Anaesth Intensive Care 2011; **39:** 804-823

Reviews

Acute pain management in opioid-tolerant patients: a growing challenge

C. A. HUXTABLE*, L. J. ROBERTS†, A. A. SOMOGYI‡, P. E. MACINTYRE§

Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine, Royal Adelaide Hospital and Discipline of Pharmacology, School of Medical Sciences and Discipline of Acute Care Medicine, University of Adelaide, Adelaide, South Australia and Department of Anaesthesia and Pain Management, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

SUMMARY

In Australia and New Zealand, in parallel with other developed countries, the number of patients prescribed opioids on a long-term basis has grown rapidly over the last decade. The burden of chronic pain is more widely recognised and there has been an increase in the use of opioids for both cancer and non-cancer indications. While the prevalence of illicit opioid use has remained relatively stable, the diversion and abuse of prescription opioids has escalated, as has the number of individuals receiving methadone or buprenorphine pharmacotherapy for opioid addiction. As a result, the proportion of opioid-tolerant patients requiring acute pain management has increased, often presenting clinicians with greater challenges than those faced when treating the opioid-naïve.

Treatment aims include effective relief of acute pain, prevention of drug withdrawal, assistance with any related social, psychiatric and behavioural issues, and ensuring continuity of long-term care. Pharmacological approaches incorporate the continuation of usual medications (or equivalent), short-term use of sometimes much higher than average doses of additional opioid, and prescription of non-opioid and adjuvant drugs, aiming to improve pain relief and attenuate opioid tolerance and/or opioid-induced hyperalgesia. Discharge planning should commence at an early stage and may involve the use of a 'Reverse Pain Ladder' aiming to limit duration of additional opioid use. Legislative requirements may restrict which drugs can be prescribed at the time of hospital discharge. At all stages, there should be appropriate and regular consultation and liaison with the patient, other treating teams and specialist services.

Key Words: acute pain, perioperative period, postoperative pain, opioid-tolerant, drug addiction, analgesics, opioid analgesics, opioid substitution treatment, drug tolerance, methadone, buprenorphine, suboxone

Opioid tolerance occurs in individuals prescribed opioids for long-term management of either chronic non-cancer pain (CNCP) or cancer pain and those who are, or have been, problematic or illicit users of opioids, some of whom may be enrolled in opioid substitution programs. There may be considerable overlap between these two groups: those prescribed opioids for relief of pain may misuse these and other drugs[1], and individuals with an opioid addiction may also experience CNCP or cancer pain[2]. Acute pain presentations in this population, in addition to elective surgery or medical illness, include surgery for CNCP and cancer as well as for the complications of drug abuse (e.g. trauma, infection).

This review examines opioid prescribing trends, considers the mechanisms underlying opioid tolerance and opioid-induced hyperalgesia (OIH) and their clinical implications, and discusses acute pain management options in opioid-tolerant patients. Most of the relevant literature relates to surgical in-patients and the focus is therefore on the management of postoperative pain. However, the information can be extrapolated to other acute pain situations.

* M.B., B.S., F.R.A.C.G.P., F.A.N.Z.C.A., M.R.C.A., Consultant Anaesthetist, , Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine, Royal Adelaide Hospital.
† M.B., B.S. (Hons), B.Med.Sc. (Hons), F.A.N.Z.C.A., F.F.P.M.A.N.Z.C.A., Director, Acute Pain Service, Department of Anaesthesia and Pain Management, Sir Charles Gairdner Hospital.
‡ Ph.C., M.Sc., Ph.D., F.F.P.M.A.N.Z.C.A., Professor, Discipline of Pharmacology, School of Medical Sciences, University of Adelaide.
§ B.Med.Sc., M.B., B.S., M.H.A., F.A.N.Z.C.A., F.F.P.M.A.N.Z.C.A., Director, Acute Pain Service, Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine, Royal Adelaide Hospital and Associate Professor, Discipline of Acute Care Medicine, University of Adelaide.

Address for correspondence: Dr C. Huxtable, Department of Anaesthesia, Pain Medicine and Hyperbaric Medicine, Royal Adelaide Hospital, Adelaide, SA 5000. Email: christine.huxtable@health.sa.gov.au

Accepted for publication on June 13, 2011.

EPIDEMIOLOGY OF OPIOID USE

From 1989 to 2009, global use of prescription opioids more than trebled[3]. Morphine use rose from

6.5 to 19.6 tons between 1989 and 1998 and then to 41.8 tons in 2009[4]. Consumption of oxycodone increased slowly from 1989 to 1998, remaining at less than 10 tons worldwide, but escalated dramatically between 1998 and 2009 to reach 77 tons[4].

In 2009, the USA (with 5.1% of the world's population) was the main consumer of these opioids, accounting for 56% of global morphine and 81% of global oxycodone use[4]. Australia and New Zealand together (0.4% of the world's population) made up 2.8% of total morphine consumption and Australia alone accounted for almost 2% of oxycodone use. Worldwide, Austria had the highest morphine consumption per person per day (where it is used for both analgesia and opioid substitution programs), USA was third (behind Canada), New Zealand was seventh and Australia was eighth. For oxycodone, the USA had the highest per person use with Australia third. New Zealand's overall oxycodone use was insignificant[4].

In Australia, between 1991 and 2007, total morphine base supply (i.e. the quantity of all formulations in kilograms per year) increased four-fold[5]. This included a 40-fold growth between 1990 and 2006 in oral morphine, almost all as slow-release (SR) – also known as controlled-release – preparations[5]. Over the same period, total oxycodone base supply rose ten-fold – most of this increase coincided with the introduction of SR oxycodone in 1999[5]. In both countries, the increased consumption has far exceeded the rate of population growth[5].

Prescribing patterns

Precise details of opioid prescribing in Australia are difficult to obtain, as neither indication for treatment nor quantity of opioid dispensed are recorded. However, there has been a significant rise in the total number of opioid prescriptions issued under the Australian Pharmaceutical Benefits Scheme (PBS)[6]. In 1992, there were nearly 2.4 million (excluding methadone and buprenorphine for the pharmacotherapy of opioid addiction)[6] for a population of about 17.5 million[7]. In 2007, despite only modest population growth to just over 21 million[7], the number of opioid prescriptions had escalated to almost seven million[6]. These figures are an underestimate as they do not include non-PBS prescriptions[6].

From 1992 to 2007, the number of PBS-listed opioids grew from four to eight and the number of formulations from 11 to 70[6]. Morphine prescriptions rose until 2000 and changed little until 2004, after which they declined slightly. In contrast, oxycodone prescriptions slowly increased until 2000 and then rapidly escalated, coinciding with the PBS listing of SR oxycodone. Prescriptions for codeine peaked in 1999 then declined steadily, whereas those for tramadol grew rapidly after its introduction in 2000 until 2004 and then reached a plateau[6]. In 2006, fentanyl prescription started to increase[6], coinciding with PBS approval of transdermal fentanyl patches for management of CNCP[8].

In New Zealand, the variety of preparations has also increased. In May 2009, the Pharmacology and Therapeutics Advisory Committee added buprenorphine to the pharmaceutical schedule which already included codeine, dihydrocodeine, fentanyl, methadone, morphine, oxycodone and pethidine[9]. As in Australia, prescribing data from New Zealand are limited. However, the number of prescriptions for morphine dispensed at community pharmacies increased by over 50% from 1996 to 2006[10].

Prescribing trends in the USA are similar to those reported in Australia and New Zealand; between 1997 and 2007, retail sales of morphine and oxycodone increased more than two- and eight-fold respectively[11].

Chronic non-cancer pain

The estimated prevalence of CNCP in adults in Australia and New Zealand is between 5 and 20%[5,12,13]. This is similar to other developed countries and is predicted to increase as the population ages[5]. In the past, the widely held medical view was that the long-term use of opioids for management of CNCP invariably led to tolerance and that there was an unacceptable risk of addiction[14]. More recently, at least in the developed world, use of opioids for CNCP has become more common and major professional bodies have developed prescribing guidelines[15,16]. However, evidence for the efficacy of long-term opioids in those with CNCP remains conflicting and generally of low quality[17,18]. Opioid use for CNCP is being re-examined in light of increasing awareness of potential adverse consequences including prescription opioid abuse and diversion[11,19]. An 'universal precautions' approach along with appropriate risk assessment and management has been recommended[20-22].

Cancer pain

It is predicted that, by the age of 85 years, one in two Australian men and one in three Australian women will have been diagnosed with cancer (excluding non-melanoma skin cancers)[23]. Although not universal in those with cancer, pain is a presenting symptom in 20 to 50% and is experienced by up to 90% in the advanced stages of disease[24]. Risks related to long-term opioid use include declining efficacy over time and neurobiological effects that may

enhance pain or adversely alter cancer progression[24]. Therapeutic advances have improved longevity. It has been recommended that pain in cancer survivors is managed using a similar approach to that used in CNCP[1].

Opioid substitution programs

Methadone and buprenorphine substitution are well accepted treatments for opioid addiction[5]. Both drugs, the latter either alone (Subutex®, Reckitt Benkiser Healthcare Ltd, UK) or combined with naloxone (Suboxone®, Reckitt Benkiser Healthcare Ltd, UK) designed to deter intravenous injection, are available in Australia and New Zealand[25,26].

Commenced in Australia in 1969, methadone maintenance therapy (MMT) was formally recognised in 1985 as appropriate pharmacotherapy of opioid addiction[25]. Subutex, introduced in the 1980s, was PBS-listed in 2000 and Suboxone in 2005 for use as buprenorphine maintenance therapy (BMT)[27]. From 1998 to 2009, the number of Australians receiving MMT or BMT increased from 24,657 to 43,445[25].

Many patients enrolled in opioid substitution programs report ongoing opioid or polydrug abuse. In Australian post-marketing surveillance studies of Suboxone, approximately one-quarter admitted to injecting their dose at least once in a six-month period[28]; one in five acknowledged occasionally selling or giving away their medication and a small number were identified as 'doctor shoppers'. Self-injection was most prevalent in those using Subutex and less common with methadone and Suboxone[28].

Illicit opioid use

In 2008, it was estimated that illicit opioids (i.e. opium, heroin or other opioids that were not prescribed for the individual or bought legally) were used by 12 to 22 million people worldwide, representing 0.3 to 0.5% of those aged 15 to 64 years[3]. From 1995 to 2009, despite a 13% fall in 2008/2009, worldwide illicit opium production increased by almost 80%[3]. This is similar to the rate of global population expansion and use prevalence has thus remained relatively stable. However, the pattern of illicit opioid use has changed with the illicit use of prescription opioids increasing[3].

As licit (i.e. prescribed for the individual) opioid use has increased in the USA, so has its abuse[29]. The United States Food and Drug Administration has responded to the 'societal crisis' of prescription opioid abuse by increasing regulatory controls and developing risk evaluation and mitigation strategies for long-acting opioids as part of approval processes[29].

