British Journal of Anaesthesia 1998; **81**: 58–68

Opioid tolerance: the clinical perspective

B-J. COLLETT

Uncertainty about the clinical significance of tolerance to opioid analgesia has important and diverse implications. Although understanding of the characteristics and mechanisms of experimental tolerance has grown, the clinical correlates and ramifications of these findings remain ambiguous to practitioners prescribing long-term opioid therapy to patients for the treatment of malignant and non-malignant pain. In this review I shall discuss clinical aspects of tolerance and the associated phenomena of dependence, withdrawal and addiction to opioids as they apply to the practice of clinicians who manage patients with chronic malignant and non-malignant pain.

Why is tolerance important?

Most cancer pain can be successfully treated using pharmacological measures based on simple principles promoted by the World Health Organisation[100] and extensively validated.[94 103] Opioid medication, commonly oral morphine, is the third step on the 'analgesic ladder' and has been widely used for the management of acute and chronic cancer pain for many years, providing excellent analgesia without respiratory compromise often for months or even years.[38 92]

However, morphine has long been feared by the general public and by doctors. Concerns about addiction and tolerance are common among cancer patients. Hodes questioned 40 patients with metastatic cancer taking opioids and their spouses on a variety of issues related to cancer pain. Forty-five percent of patients and 43% of their spouses reported either moderate or extreme concern about addiction to their medications, and concerns about tolerance were expressed by 50% of patients and 63% of their spouses.[40] Recent interest in euthanasia has resulted in media coverage that portrays morphine as the physician's ultimate weapon to cause respiratory depression and subsequent death in patients who are terminally ill.[3 32] Fears evoked by these concerns may have an impact on compliance with regular analgesia and medication for breakthrough pain.

Current interest in the prescription of opioids for non-malignant pain and in the development of potential guidelines in this area has also made the complex phenomena of tolerance, physical dependence and addiction increasingly important to the clinician.[35 62 71 73 75]

(*Br. J. Anaesth.* 1998; **81**: 58–68)

Keywords: analgesics opioid; pain, chronic; cancer; children; opioid addiction; opioid tolerance

Nomenclature of tolerance and related phenomena

Confusion exists among physicians who treat patients with cancer pain about the definitions of tolerance and related phenomena,[47 97] and understanding of the precise terminology is important.

TOLERANCE

Tolerance refers to a phenomenon in which exposure to a drug results in the diminution of an effect or the need for a higher dose to maintain an effect.[45]

There are various types of tolerance, as shown in table 1.[67]

Innate tolerance refers to the genetically determined sensitivity (or lack of sensitivity) to a drug that is observed the first time that the drug is administered. Acquired tolerance can be divided into three types: pharmacokinetic, pharmacodynamic and learned tolerance.

Pharmacokinetic or dispositional tolerance refers to changes in the distribution or metabolism of the drug after repeated drug administrations that result in reduced concentrations in the blood and subsequently at the sites of drug action. The most common mechanism is an increase in the rate of metabolism of the drug, as in the case of barbiturates.

Pharmacodynamic tolerance refers to adaptive changes that have taken place within systems affected by the drug, such as drug-induced changes in receptor density, so that response to a given concentration of the drug is reduced.

Learned tolerance refers to a reduction in the effects of a drug as a result of compensatory mechanisms that are learned. One type of learned tolerance is behavioural tolerance. This describes the skills that can be developed through repeated attempts to function when in a state of mild to moderate intoxication – a common example is learning to walk a straight line in spite of motor impairment produced by alcohol intoxication. This probably involves both acquisition of motor skills and a learned awareness of

Table 1 Types of opioid tolerance

Innate
Acquired
Pharmacokinetic
Pharmacodynamic
Learned tolerance
Behavioural
Conditioned

BEVERLY-JANE COLLETT, FRCA, Pain Management Service, Leicester Royal Infirmary, Leicester LE1 5WW.

the deficit that causes the individual to walk more carefully.

A special case of behavioural tolerance is referred to as conditioned tolerance. Conditioned tolerance (situation-specific tolerance) is a learning mechanism that develops when environmental cues are consistently paired with the administration of the drug. When a drug affects homoeostatic balance by producing sedation and changes in blood pressure, heart rate and gut motility, there is usually a reflex counteraction or adaptation that attempts to restore the status quo. If the drug is always preceded by the same cues, the adaptive response to the drug will be learned and this will prevent the full manifestation of the drug's effect (tolerance). If the drug is taken under novel circumstances, tolerance is reduced and the drug's effect enhanced.

Tolerance to opioids is characterized by a shortened duration and decreased intensity of the analgesia, euphoria, sedation and other effects caused by depression of the central nervous system, as well as by marked elevation in the average lethal dose.[45]

Animal studies

Tolerance to the antinociceptive effects of opioid drugs is easily demonstrated in animal models.[7 16 102]

In a variety of animal species, using varied nociceptive endpoints, the administration of opioids will evoke a powerful dose-dependent increase in the latency with which the animal will respond to thermal, mechanical and chemical stimuli. Repeated exposure of the animal to the opioid will result in a decrease in the effect produced by a given dose of the drug, in terms of the magnitude of effect or of the duration of action and, where examined, a shift to the right in the dose–response curve.

Studies on animals undergoing continuous opioid infusions by various routes have shown tolerance to be pharmacodynamic, time- and dose-dependent, receptor-specific and apparently reversible if the agonist is removed.[86 88 102]

Recent work in mice has shown that both competitive and non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists block the development of antinociceptive tolerance to morphine, but not of that to fentanyl nor to a delta selective agonist.[7] This study suggests that there may be significant mechanistic differences between the development of tolerance to morphine (with affinity at mu, delta and kappa receptors) and more selective mu agonists. The indications are that blocking of opioid tolerance by NMDA antagonists is not a general phenomenon but appears selective for tolerance induced by morphine. The potentially significant clinical implications of this have not yet been investigated. The use of ketamine in severe cancer pain uncontrolled by opioid analgesia has been described,[15] and use of this drug in difficult pain problems is increasing.

Morphine self-administration in rats with adjuvant-induced arthritis has been studied in an attempt to evaluate the development of morphine tolerance in a model of chronic pain.[54] Arthritic rats self-injected less morphine than pain-free rats and their dose remained stable over 29 days, in contrast with pain-free rats who escalated their morphine dose. Bolus doses of the anti-inflammatory drug indomethacin early in this study led to reduced morphine intake. However, with the reduction of the adjuvant-induced arthritis, arthritic rats rapidly increased their opioid intake and the administration of indomethacin did not reduce this. The authors postulated that arthritic and pain-free rats self-administer morphine initially for qualitatively different positive reinforcement. The initial positive reinforcement in arthritic rats may be analgesia – hence the dose stability and the reduction seen with administration of indomethacin. As the pain dissipates, the animals in the arthritic group may inject morphine for other positive reinforcing properties, such as euphoria or to prevent withdrawal symptoms. The investigators suggest that the presence of pain has a significant influence on the development of tolerance in these animals.

Colpaert has also postulated that chronic nociceptive stimulation acts to antagonize the apparent tolerance otherwise associated with prolonged opioid administration and proposed the system theory as an alternative model.[18]

Human studies and clinical observations in man

Assessment of the opioid tolerance of patients in pain is constrained by numerous difficulties, and few studies have directly examined the rate of development of tolerance to the analgesic effects of opioids in man.

