ketamine infusion resulted in significantly less pain but did not reduce PCA opioid requirements (Urban et al, 2008 **Level II**). The evidence for the ability of ketamine to attenuate the acute tolerance and/or OIH seen after intraoperative use of remifentanyl infusions is conflicting. Ketamine infusion reduced the area of punctate mechanical hyperalgesia around the wound and postoperative morphine consumption, following high-dose remifentanyl infusion during laparotomy (Joly et al, 2005 **Level II**). In paediatric scoliosis surgery, ketamine did not decrease postoperative morphine requirements after remifentanyl-based anaesthesia (Engelhardt et al, 2008 **Level II**).

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

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

Adverse effects with short-term systemic administration of ketamine

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

Routes of systemic administration and bioavailability

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

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

Dextromethorphan

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

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

Magnesium

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

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

Amantadine and memantine

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

Oral memantine reduced the number of demands for bolus doses of ropivacaine for analgesia via a brachial plexus catheter and, in combination with a continuous ropivacaine infusion, led to a reduction in the incidence of phantom limb pain at 6 months but not 12 months, following traumatic upper limb amputation (Schley et al, 2007 **Level II**). It was not effective in reducing the incidence of postmastectomy pain syndrome (Eisenberg et al, 2007 **Level II**).

Key messages

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

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

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

4.3.3 Antidepressant drugs

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

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

See Table 4.1 for NNTs and NNHs.

Table 4.1 Antidepressants for the treatment of neuropathic pain

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

Note: CI: confidence interval; TCA: tricyclic antidepressants; SSRI: selective serotonin re-uptake inhibitors.

Source: Adapted from Collins, Moore, McQuay & Wiffen (2000), Saarto & Wiffen (2007), Sultan et al 2008⁸

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

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

8 This meta-analysis includes a study on venlafaxine that has since been withdrawn from publication. Please refer to the *Introduction* at the beginning of this document for comments regarding the management of retracted articles. Independent reanalysis of this meta-analysis using a random effects model ($I^2 = 51.3\%$) shows RR 1.87 (95% CI 0.66–5.30). The results for venlafaxine are no longer significant and have been excluded from Table 4.1.

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

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

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

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

Note: reversal of conclusions

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

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

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

Key messages

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

Note: withdrawal of previous key message:

Antidepressants reduce the incidence of chronic neuropathic pain after breast surgery

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

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

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

4.3.4 Anticonvulsant drugs

Specific anticonvulsant agents used in the treatment of acute pain

Gabapentinoids (gabapentin/ pregabalin)

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

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

Used as an adjunct to epidural analgesia, perioperative gabapentin reduced pain scores and epidural analgesic requirements and improved patient satisfaction, despite an increase in dizziness (Turan et al, 2006 **Level II**).

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

Sodium valproate

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

Specific anticonvulsant agents used in the treatment of chronic pain

Carbamazepine

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

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

Phenytoin

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

Gabapentin

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

Pregabalin

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

Sodium valproate

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

Lamotrigine

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

Key messages

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

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

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

4.3.5 Membrane stabilisers

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

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

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

The efficacy of lignocaine in the treatment of acute migraine is unclear. Analgesia provided by IV lignocaine was similar to dihydroergotamine, but not as effective as chlorpromazine (Bell et al, 1990 **Level II**) and in one trial no better than placebo (Reutens et al, 1991 **Level II**). Results for IN lignocaine are conflicting (Maizels et al, 1996 **Level II**; Blanda et al, 2001 **Level II**).

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

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

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

Key messages

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

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

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

4.3.6 Alpha-2 agonists

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

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

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

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

Key message

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

4.3.7 Salmon calcitonin and bisphosphonates

Calcitonin

Calcitonin is a 32 amino acid peptide hormone that regulates calcium homeostasis in vertebrates. It also has analgesic properties, primarily through receptor-mediated modulation of serotonergic activity in pain pathways of the central nervous system. Salmon calcitonin has a greater potency than mammalian forms of the hormone and is therefore reproduced as a synthetic drug for pharmaceutical use. The adverse effects of calcitonin therapy such as sedation, nausea, skin flushing and diarrhoea may reflect increased serotonergic activity. In rodents, the 5HT₃ antagonist tropisetron reduced its analgesic efficacy, which may be relevant in humans during the treatment of nausea and vomiting (Visser, 2005).

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

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

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

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

Bisphosphonates

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

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

Key messages

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

4.3.8 Cannabinoids

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

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

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

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

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

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

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

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

Key message

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

4.3.9 Glucocorticoids

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

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

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

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

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

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

After orthopaedic surgery, there was no difference in analgesic effect between methylprednisolone and ketorolac (both were better than placebo); methylprednisolone led to greater opioid-sparing but there was no difference in the incidence of adverse effects (Romundstad et al, 2004 **Level II**). After mixed ambulatory surgery, ketorolac provided better pain relief than either dexamethasone or betamethasone in the immediate postoperative period, but there were no differences in pain relief or analgesic use in the 4 to 72 hour period after surgery (Thagaard et al, 2007 **Level II**). Similarly, after breast augmentation, methylprednisolone and parecoxib provided similar analgesia; however, PONV and fatigue scores were lower in the patients given methylprednisolone (Romundstad et al, 2006).

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

Glucocorticoids have also been shown to have antihyperalgesic effects in animals and humans (Romundstad & Stubhaug, 2007; Kehlet, 2007). Using experimental burn injury pain, both methylprednisolone and ketorolac reduced secondary hyperalgesia and increased pain pressure tolerance threshold compared with placebo, although the increase in pain pressure tolerance threshold was greater with ketorolac (Stubhaug et al, 2007 **Level II**). In surgical patients, preoperative administration of methylprednisolone resulted in significantly less hyperesthesia compared with parecoxib and placebo, but there was no reduction in persistent spontaneous or evoked pain (Romundstad et al, 2006 **Level II**).

Key message

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

4.3.10 Complementary and alternative medicines

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

CAMs include:

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

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

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

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

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

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

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

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

Key message

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

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

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