In Australia, illicit drug use is monitored by the Australian Institute of Health and Welfare. Their National Drug Strategy Household Survey has been conducted every two or three years since 1985. Comparison of the most recent report (2007) with that published in 2004 shows that prevalence of illicit use of heroin and methadone remained relatively stable, while illicit use of some other opioids (including morphine) decreased[30]. Overall prevalence may have fallen slightly, with the total number of individuals illicitly using opioids decreasing from just over to just under 600,000[30]. These figures are probably an underestimate as they rely on self-report and do not include the homeless or the institutionalised.

The Australian Illicit Drug Reporting System is designed to identify emerging trends in illicit drug use among injecting drug users (IDU). Information is obtained in large part from a survey of those who had injected drugs at least monthly during the six months preceding the interview. Between 2001 and 2009, heroin was the drug of choice in 48 to 58% of IDU compared with just 5 to 10% for morphine[31]. In the same period, heroin was also the drug injected most commonly in the month prior to interview (27 to 47% of IDUs compared with 6 to 19% for morphine). No time-related trends were obvious.

In 2009, 44% of the IDU sample had 'used' morphine (both licit and illicit, predominantly injected) in the six months prior to interview, ranging from 24% in South Australia to 82% in Tasmania[31]. Nationally, however, between 2000 and 2009 IDU use of morphine remained relatively stable, although significant yearly and regional fluctuations occurred[31].

Oxycodone use by IDUs is more difficult to track over time because of changes in methodology. Prior to 2005 it was included in the Australian Illicit Drug Reporting System reports under the category 'other opioids' (which also included Panadeine Forte®, Sanofi-Aventis Australia, Macquarie Park, NSW, codeine, opium and pethidine) and no distinction was made between 'licit' and 'illicit' oxycodone[31]. In 2002, this group of drugs as a whole was used by 22%, and injected by 8%, of IDUs[32]. In 2005, because of concerns about diversion and unsanctioned use, oxycodone was classified separately[31]. In that year, use by IDUs of licit and illicit oxycodone within the prior six months was 5 and 18% respectively[33]. By 2009, the rate for licit use was unchanged but 30% now reported illicit oxycodone use (injected by 93% of this group)[31]. This is reflected in data from the King's Cross Medically Supervised Injecting Centre where, since late 2006, prescription opioids have also been more commonly injected than heroin[34].

New Zealand's illicit drug market and use pattern differ. Geographical isolation and successful policing have limited heroin availability. Misused/injected opioids are more commonly prescription drugs such as morphine or methadone or 'over-the-counter' drugs converted to 'home bake' (codeine which has been refined to produce morphine/diamorphine)[35]. From 1990 to 2006 the prevalence of opioid abuse remained stable at between 0.4 and 0.6%[36,37]. In 2008, there was a sharp increase to 1.1% for uncertain reasons[3].

Serious adverse effects following prescription opioid abuse/misuse

In the past decade, hospital presentations as a result of serious adverse effects following misuse/abuse of prescription opioids have increased. In the USA between 2004 and 2009, the number of emergency department presentations increased by almost 90%[38]. The largest increases were for cases involving oxycodone (242.2%) and hydrocodone (148.3%) while presentations resulting from misuse of cocaine, marijuana and heroin fell by just 1.8%[38]. In Australia, the number of patients treated for poisoning by opioids other than heroin or methadone increased almost three-fold (from 605 in 1998/1999 to 1700 in 2007), while poisoning from heroin fell (1712 to 446)[39].

In the USA, both opioid prescription rates and opioid-related fatalities have increased, raising concerns about causation[5,11]. Examples include oxycodone (associated with 14 deaths in 1998 and 1007 in 2005), morphine (82 and 329 respectively), fentanyl (92 and 1245) and methadone (8 and 329)[5]. There is also evidence from the USA that among those prescribed opioids for CNCP, the higher the dose prescribed the greater the risk of opioid-related fatality[40]. The correlation between overall oxycodone use and oxycodone-related mortality has also been reported in Victoria, Australia (Figure 1). In 2000 there were four coronial cases in which oxycodone was detected; by 2009 this had increased to 97. Over the same period oxycodone supply to the state increased nine-fold[41].

MOLECULAR BASIS OF TOLERANCE AND OPIOID-INDUCED HYPERALGESIA

Tolerance describes the decrease in effect following repeated administration of a drug that can be overcome by an increase in dose (right-shifted dose-response curve). Previously, in patients taking long-term opioids without disease progression, a decrease in the effect of these drugs has usually been attributed to the development of tolerance. However, it is now thought that administration of opioids can also lead to OIH, an enhanced response to a stimulus that is normally painful[42], which will also reduce the analgesic effect. It is important to recognise that opioid tolerance and OIH are distinct but likely overlapping phenomena, whereby tolerance causes an increase in ED_{50},

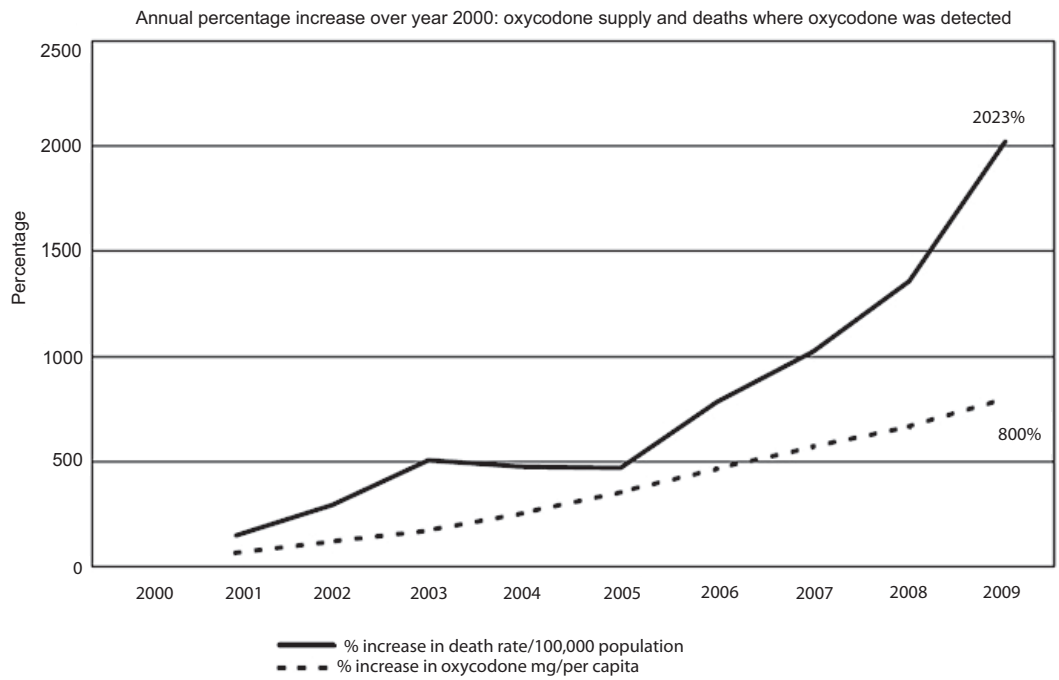

FIGURE 1: Coronial deaths involving oxycodone and oxycodone supply, Victoria, 2000-2009. Reproduced with permission from Rintoul et al[41].

but OIH leads to a decrease in the response at dose zero (E_0-baseline)[43].

Evidence for OIH comes mainly from human volunteer studies and small clinical studies in individuals taking long-term opioids. To date, the strength of that evidence has been modest and limited[44,45]. The major difficulty in documenting clinical evidence of OIH is that any increase in pain in patients taking long-term opioids could also be due to ongoing tissue damage (e.g. from progression of cancer) or opioid tolerance[46].

In studies using experimental pain induction, subjects on MMT are hyperalgesic and have a much lower tolerance to the cold pressor test compared with control groups[47-49]. Similar studies have been reported in subjects on BMT[50,51] and morphine-maintenance[49]. In addition, in those receiving morphine or methadone for CNCP, cold pressor tolerance times were almost half those of age- and gender-matched controls, but similar to those on MMT[52]. Other studies have addressed the onset of OIH (occurred within a month after starting oral morphine)[53] and its resolution (takes at least one month)[54].

There is limited evidence for rapid development of OIH. After surgery, pain scores and opioid requirements were increased in patients given higher doses of fentanyl[55] and remifentanil[56] intraoperatively. However, these results, based on increased pain scores and opioid consumption only, could indicate either OIH, tolerance to opioids or a combination of both. A formal diagnosis of OIH would require quantitative sensory testing, before and after surgery[57].

In the experimental pain setting, rapidly developing OIH has been reported in healthy subjects receiving remifentanil[58,59]. A study investigating tolerance, however, showed no significant difference before and after "two different but clinically relevant doses" of remifentanil[60].

Mechanisms underlying tolerance and OIH

The mechanisms underlying tolerance and OIH are still not fully understood. However, it seems clear that the neurobiology is complex and multifactorial[61]. Tolerance may involve not only alterations in receptor regulation, desensitisation and internalisation, but other mechanisms including glial activation[62]. For OIH, proposed mechanisms include a role for glutaminergic activation (also implicated in tolerance), altered opioid intracellular signalling involving G protein-coupled receptor switching, a role for substance P and neurokinin 1 (NK-I) receptors and spinal dynorphin and, finally, increasing evidence implicating Toll-like receptor (TLR) signalling and glial cells.

Glutaminergic activation

The main mechanisms by which opioids trigger the glutaminergic system involve glutamate-associated activation of n-methyl-d-aspartate (NMDA) receptors, inhibition of glutamate transport reuptake and calcium-regulated intracellular protein kinase C[63]. In animals, the NMDA receptor antagonist, ketamine, has been shown to attenuate the development of OIH when given systemically or intrathecally[61]. In humans, S-ketamine blunted remifentanil-induced hyperalgesia caused by intradermal electrical stimulation[58,59] and low dose ketamine prevented remifentanil-induced postoperative wound hyperalgesia[64].

Spinal dynorphin

During chronic pain, spinal dynorphin A increases. This acts on bradykinin receptors causing a switch in the G protein to a stimulatory G protein (Gαs). This ultimately causes an increase in intracellular calcium levels, release of the excitatory neuropeptide calcitonin gene-related peptide and potentiation of pain and neuronal hyperalgesia[65]. Whether exogenous opioids are able to perform similarly remains unclear.

Substance P and NK-1

In animals, chronic morphine increased substance P and NK-1 receptor expression in the spinal dorsal horn. This was associated with hyperalgesia, could be reversed using NK-1 antagonists and was not seen in NK-1 receptor knock-out mice[66].

Mu receptor G protein switching

In animals, acute hyperalgesia elicited by low dose morphine can be blocked by an ultra-low dose of naloxone[67]. At such low doses, it is believed that morphine activates Gαs which induces hyperalgesia. Naloxone binds to a scaffolding protein, filamin A, which interacts with the mu-opioid receptor to disrupt the morphine-induced mu-opioid receptor Gαs coupling[68].