ACUTE TOLERANCE

Studies on acute tolerance in man have yielded conflicting results. McQuay investigated acute tolerance to fentanyl in a perioperative study. He found no significant difference in postoperative pain, respiratory function and analgesic demands in patients who had received varying doses of perioperative fentanyl and who had significant differences in plasma fentanyl levels. He suggested that this supported the hypothesis of acute tolerance.[58]

In contrast, Inturissi studied the pharmacokinetic–pharmacodynamic relationships of methadone during a brief infusion. Analysis of plasma concentration and analgesia during and after the infusion did not demonstrate a clockwise hysteresis, which would be expected if acute tolerance, or any other process that reduced analgesic efficacy during this brief period, had occurred.[42]

Chapman and Hill studied patients with mucositis in a bone-marrow transplant unit.[13] Marrow transplant is used in the aggressive treatment of malignancies unresponsive to other therapies. High-dose chemoradiotherapy is used before bone-marrow transplant and toxicity from this is unavoidable. The onset of intensely painful mucositis, thinning and breakdown of mucosal tissue and mucosal desquamation is predictable. The condition develops a few days after transplant, intensifies rapidly and remains severe for 1–3 weeks until healing is complete. The pain is most severe in the oral cavity, rendering patients being unable to speak or eat without pain, and opioid analgesics are often needed.

Morphine usage in patients self-administering the drug for 2 weeks was compared with that in patients who received morphine via routine staff-controlled

continuous infusion. In both groups, the morphine intake increased steadily over several days as the mucositis worsened and then levelled off. The self-administering group used less morphine overall than the continuous-infusion group. There was no evidence of the development of tolerance in the group who self-administered morphine, whereas the group receiving the continuous infusion needed an increasing amount of drug to maintain the same level of pain control. Withdrawal symptoms did not occur in the self-administering group and this group stopped using morphine sooner than the continuous-infusion group. This study has been replicated with similar results showing no evidence of tolerance, withdrawal or addiction,[39] and suggests that patients do not increase their opioid dose unless there is an increase in pain intensity and that as this reduces, reduced morphine usage follows.

PROLONGED ADMINISTRATION

Houde and colleagues studied tolerance to analgesia in the patient with cancer pain. The analgesic effects of graded doses of morphine on pain relief were studied in 10 patients on two occasions 2 weeks apart; during this interval, patients received morphine analgesia. A clear shift to the right in the dose–response curve indicated a degree of tolerance to the analgesic effects of morphine.[41]

In a study to compare the analgesic activities of diamorphine and hydromorphone, a relatively smaller analgesic response to these drugs was associated with a greater degree of opioid consumption in the 48 h before the start of the study.[96]

Cancer pain

Foley has written extensively on opioid tolerance in the cancer patient and critically addressed the extent to which tolerance limits the patient's ability to obtain adequate analgesia from opioid therapy during their illness.[27–29] She describes three patterns of drug use: (1) rapidly escalating doses of opioids, associated with escalating pain, anxiety or both; (2) stable doses of opioids, for periods of weeks or months, without dose escalation and reduction; and (3) discontinuance of opioid drugs with effective analgesia from anticancer therapies, neurolytic nerve block or neurosurgical procedures. These patterns have been described in outpatients, inpatients, in a group of patients with-terminal illness,[19 20 49] and also in a group of patients with non-malignant pain.[71]

Many other studies have shown that most cancer patients with severe pain, taking opioids by a variety of routes, have long periods (weeks, months or years) of stable opioid dose.[5 8 34 83 92] In addition, Plummer has demonstrated poor correlation between the ratio of maximum dose/minimum dose (a measure of dose escalation) and the duration of extradural analgesia in a group of cancer and non-cancer patients. In fact, the morphine dose was more stable in patients with chronic non-malignant pain than in the cancer patients, suggesting that increasing nociceptive stimulus was the major influence on opioid dose.[70]

While it is generally agreed that tolerance to opiate analgesia occurs, it does not appear to be a limiting factor. Dose escalation is considered to be predominantly a consequence of increasing pain as a result of increasing nociceptive input as the disease progresses.[17 19 20 28 29 49 83 92]

Table 2 A 'differential diagnosis' for declining analgesia in the clinical setting (adapted from reference 74)

Increased activity in nociceptive pathways
Increasing activation of nociceptors in the periphery because of
mechanical factors (e.g. tumour growth)
biochemical changes (e.g. inflammation)
peripheral neuropathic processes (e.g. neuroma formation)
Increased activity in central nociceptive pathways, because of central neuropathic processes (e.g. sensitization, shift in receptive fields, change in modulatory processes)
Psychological processes
Increasing psychological distress (e.g. anxiety, depression)
Change in cognitive state leading to altered pain perception or reporting (e.g. delirium)
Conditioned pain behaviour independent of the drug
Tolerance

Portenoy has elaborated on other major factors that are important for declining analgesia in the patient with cancer pain, and produced a "differential diagnosis" (table 2).[74]

Increasing nociceptive input may occur with disease progession. It may also occur with inflammation and with the development of peripheral or central neuropathic processes (for example, neuroma formation or expansion of receptive fields). Psychological processes, such as anxiety or depression, and alteration in cognitive state (for example, delirium[21]) can also lead to worsening pain. Humans present a complex interplay of processes, and pain reporting can also change as a reaction to the responses of "significant others".

Portenoy concludes that loss of analgesic effects cannot be attributed to pharmacodynamic tolerance unless an alternative explanation for increasing pain cannot be found.

It has also been suggested that tolerance-like problems are more commonly seen in patients who have pain that appears to be relatively resistant to opioids.[4] The nature of opioid responsiveness is controversial.[24] There are two extremes of opinion. One view is that opioid responsiveness is a relative phenomenon, and that any pain can be controlled by opioids provided there is an adequate dose and control of adverse effects.[72] At the other extreme, some investigators believe that the lack of response can be predicted from the clinical characteristics of the pain. Nociceptive pain is thought to be responsive to opioids, whereas neuropathic pain is regarded as non-responsive.[4 6 51 52] However, recent studies have shown that pain judged to be neuropathic may be responsive to opioids, although it is generally less so than nociceptive pain.[44 61]

Portenoy has proposed that opioid responsiveness is a continuum of responses, that can be defined operationally as the degree of analgesia obtained after upward dose titration to an end-point defined by analgesia or by the onset of intolerable and unmanageable side effects. Implicit in his conceptualization is the view that both patient-related and pain-related factors are important.[72]

A validation study of the Edmonton staging system for cancer pain was able to identify patients who were relatively less likely to attain satisfactory analgesia during opioid therapy.[10] Features of these patients

were an inferred neuropathic aetiology for the pain, the presence of incident pain, impaired cognitive function, major psychological distress, a high initial opioid dose, a rapid increase in opioid dosage (more than 5% of the initial dose per day) and a history of alcoholism or drug abuse.