Opioids, glial signalling and pro-inflammation

A newer mechanism has recently been proposed to explain, at least partially, OIH and tolerance. Glia, the immune-like cells in the brain and spinal cord, have a number of metabolic functions, and molecules released by glia can interact with neurons providing a glia-neuron communication[69]. Specifically, TLRs expressed on glia and opioids independently activate a TLR4 signalling cascade and consequently activate glia. Although opioids bind to the mu-opioid receptor on neurons, leading to their analgesic and other effects, they also dock onto glia via TLR4. Docking of opioids to TLR4 causes intracellular signalling that results in the expression of a number

of pro-inflammatory mediators, especially IL-1ß and IL-6. These cytokines bind to their receptors on neurons and are pro-nociceptive. IL-1ß increases extracellular glutamate by down-regulating the glutamate transporter GLT-1. It also phosphorylates the NMDA receptor leading to an increase in channel opening, allowing an influx of calcium which causes increased nitric oxide and PGE2, amplifying the excitability of pain projection neurons[69,70]. Blockade of opioid-induced TLR4 signalling through genetic and pharmacological methods enhanced opioid analgesia and attenuated the development of opioid analgesic tolerance and hyperalgesia[71].

This effect of glial activation by opioids has the potential to provide a unifying mechanism through which the final pathway of neuronal sensitisation leads to both OIH and opioid-induced tolerance. Caution is required as the mechanism, although elegantly delineated from animal studies, has not been verified in humans.

PRINCIPLES OF ACUTE PAIN MANAGEMENT

The main aims of management in opioid-tolerant patients are to promote adequate perioperative analgesia, prevent drug abstinence (withdrawal) syndromes, and assist with any related social, psychiatric and behavioural issues. Management should commence at the time of preoperative assessment, often prior to admission, and include appropriate discharge planning.

A collaborative, interdisciplinary approach, working closely with other treating clinicians in both the hospital and community, in order to maintain continuity of patient care, is particularly important[72]. Although treatment in many patients is relatively straightforward, assessment and management can be time-consuming in those with more complex issues. The anaesthetist/pain medicine specialist is also in a position to ensure that individual and staff expectations about acute pain management are realistic, that risk management strategies are put in place and that all members of the team (including the patient) are working towards common goals.

Evidence relating to the perioperative management of the opioid-tolerant patient is limited and largely based upon case reports, case series and expert opinion. While some treatment strategies may be extrapolated from studies in the opioid-naïve, there are self-evident limitations to this approach. While the principles outlined in the following sections apply to anyone who is opioid-tolerant and has acute pain, most of the relevant literature relates to surgical inpatients. The focus will therefore be on the management of acute pain in opioid-tolerant patients admitted for surgery.

PREOPERATIVE MANAGEMENT

Identification of opioid tolerance is an important first step. If overlooked at the time of preoperative assessment, it may become apparent only when

TABLE 1

Pain-related assessment in opioid-tolerant patients

Information from all opioid-tolerant patients	Additional information in patients with CNCP or cancer pain	Additional information in patients with an addiction
Current treatment providers	Pain diagnosis	Opioid substitution therapies and doses (methadone, buprenorphine)
Opioid and non-opioid medications	Usual pain scores	Other prescribed or illicit substance use (polyabuse is common)
Dose verification of all relevant medications	Functional status	Routes of administration
Non-prescribed drugs (e.g. over-the-counter and illicit drugs, alcohol, nicotine)	Prognosis (cancer pain)	Where relevant, registered prescriber and dispensing pharmacy
Drug allergies and reactions	Psychospiritual issues (including end-of-life issues, anxiety, depression, coping style and strategies)	Medical and psychiatric co-morbidities (e.g. blood-borne viruses, hepatic disease, other infections, chronic pain, personality disorder)
Experiences and expectations of acute pain management	Where relevant, the authorised prescriber of any opioids	
Support systems after discharge	Presence of invasive pain treatment (e.g. intrathecal pump, spinal cord stimulator)	
	Medication misuse or addiction	
	Expectations about their admission (e.g. expectation that chronic back pain will be improved after spinal surgery; palliative vs curative surgery in patients with cancer)	

CNCP=chronic non-cancer pain.

postoperative pain is difficult to control. In addition to a routine preoperative history, targeted information should be sought (Table 1). Documentation of all usual drugs and doses is especially important if good postoperative analgesia is to be achieved and withdrawal from drugs such as opioids, benzodiazepines and alcohol avoided. A non-judgemental approach, along with an explanation that knowledge of all drugs used (prescribed and illicit) is necessary in order to provide good pain control, will improve information gathering.

Doses of relevant prescribed drugs must be verified[73,74], either from the dispensing label on the prescription packaging or by contacting the general practitioner, dispensing pharmacist, drug treatment centre or appropriate regulatory authority. Dose verification may not be possible in emergency settings or after-hours. In this case, as a temporary measure, and in order to avoid the risk of opioid withdrawal, the reported daily opioid amount can be given in two to four divided doses, with response monitored closely – using repeated assessment of a patient's level of sedation and respiratory rate (see later comments regarding sedation and respiratory rate as clinical indictors of early respiratory depression) – after each dose until confirmation is obtained[74]. In some cases, admission to a high-dependency setting may be considered, especially if the reported 'usual' dose is high. In addition, if there is doubt about whether the verified dose is being taken in full (for example, if there is concern about diversion of any part of the prescribed amount), it may be prudent to give a portion of the reported dose and repeat this over the day as needed (if the patient is not sedated)[75].

The plan for pain relief should consider patient preferences, past experiences[76] and long-term management plans. Reassurance of patients that acute pain management is a priority is often required and that adequate analgesia, although potentially more difficult than in the opioid-naïve, is not precluded by previous bad experiences of pain management or opioid addiction[77-79].

All regular opioids and other drugs prescribed for pain management should be taken or administered on the day of surgery, even if the patient is fasting, unless there is a specific reason for not doing so (e.g. non-selective nonsteroidal anti-inflammatory drugs [NSAID] if perioperative bleeding is a concern). Those enrolled in an opioid substitution program, who are to be admitted on the day of surgery, may be able to arrange a 'take-away' dose that can be self-administered preoperatively.

INTRAOPERATIVE MANAGEMENT

If the prescribed long-term opioid has not been taken preoperatively or if the surgery is prolonged, intraoperative doses should be adjusted accordingly. Opioid-tolerant patients may have much higher than expected additional intraoperative opioid requirements. However, assessment of adequate opioid administration is difficult. In spontaneously breathing patients, opioid titration to respiratory rate is a reasonable guide. With a general anaesthetic-relaxant technique, re-establishing spontaneous ventilation towards the end of anaesthesia and titrating opioid to achieve a respiratory rate of eight to ten breaths per minute may assist. Particular care should be taken to ensure adequate intraoperative loading with a longer acting opioid when using an infusion of remifentanil.

Opioid-tolerant patients are at increased risk of awareness[80] and depth of anaesthesia monitoring (with cautious interpretation of results, especially if using ketamine) may be indicated[81]. Care should be taken with the placement of warming devices in those with transdermal drug delivery systems, as the heat may accelerate drug release[82].

POSTOPERATIVE MANAGEMENT

Effective management of acute pain is often more difficult in opioid-tolerant patients compared with their opioid-naïve counterparts. Analgesic drugs and techniques may also be required for longer periods[83] and involve significant deviations from 'standard' treatment protocols[84]. In all patients, appropriate assessment and monitoring is needed so that analgesia can be individualised. For those with pre-existing pain, it may be reasonable to differentiate the 'new' acute pain from the 'usual' site of pain and explain that the primary focus of management will be the former.

Assessment and monitoring

Postoperative pain scores may be higher and decrease more slowly than in the opioid-naïve[83,85]. Interpretation of elevated pain scores can be difficult, particularly if considered in isolation, and comparison with pre-existing ('usual') pain scores can help. Dynamic measures of pain (ability to deep breathe, cough and ambulate) should also be assessed[86]. These can be quantified using the Functional Activity Score[87], where 'A' is no limitation of relevant activity due to pain (relative to baseline), 'B' is mild limitation and 'C' is severe limitation. Persistently high pain scores as well as misplaced assumptions about 'pain patients' and 'addicts' can hinder assessment and diagnosis. If pain scores escalate or fail to decline in the postoperative period, other reasons for pain (e.g. surgical complications) should be considered.

If opioid tolerance has not been identified preoperatively, it should be suspected if the following triad is present after surgery: elevated pain scores, high opioid use and low incidence of side-effects (apart from sedation)[83]. Identification of opioid-tolerance can be even more difficult in intensive care settings, in part because of competing clinical goals, particularly with urgent admissions or because of a patient's inability to communicate (e.g. due to injury or sedation for ventilation)[88]. Strategies that may help include obtaining history from family, friends and usual doctors, consultation with specialist services and anticipation of illicit drug use in certain settings (e.g. trauma)[88].

Monitoring for the onset of opioid-related side-effects is also required. While tolerance to the analgesic effects of opioids, as well as many of their side-effects including nausea, sedation and respiratory depression, occurs reasonably quickly[89], it is possible, especially if opioid doses are significantly and rapidly escalated above baseline levels, that respiratory depression may still develop.

In one study, opioid-tolerant patients using patient-controlled analgesia (PCA) were less likely to report nausea, vomiting and pruritus than opioid-naïve controls[83]. However, the incidence of moderate or severe sedation in the opioid-tolerant group was 50.3% compared with 19.0% in the control group. Anxiolytics were more commonly given to the opioid-tolerant (17.5% compared with 0.7% of controls), but no significant correlation with sedation was found. Despite this, the risk of central nervous system (CNS) depression is higher when opioids are combined with other CNS depressants, such as benzodiazepines and clonidine[74]. Therefore, as with all patients given opioids for the management of acute pain, monitoring must include indicators of excessive dose and adverse effects. Respiratory rate and level of sedation (known to be a better clinical indicator of early respiratory depression than a decrease in respiratory rate[84,87]), should be assessed on a regular basis irrespective of concurrent sedative administration.

Effective analgesia

Opioids and tramadol

As with opioid-naïve patients, opioids are the mainstay of effective management for moderate to severe acute pain. However, the amount of opioid needed in addition to usual long-term opioids may be much higher. After a variety of surgical procedures, first 24-hour PCA morphine requirements were, on average, three times greater in the opioid-tolerant compared with opioid-naïve controls[83]. However, there is great variability in opioid requirements and it is worth noting that in some opioid-tolerant patients, opioid requirements were similar to those who were opioid-naïve.

When moderate to severe pain is anticipated, PCA is a useful way of delivering additional opioids as it allows self-titration, minimises the risk of under-dosing (with appropriate review and adjustment) and reduces opportunities for conflict with and demands on ward nursing staff. There is no simple method for predicting the total dose that will be required by those with opioid-tolerance.

Use of individual preoperative 'fentanyl challenge', given to the point of respiratory depression followed by pharmacokinetic modelling to predict intra- and postoperative opioid requirements, has been used to calculate PCA bolus dose and background infusion rate[90]. Alternatively and more simply, calculation of the PCA bolus dose can be based on the dose of long-term opioid already being taken[84,91]. Use of PCA background infusions is not usually recommended in the opioid-naïve, because of the increased risk of respiratory depression[92]. However, in opioid-tolerant patients, this may be an appropriate way to deliver the equivalent dose of long-term oral opioid if oral administration is not possible[84]. Opioid-tolerant patients may also require more frequent PCA prescription changes[93] and the care of an acute pain service for longer[83,93].

In those with CNCP or cancer pain taking opioids on a long-term basis, the relative roles played by opioid-tolerance and OIH are unknown, but likely to be interrelated[43,89]. If inadequate pain relief is thought to be due to OIH, a reduction in opioid dose may improve analgesia[43,89]. However, no such studies have been performed in the acute pain setting where, if pain increases and after there has been a thorough assessment to exclude other causes of this increase, the initial response should be to escalate the opioid dose aiming for effective pain control without adverse effects[74]. If pain does not respond to this approach, then acute neuropathic pain or OIH may be suspected and use of additional non-opioid agents and opioid rotation (or reduction) considered.

Tramadol is an attractive choice of analgesic in some opioid-tolerant patients because of its lower abuse potential. However, using tramadol alone may not prevent opioid withdrawal or provide sufficient analgesia[74].

Non-opioid analgesic agents

In opioid-naïve patients, paracetamol, non-selective NSAIDs and COX-2 selective NSAIDs were opioid-

sparing, although the decrease in morphine use was small – just 6 to 10 mg in 24 hours[94]. A decrease in postoperative nausea and vomiting was seen only with use of non-selective NSAIDs[94]. Despite a lack of evidence in the opioid-tolerant, if there are no contra-indications, it seems reasonable to include these drugs in treatment regimens.

Regional analgesia

Regional analgesia may be useful in the early postoperative period as it theoretically removes the need for additional systemic analgesia. However, neuraxially administered opioids may not prevent opioid withdrawal and additional systemic opioids are often required[72,74]. In the absence of clear evidence about the use of larger than 'standard' doses of intrathecal and epidural opioids in opioid-tolerant patients, it may be difficult to estimate an appropriate or safe dose. In some institutions, policies dictate that epidural opioids should not be used concurrently with systemic opioids, because of the increased risk of respiratory depression; this may or may not apply to the opioid-tolerant.

Attenuation of tolerance and OIH

NMDA receptor antagonists

In opioid-naïve patients, concurrent use of low dose ketamine with opioids improved analgesia and was opioid-sparing, with minimal or no side-effects related to ketamine[95,96]. Given in conjunction with PCA opioids (not necessarily added to the PCA opioid solution), it also reduced the incidence of postoperative nausea and vomiting[95].

Ketamine may also be useful when given in addition to opioids for the management of acute pain in the opioid-tolerant[74,84]. The effect of ketamine in opioid-tolerant patients undergoing spinal surgery has been the subject of two randomised controlled trials. In one, intraoperative ketamine (bolus dose followed by infusion to skin closure) reduced pain and opioid requirements in the first 48 hours after surgery as well as at six weeks[97]. In the other study, ketamine, given on induction and followed by an infusion for 24 hours, improved postoperative analgesia, but PCA hydromorphone use was not significantly reduced[98].

Reported infusion regimens for ketamine vary. However, initial rates of 100 to 200 mg/24 hours or 0.1 mg/kg/hour have been suggested[84]. As the elderly may be more sensitive to the effects of ketamine, lower doses may be appropriate[74]. Due to very variable PCA opioid requirements in the opioid-tolerant patient, a fixed ratio of ketamine to opioid may lead to a higher incidence of side-effects such as dysphoria and hallucinations. It is therefore recommended that ketamine is administered separately at a fixed rate, rather than included in the PCA opioid solution[84].

Naloxone

Ultra-low dose naloxone has reduced opioid tolerance in animal studies[99-101]. It has also enhanced buprenorphine analgesia in experimental pain studies in humans[102]. Evidence from the acute pain setting is limited and not specifically related to opioid-tolerant patients. When given concurrently with PCA, naloxone has been reported to have no effect on postoperative pain relief[103,104] and to increase pain[105], although in 'ultra-low' doses it may reduce the incidence of opioid-related nausea and pruritus[104]. Therefore, there is currently no good evidence to support the use of low dose naloxone for this indication.

Opioid rotation

Opioid rotation ('switching'), changing from one opioid to another, is widely used in palliative care practice to improve analgesia and reduce opioid-related side-effects. Evidence for its efficacy consists mainly of case series and expert opinion[106,107]. Putative mechanisms include incomplete opioid cross-tolerance, differing receptor activity and the presence of active metabolites in some cases. Using an opioid that is different from the pre-admission opioid may be a useful strategy for acute pain management[91].

Opioid rotation is undertaken by converting opioid doses using published equivalence tables and, in view of incomplete cross-tolerance, commencing with 30 to 50% of the calculated equianalgesic dose. Opioid conversion ratios are complex and influenced by the switch direction[108,109], pharmacokinetic factors (including bioavailability and active metabolites), variable opioid and non-opioid receptor activity[108] and pain type[110]. Many conversion tables represent an oversimplification of the process of changing opioids and it is critically important that they are not used as 'recipe books'[108].

In rodents, studies examining combinations of oxycodone and morphine[111] and methadone and morphine[112] have supported the hypothesis that mixtures of opioids are synergistic, leading to better pain relief and fewer opioid-related side-effects compared with equianalgesic doses of each opioid given alone[113]. This may be a result of individual opioids interacting with different opioid receptor subpopulations or modulating mu-opioid receptor signalling in different ways[113]. Limited evidence

of benefit exists in the acute pain setting. For example, after spinal surgery, co-administration of oral oxycodone to patients given PCA morphine resulted in better analgesia, lower morphine requirements (although total opioid use – oxycodone and morphine – in morphine equivalents was little different), less nausea and vomiting and earlier recovery of bowel function[114].

Prevention of withdrawal

A physical dependence on a drug, including an opioid, is "characterised by the emergence of a withdrawal (abstinence) syndrome if the drug is abruptly stopped, reduced in dose or antagonised"[84]. Perioperative administration of the usual long-term opioid, or its equivalent, will usually prevent this.

Those taking other CNS depressants or CNS stimulants are also at risk of withdrawal from these drugs; however, symptoms may vary according to drug class. Withdrawal from alcohol and benzodiazepines in particular can cause life-threatening abstinence syndromes. If benzodiazepines are administered for the treatment of withdrawal signs and symptoms, especially when given concurrently with opioids, patient sedation levels must be monitored[74]. Symptoms of withdrawal from CNS stimulant drugs are predominantly affective rather than physical[74] but withdrawal from methamphetamines can lead to sedation[115].

Key steps in the management of withdrawal are identification of risk (see 'Preoperative Management'), monitoring, drug replacement and symptom management. Clinicians should be able to recognise the withdrawal picture for each of the major drug classes[74]. Withdrawal charts and protocols are used in many institutions but have limitations and cannot replace careful clinical assessment. Advice from a specialist drug and alcohol service may be needed[116]. 'Anxiety' may be caused by drug withdrawal, a comorbid psychiatric diagnosis or by other factors and should be carefully evaluated.

Clonidine has long been used to manage opioid withdrawal symptoms[117]. Although primarily an antihypertensive, when given in conjunction with opioids (in opioid-naïve patients at least), it can also be opioid-sparing, though evidence is conflicting[74]. Sedation and hypotension may also be more frequent[118].

Liaison with other clinicians, clinical services and healthcare workers

A collaborative, interdisciplinary approach, maintaining continuity of care and ensuring communication with usual care providers is crucial[72]. Useful resources include: a pain clinic/pain medicine specialist, drug and alcohol service/addiction medicine specialist, consultation-liaison psychiatrist, the patient's general practitioner, physiotherapy and social work. Referral to specialised services may need to be initiated, either as an inpatient or after discharge.

If problems are complex or the hospital admission prolonged, there is potential for dysfunctional interactions, such as fragmentation and conflict, either within the team or between the patient and members of the team[79,119]. Strategies that may help minimise this include education of staff[120], clearly defined team member roles with one specialist/service in charge of pain management decisions, good communication (including documentation), team meetings and providing the patient with a consistent message about management along with explicit behavioural limits[79]. It is important that medical causes of disruptive behaviour, for example delirium from drug withdrawal, are excluded[79].

Specific issues in patients with an addiction

Addiction is characterised by a pattern of aberrant drug-taking behaviours and the compulsive use of a substance "despite the risk of physical, psychological or social harm to the user"[84]. Patients with an opioid addiction may express concerns about inadequate pain relief, the possibility of withdrawal, and disrespectful treatment by staff due to stigmatisation[72]. Specific strategies may be needed to deal with the sometimes difficult interactions that can occur[72,120]. These include: ensuring a non-punitive, respectful approach to treatment in what may be challenging situations; recognising and acknowledging conditions that are painful; listening and responding to specific requests; recognising that 'difficult' behaviours may represent attempts to seek pain relief and providing reassurance that attempts are being made to provide good analgesia, while setting reasonable limits in terms of the medications that will be prescribed, including how much and how often[72].

Clinician concerns about possible 'drug-seeking' behaviour increase the complexity of acute pain management. It is probably preferable to err on the side of over-treating the occasional 'drug-seeker', rather than under-treating the patient in pain. Approaches include careful clinical judgement, assessing for legitimate causes of pain, challenging one's own stereotyping, communication with usual providers and jurisdictional authorities, drug security and use of rational prescribing policies and protocols promoting a standardised approach

to management[121]. On occasion, individuals with a history of addiction may use illicit drugs, for example those brought in by associates, while in hospital. Institutional guidelines about the management of such behaviour should be widely publicised[79].

Those in drug-free recovery or in addiction treatment programs may be concerned that their progress will be derailed by the acute pain episode and express a preference not to receive opioids in addition to their usual MMT or BMT[122]. This requires reassurance, optimisation of non-opioid strategies, rational prescription of opioids and ongoing follow-up to support recovery maintenance. However, it is also important to explain that there is no evidence that the use of opioids to treat acute pain increases the rate of relapse and that a more likely trigger may be unrelieved pain[73].

Methadone maintenance therapy

MMT is usually given once a day. This is usually enough to suppress symptoms of opioid withdrawal for 24 hours but the duration of analgesia may be shorter[73,123]. In those requiring treatment for acute pain, the usual daily methadone dose (or its equivalent if the patient is unable to take oral methadone) should be continued, with an alternative opioid given for additional analgesia. Sometimes, dividing the daily dose on a temporary basis, with or without an overall dose increase, may provide a background analgesic effect but additional opioid will usually still be required[74]. If the methadone dose is increased, this should be done in consultation with the registered prescriber/addiction medicine specialist. Patients undertaking supervised reduction of their daily methadone dose in the community may be resistant to even a short-term dose increase for analgesia, as it may be viewed as a backward step in addiction recovery.

If enteral absorption is unreliable, methadone can be administered parenterally. Doses of half to two-thirds of the total daily oral dose can be given in three to four divided doses by intermittent intra-muscular or subcutaneous injection or by continuous infusion[74,124]. This is a specialised area of practice and consultation with those experienced in using parenteral methadone is advised. There is some evidence that sublingual methadone may be effective, safe and well tolerated[125].