The pragmatic response of the clinician when the analgesic effect of the opioid becomes inadequate is to increase the dose. This is satisfactory if: (1) the dose given is sufficient to overcome the factors that have reduced the analgesic effects of the agent; (2) side effects do not limit the dose of drug that can be given; or (3) if the pathological substrate that mediates the pain remains opioid sensitive. A two- to 10-fold increase in dose may be necessary to achieve analgesia because the dose–effect relationship is based on a log dose concentration. As Foley has stated "the dose that works is the dose that works".[29]

Non-cancer pain

A continual increase in nociceptive focus is less likely in patients with non-malignant pain than those with cancer. Patients with non-cancer pain have demonstrated more stable morphine dosage that those with pain of malignant origin.[70] Penn has shown that tolerance to intrathecal morphine in non-malignant pain was not a problem and in his series dose increase was also related to increasing pathology.[69] Clinical surveys concerning the long-term use of opioids in patients with non-malignant pain are more limited than those in cancer patients, but have not shown the development of tolerance to be a clinical problem.[30 68 69 70 89 91 93 104]

More objective data indicate that the minimum effective analgesic blood concentration of pethidine did not change significantly when measured over time (3–12 months) in three patients with chronic pain, and was independent of the route of administration.[33]

SELECTIVE TOLERANCE

Various studies and clinical experience suggest that tolerance to different opioid side effects develop at different rates and this has been termed 'selective tolerance'.[89]

Initial manifestations of opioid administration in most individuals are analgesia, sedation, nausea and vomiting, respiratory depression, pupillary constriction, constipation and euphoria or dysphoria. Tolerance to nausea and vomiting, sedation, euphoria and respiratory depression occur rapidly, while tolerance to constipation and miosis is minimal.[9 50 53 67]

Constipation

Constipation is the most common adverse effect of opioid analgesics when they are used for chronic cancer pain. Opioid analgesics bind directly to peripheral opioid receptors in the gastrointestinal tract, causing decreased peristalsis, diminished biliary, pancreatic and intestinal secretions and increased ileocaecal and anal sphincter tone. Stool transit time increases and desiccation of faeces results. If the clinical effect is sufficiently severe, opioids can produce narcotic bowel syndrome, which is characterised by nausea and vomiting, mild abdominal discomfort, constipation, gaseous abdominal distention and functional colonic obstruction.[81] As tolerance to constipation develops very slowly or not at all, constipation must be anticipated and treated prophylactically with adequate laxatives.

The development of tolerance to emesis and sedation is clinically apparent and obviously beneficial to the patient.

Nausea

Nausea has been estimated to occur in up to 40% and vomiting in 15% of ambulatory patients treated with opioids. In many patients it is an initiation side effect and resolves after a few days. As most patients will not develop nausea and vomiting while taking opioids, prophylactic antiemetic treatment is not usually indicated.

However, when patients are first prescribed opioids they should have ready access to antiemetics if these side effects occur. Then, the opioid and anti-emetic regimen should be concurrently administered in a regular fashion for 4–7 days. After this time, tolerance to emetic effects of opioids usually develops and the antiemetics can gradually be withdrawn. Patients may err by taking analgesia and antiemetics sporadically rather than regularly. Intermittent use in this way can impair the development of tolerance to this side effect, and patients should be advised accordingly.

Sedation

Sedation and cognitive impairment can be demonstrated during the administration of opioid analgesics by various routes.[84] Impaired concentration has resulted in sub-optimal treatment for pain when patient-controlled analgesia (PCA) has been used for severe mucositis.[13]

However, tolerance to the sedative and cognitive effects of opioid analgesics usually develops rapidly, and these side effects are again most problematic at the start of treatment or when the dose is increased. Bruera showed that patients experience significant cognitive impairment after a recent increase in the dose of opiates but patients on a stable dose of opiate showed no evidence of cognitive impairment, thus suggesting that tolerance develops to cognitive effects.[9] This study also suggested that patients were less aware of cognitive impairment than other opioid-induced symptoms. Consideration needs to be given to these findings when patients request advice on driving, working and decision-making while taking opioid analgesics.

However, if sedation persists and pain control is adequate, a 10–25% reduction in dose or continuation of the same dose administered in smaller but more frequent boluses may lessen this side effect. Alternatively, the administration of oral methylphenidate on wakening and at midday is effective and safe in reducing sedative opioid effects.[11]

Respiratory depression

All opioid agonists have similar depressant effects on the brain-stem respiratory centre and respiratory depression is potentially the most serious adverse effect of opioids.

In man, death from overdose of an opioid is nearly always the result of respiratory arrest. When respiratory depression occurs as a result of opioid administration, it is usually in opioid-naïve patients after acute administration of an opioid; it is associated with other signs of central nervous system depression, including sedation and mental clouding.

Tolerance appears to develop rapidly to respiratory depression with repeated drug administration, allowing opioid analgesics to be used in the management of chronic cancer pain without significant risk of respiratory depression.

However, pain acts as an antagonist to the central nervous system depressant and in particular to the respiratory depressant effects of opioids.[36 37 59 60] McQuay has postulated that the respiratory centre in the medulla might receive nociceptive input.[59] Particular care is indicated in the continued management of patients receiving high doses of opioid who undergo a neurolytic or neurosurgical procedure that abruptly reduces nociceptive input. Removal of the stimulatory effect of the pain may lead to an unopposed opioid-mediated respiratory depressant effect, and may result in somnolence or respiratory depression.[36 37] In the case of a successful neuroablative procedure, the dose of opioid should be tapered and the patient carefully observed.

Opioid-induced respiratory depression is infrequent. Doctors' and nurses' inordinate fear of this complication is an important impediment to adequate control of cancer pain.

CROSS-TOLERANCE

Repeated doses of a drug in a given category confer tolerance not only to the drug being used but also to other drugs in the same structural and mechanistic category[67]; this effect is known as cross-tolerance.

Animal studies have shown cross-tolerance to be incomplete.[43 64 66 88] Neil demonstrated that mice pretreated with morphine were tolerant to morphine only, while methadone-treated mice were tolerant to methadone, morphine, codeine and D-propoxyphene and more so to morphine than to methadone itself.[66] Evidence suggests that incomplete cross-tolerance results from selective tolerance at different subpopulations of opioid receptors. It has been shown that a mu-selective drug induces only minimal tolerance at kappa or delta receptors.[88] Moulin has shown that rats chronically infused with levorphanol (an agonist at mu, kappa and delta receptors) develop substantial cross-tolerance to the analgesic effects produced by a dose of morphine (a relatively selective mu agonist), whereas rats infused with morphine demonstrate little tolerance when challenged with a dose of levorphanol.[64] This raises the possibility that there is clinical advantage in using morphine before levorphanol in the management of severe pain and indicates the need for controlled clinical studies to determine whether patterns of cross-tolerance between commonly used opioid drugs could dictate the sequence in which they should be used.

The patterns of cross tolerance to various opioids exhibited by patients are unpredictable, but appear to be incomplete.[25] Patients who have pain uncontrolled by morphine in spite of intolerable side effects may be switched to an alternative opioid that allows pain control to be achieved without disabling side effects.[1 12 26 31]

The variability in response to different opioid drugs has important clinical implications. It has been suggested that in difficult pain problems, when dose escalation with morphine or any other opioid yields intolerable side effects, sequential drug trials may identify an opioid that provides the favourable balance between analgesia and side effects.

Table 3 Symptoms and signs of opioid withdrawal

Symptoms	Signs
Craving for opioids	Pupillary dilatation
Restlessness	Sweating
Irritability	Piloerection
Increased sensitivity to pain	Tachycardia
Nausea	Vomiting
Abdominal cramps	Diarrhoea
Myalgia	Hypertension
Dysphoria	Yawning
Insomnia	Fever
Anxiety	Rhinorrhoea

PHYSICAL DEPENDENCE

Physical dependence is defined as the potential for an abstinence syndrome, or withdrawal, after abrupt dose reduction, discontinuation of the drug or administration of an antagonist drug.[45]

Physical dependence and withdrawal symptoms have been extensively studied and described in animals[56 78] and in man[22 53] (table 3).

In the clinical setting, the lowest dose and shortest duration of treatment that may predispose to a significant abstinence syndrome is not known. Physical dependence probably starts with the first dose of an opioid drug and should be presumed to exist if opioids are given repeatedly for a few days. However, patients who receive therapeutic doses of morphine several times a day for 1–2 weeks will have only mild withdrawal symptoms that may not be recognized as such when the drug is stopped. Symptoms are even less pronounced when the drug is one that is slowly eliminated, such as methadone. However, by administering naloxone, an opioid antagonist, withdrawal symptoms can be precipitated after only one or two therapeutic doses of morphine, even in individuals who have no prior history of opioid dependence.[46]

The prevention of unpleasant withdrawal symptoms has been suggested as a positive reinforcer for continued morphine self-administration in animals.[54] The fear of withdrawal has been considered to be one of the major forces behind persistent drug abuse in addicts.

Neither the prevalence nor the pattern of opioid withdrawal has been systematically studied in patients with pain. In the cancer population, effort is usually made to reduce opioid dose slowly in patients whose pain has been relieved by alternative methods, such as neurolytic block or radiotherapy, and with this practice withdrawal symptoms do not appear to be a problem. However, abrupt cessation of opioids or administration of opioid antagonists in this situation can result in classical withdrawal symptoms, which can be controlled by the resumption of low-dose opioids.[37 49]

In a population with chronic non-cancer pain undergoing opiate reduction during an inpatient pain-management programme, withdrawal symptoms were not recorded as problematic.[77]

The implications are that although patients who take long-term opioids may become physically dependent (and thus display an abstinence syndrome if the dose is abruptly decreased or an antagonist given), reduction and subsequent discontinuation can occur without adverse effects if the dose is tapered slowly.

ADDICTION

Standard definitions of addiction have been developed from experience with substance abusers and must be cautiously interpreted when applied to patients who are receiving a potential drug of abuse prescribed for an appropriate medical indication.

Addiction has been defined as "a behavioural pattern of drug use, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and the high tendency to relapse after withdrawal".[45]

A task force of the Panels on Alcoholism and Drug Abuse of the American Medical Association (AMA) Council on Scientific Affairs formulated the following definitions:

Addiction: "a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological or social harm to the user and continued use despite that harm".[79]

Addict: a person who is physically dependent on one or more psychoactive substances, whose long-term use has produced tolerance, who has lost control over his intake, and would manifest withdrawal phenomenon if discontinuance were to occur.

Although the AMA Task Force decided to include the finding of physical dependence in the definition of an addict, the criteria for the latter still include the loss of personal control over drug use; the Task Force is thereby proposing a distinction between the addict and the physically dependent patient. Both these definitions emphasize that the development of addiction is a psychological and behavioural process.

Opioid pseudoaddiction

Pseudoaddiction has been used to describe the iatrogenic syndrome of behavioural changes similar to those seen with idiopathic opioid addiction that can develop as a direct result of inadequate pain management.[98]

Uncontrolled pain from both malignant and non-malignant causes (such as sickle-cell crisis, tuberculosis) combined with inadequate analgesia can result in increasing demands and bizarre drug-seeking behaviour by the patient. The patient feels angry and emotionally isolated from the health care team, who in turn try to avoid contact with the patient because of frequent pain complaints and demands for analgesia. These patients are often described as 'clock watchers'. A vicious cycle of anger, isolation, and avoidance lead to complete mistrust. The importance of recognizing this syndrome cannot be over-emphasized. Treatment strategies start by acknowledgement that the pain is real and the establishment of trust between the patient and the health care team. Appropriate and timely analgesia to control the patient's pain then needs to be prescribed and given using scheduled rather than 'as required' dosing, with additional medication for breakthrough pain and frequent re-evaluation.

There is ample support both from animal studies and from observation of human addicts for the proposition that opioids are inherently reinforcing drugs. Addicts usually report euphoric effects from opioid drugs and it is thought to be this and the avoidance of the aversive effects of withdrawal that are involved in the pathogenesis of addiction. In contrast, administration of opioids to human volunteers and patients can produce dysphoria and not a consistent euphoria.[46]

Although an improvement in mood has been demonstrated in post-operative cancer patients following the administration of morphine and diamorphine, this coincided with relief of pain.[46 48]

Addiction has been shown to be more complex than just the result of repeated exposure to a drug. There was a high prevalence of opioid addiction among US soldiers in Vietnam; however, surveys of returning veterans demonstrated that a large proportion of those who abused heroin stopped this activity abruptly on return to a normal life in the US and that the relapse rate was low.[80] In sharp contrast, a group who underwent a 6-month inpatient treatment programme under the Narcotic Addict Rehabilitation Act were readdicted within 6 months of their release.

Addiction in patients with chronic pain

Two early surveys (in 1925 and 1939) of addicts undergoing treatment reported that 9% and 4% respectively began their addiction with a medical prescription of an opioid drug for a painful disorder.[73] In 1954, a report noted that 27% of white male addicts and 1.2% of black male addicts began abuse as medical patients treated for pain.[73] Surveys of addicted populations are clearly subject to bias and a different view has emerged from more recent data on medical patients who were assessed for the development of addiction after receiving opioids for the treatment of pain.

The Boston Collaborative Drug Surveillance Programme reported only four cases of well documented addiction in 11 882 hospitalized patients with no previous history of addiction who had received opioids.[76]

Furthermore, abnormal drug-seeking behaviour was not seen when long-term opioids were used for postherpetic neuralgia,[68] phantom limb pain,[93] chronic spinal pain[30] and pain of mixed but well defined origin.[91] Taub described 313 personally treated patients with intractable pain who were maintained on opioid analgesics for up to 6 years. Only 13 patients presented serious management problems, and each of them had a history of substance abuse (opiates or alcohol).[89] Portenoy also identified this risk factor in his study of 38 patients treated with opioids for non-malignant pain; the two patients who required escalating doses of opioids each had a history of drug abuse.[71]

However, Maruta found that 65% of 144 consecutive patients referred for chronic non-malignant pain management were abusing or dependent on (using

their definition) weak and strong opioid drugs and had a strong family history of alcohol abuse.[57]

Therefore, clinical experience suggests that there may be a spectrum of responses to pain in patients treated with opioids, ranging from appropriate and acceptable drug-seeking in patients with unrelieved pain to a group of clearly pathological responses that can occur even in those with severe pain. Most of the patients who developed drug-seeking behaviour had a prior problem with illicit drug abuse.