Buprenorphine maintenance therapy

BMT is also usually given once a day, but in some patients the dose intervals may be extended further. Like methadone, the duration of analgesia may be shorter than the time over which opioid withdrawal is suppressed. Dividing the daily dose on a temporary basis (e.g. giving the buprenorphine in two to four equal doses throughout the day) may provide a background analgesic effect but again additional opioid will still be required[73,74].

Buprenorphine is often described as a partial mu-agonist and kappa-antagonist. Clinically however, it behaves as a full mu-opioid agonist for analgesia[126] and may have anti-hyperalgesic properties[126]. It is also reported to have high opioid receptor affinity and slow offset kinetics, leading to concerns that the resultant blockade could interfere with effective acute pain management using other full mu-opioid agonists. As a result, conflicting recommendations exist (none based on high level evidence) as to whether high-dose buprenorphine (Subutex and Suboxone) should be continued or ceased in the perioperative period[73,127].

In a small series of five patients, good pain control after major surgery was achieved when usual sublingual buprenorphine doses (ranging from 2 to 24 mg/day) were continued and other full agonist opioids were given as needed[128]. In an uncontrolled comparison of 22 BMT patients (daily buprenorphine dose 13.7±6.6; range 4 to 32 mg) and 29 MMT patients (daily methadone dose 78.9±49.0 mg; range 12.5 to 180 mg), first 24 hour postoperative PCA opioid requirements (in morphine equivalents) were 196±128 mg and 180±139 mg for BMT and MMT patients respectively. Pain scores (at rest and with movement) were similar[129]. In both groups of patients, first 24 hour PCA requirements were higher, but again similar, when the maintenance drugs had been ceased perioperatively: BMT 245±109 mg; methadone 281±129 mg.

Therefore, continuation of usual BMT throughout the perioperative period is recommended with additional opioids given as required for management of acute pain.

Specific issues in patients with chronic pain

Chronic pain occurs in a psychosocial context and many factors may affect acute presentations (Table 1). Antidepressant, anti-anxiety and anti-neuropathic pain treatments should be continued where possible, although, this can be challenging in those who are unable to absorb oral medications[72]. Many of these agents are not available in parenteral formulations.

Methadone has had a resurgence for use in the management of CNCP and cancer pain, particularly if there is a neuropathic component[130]. In these settings it is commonly given as two to four doses per day and these should be continued or replaced perioperatively.

Transdermal buprenorphine patches are commonly prescribed for chronic pain[126] at doses far lower (480 μg/day for a 20 μg/hour delivery system) than those used in BMT (typically 4 to 32 mg/day). Except in circumstances of extreme haemodynamic compromise with poor peripheral perfusion, transdermal buprenorphine (and fentanyl) patches should be continued.

For those with cancer or non-cancer pain treated with ongoing continuous neuraxial (intrathecal or epidural) drugs, advice should be sought from the usual treating specialist[72]. The neuraxial drugs can be treated as background requirements and the patient managed as for other opioid-tolerant individuals. Care should be taken if undertaking a neuraxial block or a surgical procedure close to the neuraxial drug delivery system.

Sleep disruption is common with chronic pain[131]. Recommended management is a tricyclic antidepressant (amitriptyline or nortriptyline) in preference to benzodiazepines, which are associated with tolerance, addiction and disruption of sleep architecture. Tricyclic antidepressants have also demonstrated some OIH blocking effects in animal studies[132]. Those taking benzodiazepines on a long-term basis should have these continued in hospital to avoid withdrawal symptoms. If in doubt, ensure drug withdrawal charts and protocols are used.

Other non-opioid strategies

During the past decade there has been increasing use of a wide range of adjuvant drugs in acute pain, aiming to improve quality of analgesia and reduce opioid requirements and opioid-related side-effects[74]. Potential advantages of adjuvant drugs in opioid-tolerant patients include possible anti-hyperalgesic and anti-tolerance effects as well as lack of addictive potential or physical dependence. However, evidence of benefit, if any, has been reported only in opioid-naïve patients.

Gabanoids are gaining popularity for use in acute pain, although evidence of benefit is conflicting. Meta-analyses have shown that use of perioperative gabapentin improved analgesia and reduced postoperative opioid consumption but increased the incidence of sedation[133,134]. Perioperative pregabalin resulted in a significant, but small reduction in opioid requirements and a lower incidence of opioid-related side-effects, but no improvement in pain relief[135]. The role of gabanoids in opioid-tolerant patients with acute pain has not been studied.

Examples of other adjuvant drugs for which there is some evidence of benefit in the opioid-naïve, and for which more investigation in the opioid-tolerant patient may be warranted, include lignocaine[136,137], dexmedetomidine[138] and duloxetine[139].

DISCHARGE PLANNING AND MANAGEMENT

The main aims of management in opioid-tolerant patients are to treat acute pain as effectively as possible and facilitate return to the community and usual treating clinicians. There is no 'one size fits all' approach to management in this growing and heterogeneous group. The desire to minimise suffering and maximise rehabilitation opportunities must be tempered by the growing awareness, noted earlier, of prescription opioid abuse and diversion. The potential contribution of discharge opioid prescriptions to this community-wide problem necessitates a mindful approach to discharge planning.

Important considerations include the projected time to resolution of the acute episode, choice of analgesic agents and treatment duration, potential risks of opioid prescription and their management, varying legislative requirements in relation to opioid prescribing, communication with the patient's other treating practitioners (verbal and written as required) and follow-up arrangements, along with patient education and support. These issues should be considered and discussed with the patient and the treating team at an early stage in the admission so that unrealistic expectations are minimised. Usually the goal will be maintenance or resumption of usual medications as soon as possible, with any changes being for the short-term only.

For those with chronic pain, the underlying pain may not have changed. In most cases, the discharge plan will be to minimise alterations to preadmission medications prescribed for that pain. Exceptions to this may include situations where the admission opioids do not conform to acceptable guidelines[16] (e.g. where there may be inappropriate use of parenteral or very high doses of oral opioids). This may warrant consultation with or referral to a specialist service, either as an inpatient or an outpatient.

Similar considerations apply to those with a drug addiction, including those in an opioid substitution program with an authorised prescriber. Individuals outside such programs may prove more challenging to manage.

Prescription of additional opioids at time of discharge

In hospital, there are usually few limitations placed on the prescribing of opioids to patients who have an authorised prescriber (see footnotes, page 819) or an

addiction to opioids (or other controlled drugs) other than a possible requirement to inform that prescriber. However, jurisdictional legislation may limit opioid prescribing in the community. Prescribers need to be aware of the relevant legislation in their country, state or territory. Links to information relevant to each Australian jurisdiction can be found on the Therapeutics Goods Administration website[140].

Formal authorisation may be required for opioid prescription for periods of longer than two or three months[141-144]. Changes to the usual prescription, if considered necessary, may be possible if done in consultation with and with the agreement of the authorised prescriber. Prescription of opioids to those believed to be 'dependent' (see footnotes, page 819) on any controlled drug is commonly prohibited. Unlike most other Australian states, South Australian legislation allows patients on long-term opioid therapy, or with an addiction to a controlled drug, to be provided with opioids on discharge (that is, in addition to any authorised opioid and dose) for up to 14 days, as long as the authorised prescriber has been notified[145].

Even if there are no legislative restrictions on discharge opioid prescriptions, it would seem prudent to limit the planned duration of treatment with additional opioids in most opioid-tolerant patients, as for anyone prescribed opioids for acute pain management. Tighter restrictions may be appropriate for those with a drug addiction. When prescription of opioids (for self-medication) to known addicts is not permissible, it may be possible to arrange (through the authorised prescriber) daily or second-daily pick up of a limited and progressively decreasing amount of opioid, along with the usual MMT or BMT[75]. Pain clinics can sometimes arrange similar administration schedules.

Potential risks of additional opioids

In many opioid-tolerant patients, prescription of opioids in limited doses for a limited period presents little risk. As in other acute pain settings, opioids may provide effective analgesia for early rehabilitation after surgery. However, care may be required in those for whom there is an increased risk of misuse or diversion. In the USA over half of the nonmedical users of prescription drugs reportedly sourced the drugs from friends or relatives who, in turn, often obtained them from just one doctor rather than a drug dealer or other stranger[146]. In Australia in 2009 the most common sources of illicit morphine and oxycodone were a 'friend' (43 and 54% respectively) or known dealer (23 and 24%)[31].

While it is reasonable to take the potential for abuse and/or diversion into account, predicting those who might be 'at risk' – of either diversion or (usually unintentional) harm, or where there is a risk to or from family and friends – is difficult. The ability of clinicians to predict those who misuse or abuse opioids is poor[147]. While estimated rates vary widely, the risk is said to be low in those with CNCP who have no current or past history of addiction or alcohol abuse[14]. A number of tools are available to screen for potential opioid addiction or aberrant drug-taking behaviour[15,20,148,149]. Based on this risk assessment, the decision can be made as to whether limited duration opioid prescription is appropriate or not.

Choice of analgesic agents

Opioids

If prescribing opioids on discharge (in addition to the patient's usual opioid and/or dose), consideration should be given to both the opioid type and duration of therapy. There is no evidence for 'best choice' or 'best' formulation (immediate or slow release). As acute pain is likely to vary with activity (which should be encouraged), it may be reasonable to use an 'activity-based' immediate-release opioid regimen. In other cases it may be appropriate, after discussion with the authorised prescriber, to temporarily increase the dose of the usual long-term opioid. Whatever choice is made, the duration of treatment should be limited and progressive weaning from the additional opioid is advisable, for example over seven days with continuation of opioid use after this time subject to review.

In some patients, choice of opioid will be determined by abuse liability (the 'attractiveness' of a substance for abuse). This depends upon factors such as availability, cost, peer preferences and features of the drug such as speed of onset, ability to use via different routes, psychotomimetic properties and potential to produce withdrawal syndromes[150,151]. In a survey of nearly 500 recreational opioid users in the USA, the opioids rated most highly for attractiveness were immediate-release hydromorphone followed by SR oxycodone, transdermal fentanyl patches and SR morphine preparations[150]. Some abuse-deterrent formulations of drugs have been developed (e.g. Suboxone, Targin®, Mundipharma Pty Limited, Sydney, NSW [oxycodone and naloxone] and Talwin NX®, Sanofi-Aventis U.S., Bridgewater, New Jersey, USA [pentazocine and naloxone]). In future, it is likely that more will become available[152].