Redefinition of addiction in patients taking opioids for chronic pain

Portenoy has suggested redefining addiction in patients taking opioids for chronic pain as follows: "a psychologic and behavioural syndrome characterized by: (1) an intense desire for the drug and overwhelming concern about its continued availability (psychologic dependence); (2) evidence of compulsive drug use (characterized, for example, by unsanctioned dose escalation, continued, dosing despite significant side-effects, use of drug to treat symptoms not targeted by therapy, or unapproved use during periods of no symptoms); and/or (3) evidence of one or more of a group of associated behaviours, including manipulation of the treating physician or medical system for the purposes of obtaining additional drug (altering prescriptions, for example), acquisition of drugs from other medical sources or from a non-medical source, drug hoarding or sales, or unapproved use of other drugs (particularly alcohol or other sedatives/hypnotics) during opioid therapy."[73]

USE OF OPIOIDS IN NON-MALIGNANT PAIN

The long-term use of opioid analgesics for the treatment of chronic non-malignant pain is controversial. The possibility of rapid dose escalation as a result of tolerance and the development of physical dependence, addiction and increasing disability have been major concerns.[57 82] However, clinical experience demonstrates that some patients with chronic pain derive benefit from opioids.[30 71 89 91 93 104]

Current opinion is that there is a small group of patients with chronic non-malignant pain who may benefit from long-term opioid therapy. Guidelines have been produced to assist in the assessment, selection and subsequent management of patients who might be considered suitable for long-term opioid therapy.[35 62 73 75 90]

OPIOPHOBIA

Opiophobia is the phenomenon of failure to administer legitimate opioid analgesics because of a fear of the power of these drugs to produce addiction.[63]

Underutilization of opioid drugs in acute and cancer pain results in unnecessary suffering.[2 63 106] The major reasons for this underuse are overestimation of the risks of opioid toxicity, intense concern among health care professionals, patients and their families about addiction and tolerance, legal sanctions that impede the prescription of opioid drugs to those who need them and a lack of systematic education. Undertreatment (in terms of both prescription and administration) also occurs because of custom and culture. Individuals perceived to be at greater risk of addiction, such as those who belong to the lower socioeconomic groups, the young and non-white patients may receive less opioids.[63] Zenz has eloquently rebutted the "morphine myths" relating to sedation, addiction and tolerance.[105] He has highlighted the overemphasis on the potential hazards of opioids, and calls for better education to reduce prejudice against their proper use.

Opioid tolerance in children

The development of opioid tolerance in children is variable and depends on the clinical context. When opioids are used to treat cancer pain in children, tolerance appears to develop quite slowly and, in most cases, dose escalation is caused by spread of disease rather than tolerance per se. The dose can be increased as in the adult patient to obtain pain relief, and dose increases are limited only by the occurrence of unmanageable side effects. The effective dose of a strong opioid will vary widely from child to child. Some patients will require a high dose to achieve pain relief.

As in adult patients, cross tolerance between opioids is incomplete. It is suggested that, if it is necessary to switch from one strong opioid to another, half the generally accepted conversion dose should be used initially, followed by upward titration as needed. Tolerance to opioids appears to be rapidly reversible once administration is discontinued. Therefore, if the child has a history of requiring massive doses of opioids previously, but has recently had a drug-free interval, standard opioid doses should be used initially with escalation as necessary.

There is no evidence that preadolescent or adolescent children are at a higher risk of developing addiction or psychological dependence than the general population when given opioids for the management of pain.

However, in newborns receiving opioids to help them endure mechanical ventilation and extracorporeal membrane oxygenation, the development of opioid tolerance does appears to be problematic.[101] Fentanyl may produce tolerance more rapidly than morphine. In addition, it appears that tolerance will develop more rapidly if the opioid infusion is continuous rather than intermittent. Work is ongoing to ascertain whether tolerance is different in the neonate and to elucidate the factors influencing the development of tolerance in this group of patients.

Case report

The following case report illustrates many of the points about tolerance discussed in this review.

In 1988, a 52-year-old man was diagnosed with multiple myeloma and underwent conventional therapy for his disease. In 1992, he presented with pain in his right groin and X-ray examination revealed a myelomatous deposit in his right pubic ramus. Nausea and vomiting precluded morphine analgesia for the pain, which was subsequently relieved by radiotherapy.

In March 1993, the patient developed back pain and further myelomatous deposits were discovered. He began oral morphine 10 mg 4-hly; radiotherapy achieved little reduction in his pain and his medication

was changed to sustained-release morphine 120 mg daily, with 10 mg immediate-release morphine for breakthrough pain. An episode of sepsis increased his morphine requirements to 160 mg daily. When this was treated with antibiotics, he reduced the dose again to 120 mg daily.

From May 1993 until August 1994, the patient's oral morphine dose was stable at 140 mg daily. Tolerance to analgesia was not clinically apparent. During this period, he required multiple laxative therapy and one inpatient admission for constipation.

In August 1994, he developed pain in his cervical and lumbar spine, occipital neuralgia and severe leg pain. Disease progression was confirmed by a rise in plasma light-chain levels and X-rays revealed a fracture of the spinous process of his second cervical vertebra and further deposits in his lumbar spine. Radiotherapy was helpful for the cervical pain but not the leg pain, which was relieved by an extradural steroid injection.

In April 1995, the patient developed pain in the lumbar region and down his left leg. Further lytic lesions were noted in his 4th lumbar vertebra, his left hemipelvis and his left femur. His morphine requirements rose to 800 mg per day. He underwent radiotherapy and started amitriptyline, with only moderate relief of his symptoms. In May 1995, a second extradural steroid injection was given. Three days after this, he had only minimal rest pain, though some incident pain, and had reduced his morphine to 120 mg per day with no obvious withdrawal symptoms. In July 1995, he developed a further lytic lesion in his right ilium. Temporarily his morphine intake rose to 1000 mg per day. After successful radiotherapy, he reduced this to 160 mg. Figure 1 illustrates the patient's morphine intake over the period described.

At the end of September 1995, he was admitted to hospital with increasing pain. His dose of morphine was rapidly increased. He became confused and developed myoclonic jerks. Investigations revealed pneumonia and acute renal failure, which were treated. The patient complained of increasingly severe pain in his back and right thigh in spite of increasing doses of s.c. diamorphine (600 mg per day) and midazolam, additional oral and i.v. morphine, oral non-steroidal anti-inflammatory drugs and other coanalgesic drugs.

It was decided to insert an extradural catheter and begin an infusion of diamorphine and bupivacaine. An extradural catheter was inserted at the level of L2/3 and the position verified with contrast medium. Following a bolus dose of bupivacaine 0.5% plain 10 ml, there was an immediate improvement in the patient's pain and no cardiovascular instability. An infusion of diamorphine and bupivacaine 0.25% plain was started. Twelve hours later, he became hypotensive (systolic blood pressure 70 mm Hg) and sensation to light touch was reduced up to the T9 dermatome. Cerebrospinal fluid was aspirated from the catheter. The infusion was altered to deliver diamorphine 4 mg in 4.8 ml bupivacaine 0.25% plain in 24 h and the next day an MRI scan was performed (Figure 2). This showed widespread bony metastatic disease and a large soft tissue mass arising from the lower thoracic vertebrae, destroying the vertebral bodies and encroaching on the spinal cord. The epidural catheter was noted to pass through the tumour and into the thecal sac.

Over the next 4 days the infusion needed to be increased to diamorphine 8 mg and bupivacaine 7.2 ml 0.25% plain over 24 h. Although the pain was controlled while the patient lay in bed, incident pain in his lumbar spine prevented any movement. Additional oral morphine, intrathecal clonidine (150 g/24 h), intrathecal midazolam (5 mg/24 h), s.c. salmon calcitonin and s.c. ketorolac (90 mg/24 h) was of no benefit. The incident pain could be improved by 1 ml bolus doses of intrathecal bupivacaine, which made the patient totally immobile but gave great relief.