TABLE 2
Principles of acute pain management in opioid-tolerant patients

Preoperatively	
1. Preoperative planning	Assessment (Table 1)
	Patient education including management plan (admission to discharge)
	Ensure usual prescribed opioid (including buprenorphine) is taken on the day of surgery
	In MMT or BMT, consider arranging a 'take away' dose for self-administration on day of surgery
	Liaise with other healthcare professionals as indicated
Inpatient management	
2. Intraoperative analgesia	Replace usual opioid
	Titrate additional opioid to effect
	Consider risk of awareness
	Use non-opioid and adjuvant drugs
3. Postoperative analgesia	
a. Give adequate doses of opioid in addition to usual opioid	Incremental doses that are higher than the age-based doses usually prescribed for opioid-naïve patients may be needed (including higher PCA bolus dose)
	Much higher than expected total daily opioid doses may be required
	Titration to effect for each patient remains important
	Monitor pain, functional activity scores and sedation
	Expect the need for more frequent review and adjustment of dosing
b. Strategies that may help to attenuate tolerance or OIH	Opioid rotation
	Ketamine
c. Use of non-opioid and adjuvant analgesic drugs	Limited or no evidence of benefit in opioid-tolerant patients but may be useful:
	Paracetamol and/or NSAIDs
	Gabanoids
	Lignocaine
d. Regional analgesia	Central neuraxial or other regional blockade (consider a catheter technique)
	Useful as part of a multimodal regimen
	Neuraxially administered opioids may not prevent opioid withdrawal
4. Prevention and treatment of withdrawal syndromes	Maintain usual opioid dose equivalent
	Give usual opioid (including buprenorphine) or give equivalent dose of another opioid or same opioid by a different route
	Monitor for drug withdrawal (opioids and other drugs)
	Drug replacement or symptom management (e.g. clonidine, benzodiazepines)
5. Close liaison with other treating clinicians and specialist teams	In-hospital and post-discharge pain management
	Related social, psychiatric and behavioural issues
Management after discharge	Liaison with community providers
	Discharge management plans
	Consider legislative restrictions for opioid prescribing
	Consider early follow-up or relevant new referral

MMT=methadone maintenance therapy, BMT=buprenorphine maintenance therapy, PCA=patient-controlled analgesia, OIH=opioid-induced hyperalgesia, NSAID=nonsteroidal anti-inflammatory drugs.

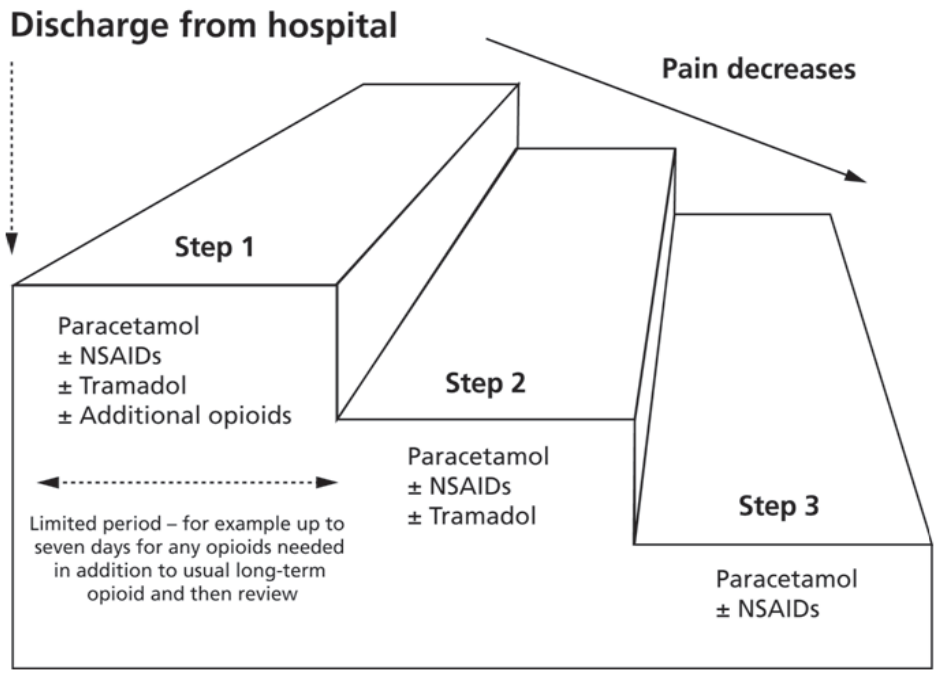

FIGURE 2: 'Reverse' Pain Ladder to be used following an episode of acute pain. Adapted from McQuay[156].

Tramadol prescription does not have the same regulatory limits, including for those with an addiction. It has a lower abuse potential. However, it should again only be used for the short-term treatment of acute pain and not with the aim of changing an individual's usual chronic pain therapy unless discussed with the usual prescriber.

Non-opioid analgesics

Paracetamol or NSAIDs that have been started in hospital can be continued after discharge, although limiting the total duration of NSAID use may be appropriate.

Combination 'over-the-counter' analgesics

Some patients may choose to use or increase their use of combination 'over-the-counter' medications – usually combinations of low-dose opioid and either paracetamol or an NSAID. In addition to being more expensive than the component drugs, there is little if any evidence of benefit for most combination analgesic preparations compared with the individual drugs alone[153]. Serious morbidity has resulted from misuse of over the counter codeine-ibuprofen combinations[154]. In the absence of supporting evidence of benefit, use of such combination analgesics is discouraged.

Duration of treatment

As the primary aim will be appropriately time-limited treatment of the acute episode after inpatient care, the discharge plan should ideally include suggestions for estimated duration of therapy and a dose reduction schedule. It is important to discuss a plan for dose reductions of any analgesics with the patient and helpful to provide the patient and his or her community medical practitioner with a written dose reduction schedule.

The World Health Organization 'Pain Ladder' was developed to guide management of cancer pain[155] with analgesic drugs to be given in ascending order (a 'step-up' approach) until the patient is comfortable: non-opioids (aspirin and paracetamol), then mild opioids (codeine) and finally strong opioids. A simple concept for patients and other staff to understand is the 'Reverse Pain Ladder' or 'step-down' approach (Figure 2) in which the same steps are used but in reverse order – at least until baseline opioid use is re-established.

Involvement of other health professionals

Discharge planning should include communication (both verbal and written as required) with the usual treating doctors. Referral to specialised services such as a pain clinic or addiction specialist may need to be initiated.

CONCLUSIONS

The number of opioid-tolerant patients requiring treatment for acute pain is increasing and effective management of that pain can be challenging. However, involvement of the patient and all treating clinicians in developing management plans

(summarised in Table 2) that start before admission where possible and continue into the post-discharge period, will promote safe and effective pain relief, along with continuity of long-term care.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the assistance of Colin M. Brown, Acting Manager, Drugs of Dependence Unit, Drug and Alcohol Services South Australia, in reviewing this paper.

A. Somogyi was supported by NHMRC Project Grants 565387 and 1011521.

FOOTNOTES

The term "authorised prescriber" is used in this review as a general term to indicate those medical practitioners who are either authorised to prescribe opioids to patients with chronic pain in the long-term or authorised to prescribe drugs used in the pharmacotherapy of opioid addiction. It may have other more specific meanings in some jurisdictions.

In legislative and regulatory terms, the word "dependence" usually has a more general meaning than "physical dependence" (defined earlier). It is often used to refer to an addiction to a controlled drug (i.e. "drug of dependence", also called "dangerous drug" in some jurisdictions).

REFERENCES

1. Ballantyne JC, LaForge K Steven. Opioid dependence and addiction during opioid treatment of chronic pain. Pain 2007; 129:235-255.
2. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. J Pain Symptom Manage 2000; 19:53-62.
3. United Nations Office on Drugs and Crimes. World Drug Report 2010. From http://www.unodc.org/unodc/en/data-and-analysis/WDR-2010.html Accessed January 2011.
4. International Narcotics Control Board. Narcotic drugs – technical reports. Estimated world requirements for 2011 – Statistics for 2009 From http://www.incb.org/incb/narcotic_drugs_reports.html Accessed January 2011.
5. Royal Australasian College of Physicians. Prescription opioid policy: improving management of chronic non-maligant pain and prevention of problems associated with precription opioid use. From http://www.racp.edu.au/page/policy-and-advocacy/ Accessed January 2011.
6. Leong M, Murnion B, Haber PS. Examination of opioid prescribing in Australia from 1992 to 2007. Intern Med J 2009; 39:676-681.
7. Australian Bureau of Statistics. Australian demographic statistics: Population change, summary – Australia ('000). From http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Mar%202010?OpenDocument Accessed March 2011.
8. Australian Government Department of Health and Aging. Public summary document: fentanyl transdermal patch. From http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-fentanylpatch-mar06. Accessed January 2011.
9. Pharmaceutical Management Agency of New Zealand. From http://www.pharmac.govt.nz/ Accessed January 2011.
10. Sheridan J, Butler R. University of Auckland, Faculty of Medical and Health Sciences. Prescription drug misuse: issues for primary care final report of findings. From http://ndp.govt.nz/moh.nsf/pagescm/7540/$File/prescription-drug-misuse-primary-care-2008v2.pdf Accessed March 2011.
11. Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. Pain Physician 2010; 13:401-435.
12. MBF Foundation. The high price of pain: the economic impact of persistent pain in Australia. From http://www.mbf.com.au/MBF/About%20MBF/Forms/MBF_Foundation_the_price_of_pain.pdf Accessed March 2011.
13. Blyth FM, March LM, Brnabic AJM, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. Pain 2001; 89:127-134.
14. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. Pain Med 2008; 9:444-459.
15. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009; 10:113-130.
16. Faculty of Pain Medicine ANZCA. PM 1: Principles regarding the use of opioid analgesics in patients with chronic non-cancer pain. From http://www.anzca.edu.au/fpm/resources/professional-documents/PM1%202010.pdf Accessed March 2011.
17. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev 2010; CD006605.
18. Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, Eriator I et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. Pain Physician 2011; 14:91-121.
19. Manchikanti L, Vallejo R, Manchikanti KN, Benyamin RM, Datta S, Christo PJ. Effectiveness of long-term opioid therapy for chronic non-cancer pain. Pain Physician 2011; 14:E133-156.
20. Smith HS, Kirsh KL, Passik SD. Chronic opioid therapy issues associated with opioid abuse potential. J Opioid Manag 2009; 5:287-300.
21. Heit HA, Gourlay DL. Tackling the difficult problem of prescription opioid misuse. Ann Intern Med 2010; 152:747-748.
22. Solanki DR, Koyyalagunta D, Shah RV, Silverman SM, Manchikanti L. Monitoring opioid adherence in chronic pain patients: assessment of risk of substance misuse. Pain Physician 2011; 14:E119-31.
23. Australian Institute of Health and Welfare. Cancer in Australia 2010: an overview. From http://www.aihw.gov.au/publication-detail/?id=6442472459&tab=1 Accessed March 2011.
24. King T, Porreca F. Opioids in cancer pain: new considerations. IASP Pain Clinical Updates 2010; 18:1-5.

25. Australian Institute of Health and Welfare. National opioid pharmacotherapy statistics annual data collection: 2009 Report. From http://www.aihw.gov.au/publication-detail/?id=6442468365 Accessed March 2011.
26. New Zealand Ministry of Health. New Zealand Clinical Guidelines for the Use of Buprenorphine (with or without Naloxone) in the Treatment of Opioid Dependence 2010. From http://www.moh.govt.nz/moh.nsf/indexmh/nz-guidelines-buprenorphine-2010 Accessed March 2010.
27. Australian Government Department of Health and Ageing National Drugs Strategy. National pharmacotherapy policy for people dependent on opioids. From http://www.health.gov.au/internet/drugstrategy/publishing.nsf/Content/pharmacotherapy Accessed March 2011.
28. Larance B, Degenhardt L, Mattick RP, O'Brien S, Lintzeris N, Bell J et al. (2009) The diversion and injection of the pharmaceutical opioids used in opioid substitution treatment: Findings from the Australian post-marketing surveillance studies of buprenorphine-naloxone, 2006-2008. From http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/resources/TR+298-302/$file/TR+302.pdf National Drug and Research Centre. Accessed March 2010.
29. Ballantyne JC. U.S. opioid risk management initiatives. IASP Pain Clinical Updates 2009; 17:1-5.
30. Australian Institute of Health and Welfare. 2007 National drug strategy household survey. From http://www.aihw.gov.au/publication-detail/?id=6442468195&tab=1 Accessed March 2011.
31. Stafford J, Burns L. National Drug and Alcohol Research Centre, University of New South Wales. Australian Drug Trends 2009: Findings from the Illicit Drug Reporting System (IDRS). From http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/resources/DRUG_TRENDS_1_NAT/$file/DT2009.pdf Accessed January 2011.
32. Breen C, Degenhardt L, Roxburgh A, Bruno R, Duquemin A, Fetherston J et al. National Drug and Alcohol Research Centre, University of New South Wales Australian Drug Trends 2002: Findings from the Illicit Drug Reporting System (IDRS). From http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/resources/Mono_6/$file/Mono.50.pdf Accessed March 2011.
33. Stafford J, Degenhardt L, Black E, Bruno R, Buckingham K, Fetherston J et al. National Drug and Alcohol Research Centre, University of New South Wales. Australian Drug Trends 2005: Findings from the Illicit Drug Reporting System (IDRS). From http://ndarc.med.unsw.edu.au/NDARCWeb.nsfresources/Mono_1/$file/Mono.59.pdf Accessed March 2011.
34. National Centre in HIV Epidemiology and Clinical Research, University of New South Wales. Sydney Medically Supervised Injecting Centre Evaluation Report No. 4: Evaluation of service operation and overdose-related events. From http://www.med.unsw.edu.au/NCHECRweb.nsf/resources/Interim_eval_rep_2/$file/EvalRep4SMSIC.pdf Accessed March 2011.
35. New Zealand Drug Foundation. Into my arms: Injecting drug use in New Zealand. From http://www.drugfoundation.org.nz/matters-of-substance/into-my-arms. Accessed March 2011.
36. Wilkins C, Casswell S, Bhatta B, Pledger M. Alcohol & Public Health Research Unit, Faculty of Medicine and Health Science, University of Auckland. Drug use in New Zealand: national surveys comparison 1998 & 2001. From http://www.aphru.ac.nz/projects/drugs%202001%20TC.htm Accessed March 2011.
37. New Zealand Ministry of Health. National Drug Policy 2007-2012. From http://www.ndp.govt.nz/moh.nsfpagescm/685/$File/nationaldrugpolicy20072012.pdf Accessed March 2011.
38. Substance Abuse and Mental Health Services Administration. Highlights of the 2009 Drug Abuse Warning Network (DAWN) Findings on drug-related emergency department visits. From http://www.oas.samhsa.gov/2k10/DAWN034/EDHighlightsHTML.pdf Accessed March 2011.
39. Australian Institute of Health and Welfare. National Hospital Morbidity Database. From http://www.aihw.gov.au/hospitals/nhm_database.cfm Accessed January 2011.
40. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011; 305:1315-1321.
41. Rintoul AC, Dobbin MD, Drummer OH, Ozanne-Smith J. Increasing deaths involving oxycodone, Victoria, Australia, 2000-09. Inj Prev 2011; 17:254-259.
42. International Association for the Study of Pain. Pain Terminology. From http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions&Template=/CM/HTMLDisplay.cfm&ContentID=1728 Accessed March 2011.
43. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006; 104: 570-587.
44. Fishbain DA, Cole B, Lewis JE, Gao J, Rosomoff RS. Do opioids induce hyperalgesia in humans? An evidence-based structured review. Pain Med 2009; 10:829-839.
45. Tompkins DA, Campbell CM. Opioid-induced hyperalgesia: clinically relevant or extraneous research phenomenon? Curr Pain Headache Rep 2011; 15:129-136.
46. Mao J. Opioid-induced hyperalgesia. IASP Pain Clinical Updates 2008; 16:1-4.
47. Compton P, Charuvastra VC, Kintaudi K, Ling W. Pain responses in methadone-maintained opioid abusers. J Pain Symptom Manage 2000; 20:237-245.
48. Doverty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. Pain 2001; 90:91-96.
49. Mitchell TB, White JM, Somogyi AA, Bochner F. Switching between methadone and morphine for maintenance treatment of opioid dependence: impact on pain sensitivity and mood status. Am J Addict 2006; 15:311-315.
50. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. Drug Alcohol Depend 2001; 63:139-146.
51. Athanasos P, Smith CS, Ling W, Bochner F, Somogyi AA, White JM. Morphine plus S(+) ketamine or tramadol elicit antinociception in opioid non-tolerant and buprenorphine maintained but not methadone maintained subjects. Abstracts of the 11th World Congress on Pain, International Association for the Study of Pain 2005.
52. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. J Pain 2009; 10:316-322.
53. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain 2006; 7:43-48.
54. Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: new evidence from a study of chronic opioid addicts and healthy subjects. Drug Alcohol Depend 2006; 82:218-223.

55. Chia YY, Liu K, Wang JJ, Kuo MC, Ho ST. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999; 46:872-877.
56. Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 2000; 93:409-417.
57. Mitra S. Opioid-induced hyperalgesia: pathophysiology and clinical implications. J Opioid Manag 2008; 4:123-130.
58. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M. Short-term infusion of the mu-opioid aganist remifentanil in humans causes hyperalgesia during withdrawal. Pain 2003; 106:49-57.
59. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schuttler J. Differential modulation of remifentanil induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology 2003; 99:152-159.
60. Angst MS, Chu LF, Tingle MS, Shafer SL, Clark JD, Drover DR. No evidence for the development of acute tolerance to analgesic, respiratory depressant and sedative opioid effects in humans. Pain 2009; 142:17-26.
61. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain 2008; 24:479-496.
62. Christie MJ. Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. Br J Pharmacol 2008; 154:384-396.
63. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011; 14:145-161.
64. Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005;103:147-155.
65. Altier C, Zamponi GW. Opioid, cheating on its receptors, exacerbates pain. Nat Neurosci 2006; 9:1465-1467.
66. King T, Gardell LR, Wang R, Vardanyan A, Ossipov MH, Malan TP Jr et al. Role of NK-1 neurotransmission in opioid-induced hyperalgesia. Pain 2005; 116:276-288.
67. Crain SM, Shen KF. Acute thermal hyperalgesia elicited by low-dose morphine in normal mice is blocked by ultra-low-dose naltrexone, unmasking potent opioid analgesia. Brain Res 2001; 888:75-82.
68. Wang HY, Frankfurt M, Burns LH. High-affinity naloxone binding to filamin a prevents mu opioid receptor-Gs coupling underlying opioid tolerance and dependence. PLoS One 2008; 3:e1554.
69. Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci 2009; 10:23-36.
70. Watkins LR, Hutchinson MR, Rice KC, Maier SF. The "toll" of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. Trends Pharmacol Sci 2009; 30:581-591.
71. Hutchinson MR, Zhang Y, Shridhar M, Evans JH, Buchanan MM, Zhao TX et al. Evidence that opioids may have toll-likereceptor 4 and MD-2 effects. Brain Behav Immun 2010; 24:83-95.
72. Roberts LJ. The opioid-tolerant patient, including those with a substance abuse disorder. In: Macintyre PE, Walker SM, Rowbotham DJ, eds. Clinical Pain Management: Acute Pain, 2nd ed. London: Hodder Arnold 2008.
73. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med 2006; 144:127-134.
74. Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM. APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute Pain Management: Scientific Evidence, 3rd ed. From www.anzca.edu.au/resources/books-and-publications Accessed March 2011.
75. Peng PW, Tumber PS, Gourlay D. Review article: perioperative pain management of patients on methadone therapy. Can J Anaesth 2005; 52:513-523.
76. Hansson KS, Fridlund B, Brunt D, Hansson B, Rask M. The meaning of the experiences of persons with chronic pain in their encounters with the health service. Scand J Caring Sci 2010; [Epub ahead of print].
77. Scimeca MM, Savage SR, Portenoy R, Lowinson J. Treatment of pain in methadone-maintained patients. Mt Sinai J Med 2000; 67:412-422.
78. Mehta V, Langford RM. Acute pain management for opioid dependent patients. Anaesthesia 2006; 61:269-276.
79. Haber PS, Demirkol A, Lange K, Murnion B. Management of injecting drug users admitted to hospital. Lancet 2009; 374:1284-1293.
80. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004; 363:1757-1763.
81. Vereecke HEM, Vanluchene AL, Mortier EP, Everaert K, Struys MM. The effects of ketamine and rocuronium on the A-Line auditory evoked potential index, Bispectral Index, and spectral entropy monitor during steady state propofol and remifentanil anesthesia. Anesthesiology 2006; 105:1122-1134.
82. Prodduturi S, Sadrieh N, Wokovich AM, Doub WH, Westenberger BJ, Buhse L. Transdermal delivery of fentanyl from matrix and reservoir systems: effect of heat and compromised skin. J Pharm Sci 2010; 99:2357-2366.
83. Rapp SE, Ready LB, Nessly ML. Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review. Pain 1995; 61:195-201.
84. Macintyre PE, Schug SA. Acute pain management: a practical guide, 3rd ed. Saunders Elsevier, London 2007.
85. Chapman CR, Donaldson G, Davis J, Ericson D, Billharz J. Postoperative pain patterns in chronic pain patients: a pilot study. Pain Med 2009; 10:481-487.
86. Rapp SE, Wild LM, Egan KJ, Ready LB. Acute pain management of the chronic pain patient on opiates: a survey of caregivers at University of Washington Medical Center. Clin J Pain 1994; 10:133-138.
87. Victorian Quality Council. Acute pain management measurement toolkit. From http://www.health.vic.gov.au/qualitycouncil/downloads/apmm_toolkit.pdf Accessed February 2011.
88. Broyles LM, Colbert AM, Tate JA, Swigart VA, Happ MB. Clinicians' evaluation and management of mental health, substance abuse, and chronic pain conditions in the intensive care unit. Crit Care Med 2008; 36:87-93.
89. Chang G, Chen L, Mao J. Opioid tolerance and hyperalgesia. Med Clin North Am 2007; 91:199-211.
90. Davis JJ, Swenson JD, Hall RH, Dillon JD, Johnson KB, Egan TD et al. Preoperative "fentanyl challenge" as a tool to estimate postoperative opioid dosing in chronic opioid-consuming patients. Anesth Analg 2005; 101:389-395.
91. Hadi I, Morley-Forster PK, Dain S, Horrill K, Moulin DE. Brief review: perioperative management of the patient with chronic non-cancer pain. Can J Anaesth 2006; 53:1190-1199.
92. George JA, Lin EE, Hanna MN, Murphy JD, Kumar K, Ko PS et al. The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. J Opioid Manag 2010; 6:47-54.