An orthopaedic opinion was sought and the patient underwent spinal fixation from T6 to S1. After the operation his pain was managed by combined s.c. infusion of diamorphine 800 mg and midazolam 20 mg and a separate infusion of ketorolac 90 mg per day. Gradually his mobility improved and he was able to sit and transfer from bed to chair. On discharge home his daily oral morphine dose was 2.5 g.

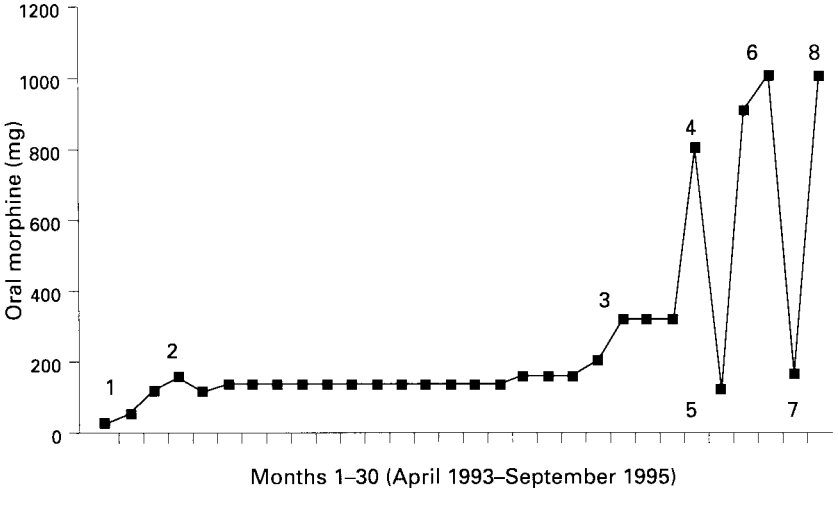

Figure 1 Daily morphine requirements (May 1993–September 1995) of a man diagnosed with multiple myeloma in 1988, at the age of 52 years. 1 = onset of pain; 2 = septic episode; 3 = disease progression (x-ray and haematological confirmation); 4 = disease progression; 5 = radiotherapy, steroid extradural injection, coanalgesics; 6 = disease progression; 7 = radiotherapy; 8 = disease progression.

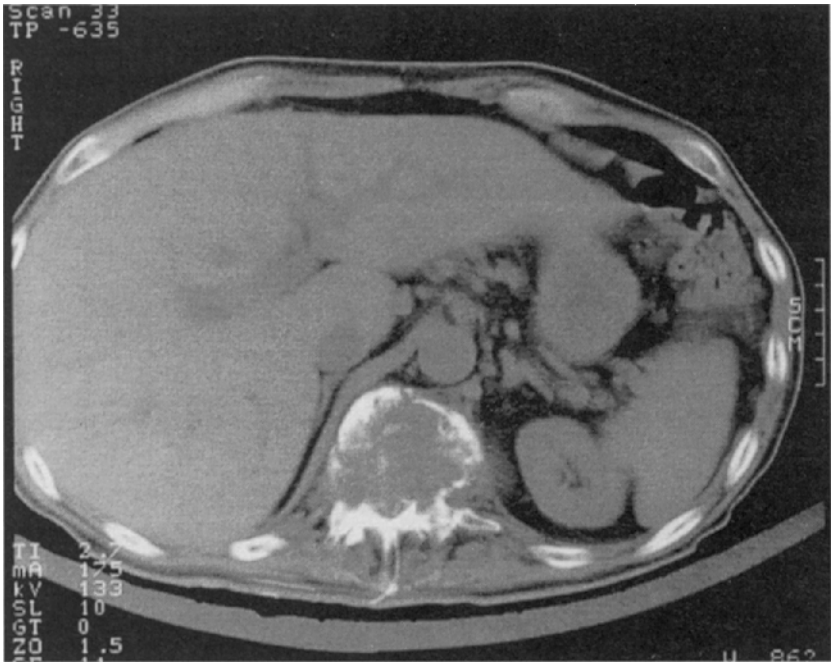

Figure 2 MRI scan of a man being treated for severe pain in the late stages of multiple myeloma. Note the extensive bone and soft tissue myelomatous disease and an extradural catheter passing through the tumour into the thecal sac.

However, he returned to the ward complaining of increasing incident pain in his lumbar spine and down his right leg. It was decided to substitute methadone for morphine. Methadone 60 mg four times daily was prescribed, with additional immediate-release oral morphine for his incident pain. Without doubt, his pain was significantly better controlled with methadone than it had been with morphine. Methadone was reduced to 60 mg three times daily and then to 150 mg per day and he needed little extra oral morphine for incident pain. He described his pain control as excellent.

Two months later, the patient's condition deteriorated and he was not able to take oral medication. A s.c. infusion of methadone (initially 50 mg/24 h, increased to 120 mg/24 h) gave good analgesia for the last 3 days of his life.

Conclusion

Tolerance to opioids has been clearly demonstrated in animal studies and the phenomenon occurs in humans with respect to both the analgesic and non-analgesic effects of these drugs.

In clinical practice, analgesic tolerance is rarely a limiting factor during opioid therapy. Concern about tolerance does not justify delay in starting opioid therapy nor should it limit dose escalation in a patient with cancer pain. Patients and their families should be reassured that tolerance to opioid analgesia is not a clinical problem and that morphine will continue to relieve their pain for many months or years. Worsening pain occurring in a patient previously on a stable dose of opioid should never be attributed to the development of tolerance unless comprehensive evaluation fails to reveal an alternative explanation.

Prevention of the development of tolerance by NMDA antagonists and the recognition that there is incomplete cross-tolerance to both the analgesic and non-analgesic effects of opioids have important potential clinical implications. The pre-eminent question – whether the very presence of pain has some modulatory effect on the development of tolerance – has yet to be answered.

References

1. Andersen S, Leikersfeldt G. Management of chronic non-malignant pain. *British Journal of Clinical Practice* 1996; **50**: 324–330.
2. Angell M. The quality of mercy. *New England Journal of Medicine* 1982; **306**: 98–99.
3. Anonymous. It's over, Debbie. A piece of my mind. *Journal of the American Medical Association* 1998; **259**: 272.
4. Arner S, Arner B. Differential effects of epidural morphine in the treatment of cancer-related pain. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 32–36.
5. Arner S, Rawal N, Gustafsson LL. Clinical experience of long-term treatment with epidural and intrathecal opioids – a nationwide survey. *Acta Anaesthesiologica Scandinavica* 1998; **32**: 253–259.
6. Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain* 1998; **33**: 11–23.
7. Bilsky EJ, Inturrissi CE, Sadee W, Hruby VJ, Porreca F. Competitive and non-competitive antagonists block the development of antinociceptive tolerance to morphine, but not to selective mu or delta opioids in mice. *Pain* 1996; **68**: 229–237.
8. Brescia FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G. Pain, opioid use, and survival in hospitalised patients with advanced cancer. *Journal of Clinical Oncology* 1992; **10**: 149–155.
9. Bruera E, MacMillan K, Hanson J, MacDonald RN. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain* 1989; **39**: 13–16.
10. Bruera E, MacMillan K, Hanson J, MacDonald RN. The Edmonton staging system for cancer pain: preliminary report. *Pain* 1989; **37**: 203–209.
11. Bruera E, Chadwick S, Brenneis C, Hanson J, MacDonald N. Methylphenidate associated with narcotics in the treatment of cancer pain. *Cancer Treatment Reports* 1987; **71**: 67–70.
12. Budd K. Drug management of chronic benign pain. *International Disability Studies* 1987; **9**: 30–33.
13. Chapman CR, Harlan FH. Prolonged morphine self-administration and addiction liability. Evaluation of two theories in a bone marrow transplant unit. *Cancer* 1989; **63**: 1636–1644.

14. Chapman CR, Donaldson GW, Jacobson RC, Hautman B. Differences among patients in opioid self-administration during bone marrow transplantation. *Pain* 1997; **71**: 213–223.
15. Clark JK, Kalan GE. Effective treatment of severe cancer pain of the head using low-dose ketamine in an opioid-tolerant patient. *Journal of Pain and Symptom Management* 1995; **10**: 310–314.
16. Cochin J, Kornetsky C. Development and loss of tolerance to morphine in the rat after single and multiple injections. *Journal of Pharmacological Experimental Therapeutics* 1964; **145**: 1–20.
17. Collin E, Poulain P, Gauvin-Piquard A, Petit G, Pichard-Leandri E. Is disease progression the major factor in morphine 'tolerance' in cancer pain treatment? *Pain* 1993; **55**: 319–326.
18. Colpaert FC. System theory of pain and of opiate analgesia: no tolerance to opiates. *Pharmacological Reviews* 1996; **48**: 355–402.
19. Coyle N. Continuity of care for the cancer patient with chronic pain. *Cancer* 1989; **63**: 2289–2293.
20. Coyle N, Adelhardt J, Foley K, Portenoy RK. Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life. *Journal of Pain and Symptom Management* 1990; **5**: 83–93.
21. Coyle N, Breitbart W, Weaver S, Portenoy R. Delirium as a contributing factor to 'crescendo' pain: three case reports. *Journal of Pain and Symptom Management* 1994; **9**: 44–47.
22. Creighton FJ, Ghodse AH. Naloxone applied to conjunctiva as a test for physical opiate dependence. *Lancet* 1989; **i**: 748–750.
23. De Leon-Casasola OA, Lema M. Epidural bupivacaine/sufentanil therapy for postoperative pain control inpatients tolerant to opioid and unresponsive to epidural bupivacaine/morphine. *Anesthesiology* 1994; **80**: 303–309.
24. Dubner R. A call for more science, not more rhetoric, regarding opioids and neuropathic pain. *Pain* 1991; **47**: 1–2.
25. Dunbar PJ, Chapman CR, Buckley FP, Gavrin JR. Clinical analgesic equivalence for morphine and hydromorphone with prolonged PCA. *Pain* 1996; **68**: 265–270.
26. Fitzgibbon DR, Galer BS. The efficacy of opioids in cancer pain syndromes. *Pain* 1994; **58**: 429–431.
27. Foley K. The treatment of cancer pain. *New England Journal of Medicine* 1985; **313**: 84–95.
28. Foley K. Controversies in cancer pain: medical perspectives. *Cancer* 1989; **63**: 2257–65.
29. Foley KM. Changing concepts of tolerance to opioids. What the cancer patient has taught us. In: Chapman CR and Foley KM, eds. *Current and Emerging Issues in Cancer Pain: Research and Practice.* New York: Raven Press, 1993; 331–350.
30. France RD, Urban BJ, Keefe FJ. Long term use of narcotic analgesics in chronic pain. *Society of Science and Medicine* 1984; **19**: 1379–1382.
31. Galer BS, Coyle N, Pasternak GW, Portenoy RK. Individual variability in the response to different opioids: report of five cases. *Pain* 1992; **49**: 87–91.
32. Gaylin W, Kass LR, Pellegrino ED, Siegler M. Doctors must not kill. *Journal of the American Medical Association* 1998; **259**: 2139–2140.
33. Glynn CJ, Mather LE. Clinical pharmacokinetics applied to patients with intractable pain: studies with pethidine. *Pain* 1982; **13**: 237–246.
34. Gourlay GK, Plummer JL, Cherry DA, Onley MM, Parish KA, Wood MM, Cousins MJ. Comparison of intermittent bolus with continuous infusion of epidural morphine in the treatment of severe cancer pain. *Pain* 1991; **47**: 135–140.
35. Gourlay GK. Long term use of opioids in chronic pain patients with nonterminal disease states. *Pain Reviews* 1994; **1**: 62–76.
36. Hanks GW, Twycross RG, Lloyd JW. Unexpected complication of successful nerve block. *Anaesthesia* 1981; **36**: 37–39.
37. Hanks GW, Twycross RG. Pain, the physiological antagonist of opioid analgesics. *Lancet* 1984; **i**: 1477–1478.
38. Hanks GW, de Conno F, Hanna M, McQuay H, Mercadante S, Meynadier J, Poulain P, Roca i Casas J. Morphine in cancer pain: modes of administration. *British Medical Journal* 1996; **312**: 823–826
39. Hill HF, Chapman CR, Kornell JA, Sullivan KM, Saeger LC, Benedetti. Self-administration of morphine in bone marrow transplant patients reduces drug requirement. *Pain* 1990; **40**: 121–129.
40. Hodes RL. Cancer patients' needs and concerns when using narcotic analgesics. In: Hill CS jr, Fields WS, eds. *Advances in Pain Research and Therapy*, Vol. 11. New York: Raven Press, 1989; 91–99.
41. Houde RW, Nathan B. Eddy Memorial Lecture: The analgesic connection. In: Harris LS, ed. *Problems of Drug Dependence 1984.* Proceedings of the 46th Annual Scientific Meeting, The Committee on Problems of Drug Dependence: NIDA Research Monograph 55: 4–13.
42. Inturrisi CE, Portenoy RK, Max MB, Colburn WA, Foley KM. Pharmacokinetic-pharmacodynamic relationships of methadone infusions in patients with cancer pain. *Clinical Pharmacology and Therapeutics* 1990; **47**: 565–577.
43. Ivarsson M, Neil A. Differences in efficacies between morphine and methadone demonstrated in the guinea pig ileum: a possible explanation for previous observations on incomplete opioid cross tolerance. *Pharmacology and Toxicology* 1989; **65**: 368–371.
44. Jadad AR, Carroll D, Glynn CJ, Moore RA, McQuay. Morphine responsiveness of chronic pain: double-blind randomised crossover study with patient-controlled analgesia. *Lancet* 1992; **339**: 1367–1371.
45. Jaffe JH. Drug addiction and drug abuse. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *The Pharmacological Basis of Therapeutics*, 7th edn. New York: Macmillan 1985; 532–581.
46. Jaffe JH. Misinformation: euphoria and addiction. In: Hill CS jr, Fields WS, eds. *Advances in Pain Research and Therapy*, Vol 11. New York: Raven Press, 1989; 163–173.
47. Kaasalainen V, Vainio A, Ali-Melkkila T. Developments in the treatment of cancer pain in Finland: the third nation-wide survey. *Pain* 1997; **70**: 175–183.
48. Kaiko RF, Wallenstein SL, Rogers AG, Grabinski PY, Houde RW. Analgesic and mood effects of heroin and morphine in cancer patients with postoperative pain. *New England Journal of Medicine* 1981; **304**: 1501–1505.
49. Kanner RM, Foley KM. Patterns of narcotic drug use in a cancer pain clinic. *Annals of the New York Academy of Sciences* 1981; **362**: 161–172.
50. Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. *Journal of the American Medical Association* 1973; **223**: 665–668.
51. Kupers RC, Konings H, Adraensen H, Gybels JM. Morphine differentially affects the sensory and affective pain ratings in neurogenic and idiopathic forms of pain. *Pain* 1991; **47**: 5–12.
52. Kupers R, Gybels J. The consumption of fentanyl is increased in rats with nociceptive but not with neuropathic pain. *Pain* 1995; **60**: 137–141.
53. Light AB, Torrance EG. Opium addiction. *Archives of Internal Medicine* 1929; **44**: 1–16.
54. Lyness WH, Smith FL, Heavner JE, Iaconno CU, Garvin RD. Morphine self-administration in the rat during adjuvant arthritis. *Life Sciences* 1989; **45**: 2217–2224.
55. Markley HG. Chronic headache: appropriate use of opiate analgesics. *Neurology* 1994; **44**(suppl 3): S18–S24.
56. Martin WR, Eades CG, Thompson WO, Thompson JA, Flanary HG. Morphine physical dependence in the dog. *Journal of Pharmacology and Experimental Therapeutics* 1974; **189**: 759–771.
57. Maruta T, Swanson DW, Finlayson RE. Drug abuse and dependency in patients with chronic pain. *Mayo Clinic Proceedings* 1979; **54**: 241–244.
58. McQuay HJ, Bullingham RES, Moore RA. Acute opiate tolerance in man. *Life Sciences* 1981; **28**: 2513–2517
59. McQuay HJ. Opioids in chronic pain. *British Journal of Anaesthesia* 1989; **63**: 213–226.
60. McQuay HJ. Potential problems of using both opioids and local anaesthetic. *British Journal of Anaesthesia* 1988; **61**: 121.
61. McQuay HJ, Jadad AR, Carroll D, Faura C, Glynn CJ, Moore RA, Liu Y. Opioid sensitivity of chronic pain: a patient-controlled analgesia method. *Anaesthesia* 1992; **47**: 757–767.
62. Merry AF, Schug SA, Richards EG, Large RG. Opioids in chronic pain of non-malignant origin: state of the debate in New Zealand. *European Journal of Pain* 1992; **13**: 39–43.
63. Morgan JP, Puder KS. Postoperative analgesia: variations in prescribed and administered opioid dosages. In: Hill CS, Fields WS, eds. *Advances in Pain Research and Therapy*, Vol 11. New York: Raven Press, 1989; 175–180.
64. Moulin DE, Ling GSF, Pasternak GW. Unidirectional analgesic cross-tolerance between morphine and levorphanol in the rat. *Pain* 1988; **33**: 233–239.
65. Moulin DE, Iezzi A, Amireh R, Sharpe W, Boyd D, Mersky H. Randomized trial of oral morphine for chronic non-cancer pain. *Lancet* 1996; **347**: 143–147.