93. Roberts LJ, Hellier L, Croy H. Opioid tolerance and perioperative pain management. Abstracts of the 11th World Congress on Pain, International Association for the Study of Pain 2005.
94. Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. Br J Anaesth 2011; 106:292-297.
95. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006; CD004603.
96. Zakine J, Samarcq D, Lorne E, Moubarak M, Montravers P, Beloucif S et al. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesth Analg 2008; 106:1856-1861.
97. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010; 113:639-646.
98. Urban MK, Ya Deau JT, Wukovits B, Lipnitsky JY. Ketamine as an adjunct to postoperative pain management in opioid tolerant patients after spinal fusions: a prospective randomized trial. HSS J 2008; 4:62-65.
99. Lin SL, Tsai RY, Shen CH, Lin FH, Wang JJ, Hsin ST et al. Co-administration of ultra-low dose naloxone attenuates morphine tolerance in rats via attenuation of NMDA receptor neurotransmission and suppression of neuroinflammation in the spinal cords. Pharmacol Biochem Behav 2010; 96:236-245.
100. Wang HY, Friedman E, Olmstead MC, Burns LH. Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling. Neuroscience 2005; 135:247-261.
101. Crain SM, Shen KF. Ultra-low concentrations of naloxone selectively antagonize excitatory effects of morphine on sensory neurons, thereby increasing its antinociceptive potency and attenuating tolerance/dependence during chronic cotreatment. Proc Natl Acad Sci U S A 1995; 92:10540-10544.
102. La Vincente SF, White JM, Somogyi AA, Bochner F, Chapleo CB. Enhanced buprenorphine analgesia with the addition of ultra-low-dose naloxone in healthy subjects. Clin Pharmacol Ther 2008; 83:144-152.
103. Sartain JB, Barry JJ, Richardson CA, Branagan HC. Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. Anesthesiology 2003; 99:148-151.
104. Cepeda MS, Alvarez H, Morales O, Carr DB. Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. Pain 2004; 107:41-46.
105. Cepeda MS, Africano JM, Manrique AM, Fragoso W, Carr DB. The combination of low dose of naloxone and morphine in PCA does not decrease opioid requirements in the postoperative period. Pain 2002; 96:73-79.
106. Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database Syst Rev 2004; CD004847.
107. Fine PG, Portenoy RK. Establishing "best practices" for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage 2009; 38:418-425.
108. Patanwala AE, Duby J, Waters D, Erstad BL. Opioid conversions in acute care. Ann Pharmacother 2007; 41:255-266.
109. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. J Pain Symptom Manage 2001; 22:672-687.
110. Christoph T, Kogel B, Strassburger W, Schug SA. Tramadol has a better potency ratio relative to morphine in neuropathic than in nociceptive pain models. Drugs R D 2007; 8:51-57.
111. Ross FB, Wallis SC, Smith MT. Co-administration of sub-antinociceptive doses of oxycodone and morphine produces marked antinociceptive synergy with reduced CNS side-effects in rats. Pain 2000; 84:421-428.
112. Bolan EA, Tallarida RJ, Pasternak GW. Synergy between mu opioid ligands: evidence for functional interactions among mu opioid receptor subtypes. J Pharmacol Exp Ther 2002; 303:557-562.
113. Smith MT. Differences between and combinations of opioids re-visited. Curr Opin Anaesthesiol 2008; 21:596-601.
114. Blumenthal S, Min K, Marquardt M, Borgeat A. Postoperative intravenous morphine consumption, pain scores, and side effects with perioperative oral controlled-release oxycodone after lumbar discectomy. Anesth Analg 2007; 105:233-237.
115. McGregor C, Srisurapanont M, Jittiwutikarn J, Laobhripatr S, Wongtan T, White JM. The nature, time course and severity of methamphetamine withdrawal. Addiction 2005; 100:1320-1329.
116. Berge KH, Morse RM. Protocol-driven treatment of alcohol withdrawal in a general hospital: when theory meets practice. Mayo Clin Proc 2008; 83:270-271.
117. Honey BL, Benefield RJ, Miller JL, Johnson PN. Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. Ann Pharmacother 2009; 43:1506-1511.
118. Marinangeli F, Ciccozzi A, Donatelli F, Di Pietro A, Iovinelli G, Rawal N et al. Clonidine for treatment of postoperative pain: a dose-finding study. Eur J Pain 2002; 6:35-42.
119. Gabbard GO. Splitting in hospital treatment. Am J Psychiatry 1989; 146:444-451.
120. Morgan BD. Knowing how to play the game: hospitalized substance abusers' strategies for obtaining pain relief. Pain Manag Nurs 2006; 7:31-41.
121. Sim MG, Hulse GK, Khong E. Acute pain and opioid seeking behaviour. Aust Fam Physician 2004; 33:1009-1012.
122. May JA, White HC, Leonard-White A, Warltier DC, Pagel PS. The patient recovering from alcohol or drug addiction: special issues for the anesthesiologist. Anesth Analg 2001; 92:1601-1608.
123. Basu S, Bruce RD, Barry DT, Altice FL. Pharmacological pain control for human immunodeficiency virus-infected adults with a history of drug dependence. J Subst Abuse Treat 2007; 32:399-409.
124. Shaiova L, Berger A, Blinderman CD, Bruera E, Davis MP, Derby S et al. Consensus guideline on parenteral methadone use in pain and palliative care. Palliat Support Care 2008; 6:165-176.
125. Hagen NA, Moulin DE, Brasher PM, Biondo PD, Eliasziw M, Watanabe SM et al. A formal feasibility study of sublingual methadone for breakthrough cancer pain. Palliat Med 2010; 24:696-706.
126. Pergolizzi J, Aloisi AM, Dahan A, Filitz J, Langford R, Likar R et al. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract 2010; 10:428-450.
127. Roberts DM, Meyer-Witting M. High-dose buprenorphine: perioperative precautions and management strategies. Anaesth Intensive Care 2005; 33:17-25.

128. Kornfeld H, Manfredi L. Effectiveness of full agonist opioids in patients stabilized on buprenorphine undergoing major surgery: a case series. Am J Ther 2010; 17:523-528.
129. Russell R, Usher K, Macintyre PE. A comparison of postoperative opioid requirements and effectiveness in methadone- and buprenorphine-maintained patients. Anaesth Intensive Care 2011; 39:726-727.
130. Brown R, Kraus C, Fleming M, Reddy S. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. Postgrad Med J 2004; 80:654-659.
131. Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The association between chronic low back pain and sleep: a systematic review. Clin J Pain 2011; 27:169-181.
132. Hutchinson MR, Loram LC, Zhang Y, Shridhar M, Rezvani N, Berkelhammer D et al. Evidence that tricyclic small molecules may possess toll-like receptor and myeloid differentiation protein 2 activity. Neuroscience 2010; 168:551-563.
133. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain – a systematic review of randomized controlled trials. Pain 2006; 126:91-101.
134. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med 2006; 31:237-247.
135. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. Br J Anaesth 2011; 106:454-462.
136. Vigneault L, Turgeon AF, Cote D, Lauzier F, Zarychanski R, Moore L et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Can J Anaesth 2011; 58:22-37.
137. Challapalli V, Tremont-Lukats IW, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database Syst Rev 2005; CD003345.
138. Coyne PJ, Wozencraft CP, Roberts SB, Bobb B, Smith TJ. Dexmedetomidine: exploring its potential role and dosing guideline for its use in intractable pain in the palliative care setting. J Pain Palliat Care Pharmacother 2010; 24:384-386.
139. Ho KY, Tay W, Yeo MC, Liu H, Yeo SJ, Chia SL et al. Duloxetine reduces morphine requirements after knee replacement surgery. Br J Anaesth 2010; 105:371-376.
140. Australian Government, Department of Health and Ageing. Therapeutics goods administration. Contacts for State/Territory drugs & poisons units. From http://www.tga.gov.au/ndpsc/stdpu.htm Accessed February 2011.
141. Government of South Australia. Controlled Substances Act 1984. From http://www.legislation.sa.gov.au/LZ/C/A/CONTROLLED%20SUBSTANCES%20ACT%201984/CURRENT/1984.52.UN.PDF Accessed February 2011.
142. Government of Western Australia. Poisons Act 1964. From http://www.slp.wa.gov.au/pco/prod/FileStore.nsf/Documents/MRDocument:20772P/$FILE/PoisonsAct1964_08-i0-01.pdf?OpenElement Accessed January 2011.
143. Government of Western Australia. Poisons Regulations 1965. From http://www.slp.wa.gov.au/pco/prod/FileStore.nsf/Documents/MRDocument:20471P/$FILE/PoisonsRegs1965_09-h0-00.pdf?OpenElement Accessed January 2011.
144. New Zealand Government. Misuse of Drugs Act 1975. From http://www.legislation.govt.nz/act/public/1975/0116/latest/DLM436101.html Accessed January 2011.
145. Government of South Australia. (1996) Controlled Substances (Poisons) Regulations 1996. From http://www.legislation.sa.gov.au/LZ/C/R/CONTROLLED%20SUBSTANCES%20(POISONS)%20REGULATIONS%201996/CURRENT/1996.4.UN.PDF Accessed January 2011.
146. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings. From http://oas.samhsa.gov/NSDUH/2k9NSDUH/2k9ResultsP.pdf Accessed January 2011.
147. Jung B, Reidenberg MM. Physicians being deceived. Pain Med 2007; 8:433-437.
148. Passik SD, Kirsh KL. Screening for opioid abuse potential. IASP Pain Clinical Updates 2008; 16:1-4.
149. Meltzer EC, Rybin D, Saitz R, Samet JH, Schwartz SL, Butler SF et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). Pain 2011; 152:397-402.
150. Butler SF, Benoit C, Budman SH, Fernandez KC, McCormick C, Venuti SW. Development and validation of an Opioid Attractiveness Scale: a novel measure of the attractiveness of opioid products to potential abusers. Harm Reduct J 2006; 3:5.
151. Schoedel KA, Sellers EM. Assessing abuse liability during drug development: changing standards and expectations. Clin Pharmacol Ther 2008; 83:622-626.
152. Raffa RB, Pergolizzi JV Jr. Opioid formulations designed to resist/deter abuse. Drugs 2010; 70:1657-1675.
153. Bandolier. Investigating over-the-counter oral analgesics. From http://www.medicine.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/OTC%20analgesics.html Accessed April 2010.
154. Frei MY, Nielsen S, Dobbin MD, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. Med J Aust 2010; 193:294-296.
155. World Health Organisation. WHO pain ladder. From http://www.who.int/cancer/palliative/painladder/en/ Accessed January 2011.
156. McQuay H. Relief of chronic non-malignant pain. From http://www.medicine.ox.ac.uk/bandolier/booth/painpag/wisdom/493HJM.html Accessed May 2011.