66. Neil A. Morphine and methadone-tolerant mice differ in cross-tolerance to other opiates. *Archives of Pharmacology* 1982; **320**: 50–53.
67. O'Brien CP. Drug addiction and drug abuse. In Hardman JG, Limbird LE, eds. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 9th edn. New York: McGraw-Hill, 1995; 557–577.
68. Pappagallo M, Campbell JN. Chronic opioid therapy as alternative treatment for post-herpetic neuralgia. *Annals of Neurology* 1994; **35**: S54–S56.
69. Penn RD, Paice JA. Chronic intrathecal morphine for intractable pain. *Journal of Neurosurgery* 1987; **67**: 182–186.
70. Plummer JL, Cherry DA, Cousins MJ, Gourlay GK, Onley MM, Evans KHA. Long-term spinal administration of morphine in cancer and non-cancer pain: a retrospective study. *Pain* 1991; **44**: 215–220.
71. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 1986; **25**: 171–186.
72. Portenoy RK, Foley KM, Inturrisi CE. The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions. *Pain* 1990; **43**: 273–286.
73. Portenoy RK. Chronic opioid therapy in nonmalignant pain. *Journal of Pain and Symptom Management* 1990; **5**: S46–S62.
74. Portenoy RK. Tolerance to opioid analgesics: clinical aspects. *Cancer Surveys* 1994; **21**: 49–65.
75. Portenoy RK. Opioid therapy for chronic nonmalignant pain: current status. In: Fields HL, Liebeskind JC, eds. *Progress in Pain Research and Therapy*. Seattle: IASP Press, 1994: 247–287.
76. Porter J, Jick H. Addiction rare in patients treated with narcotics. *New England Journal of Medicine* 1980; **302**: 123.
77. Ralphs JA, C de C Williams A, Richardson PH, Pither CE, Nicholas MK. Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff-controlled cocktail methods. *Pain* 1994; **56**: 279–288.
78. Redmond DE, Krystal JH. Multiple mechanisms of withdrawal from opioid drugs. *Annual Reviews in Neuroscience* 1984; **7**: 443–478.
79. Rinaldi RC, Steindler EM, Wilford BB, Goodwin D. Classification and standardization of substance abuse terminology. *Journal of the American Medical Association* 1988; **259**: 555–557.
80. Robins LN, Davis DH, Nurco DN. How permanent was Vietnam drug addiction? *American Journal of Public Health* 1974; **64** (suppl O): 38–43.
81. Sandgren JE, McPhee Ms, Greenberger NJ. Narcotic bowel syndrome treated with clonidine. *Annals of Internal Medicine* 1984; **101**: 331–334.
82. Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. *Journal of Pain and Symptom Management* 1993; **8**: 279–288.
83. Schug SA, Zech D, Grond S, Jung H, Meuser T, Stobbe B. A long-term survey of morphine in cancer pain patients. *Journal of Pain and Symptom Management* 1992; **7**: 259–266.
84. Sjogren P, Banning A. Pain, sedation and reaction time during long-term treatment of cancer patients with oral and epidural opioids. *Pain* 1989; **39**: 5–11.
85. Sjogren P, Jensen N-H, Jensen TS. Disappearance of morphine-induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists. *Pain* 1994; **59**: 313–316.
86. Sosnowski M, Yaksh TL. Differential cross-tolerance between intrathecal morphine and sufentanil in the rat. *Anesthesiology* 1990; **73**: 1141–1147.
87. Stein C, Yassouridis A. Peripheral morphine analgesia. *Pain* 1997; **71**: 119–121.
88. Stevens CW, Yaksh TL. Studies of morphine and D-ala-D-leu-enkphalin (DADLE) cross-tolerance after continuous intrathecal infusion in the rat. *Anesthesiology* 1992; **76**: 596–603.
89. Taub A. Opioid analgesics in the treatment of chronic intractable pain of non-neoplastic origin. In: Kitahata LM, Collins JG, eds. *Narcotic Analgesics in Anaesthesiology*. Baltimore/London: Williams & Wilkins 1982; 199–208.
90. Tennant FS, Uelmen GF. Narcotic maintenance for chronic pain: medical and legal guidelines. *Postgraduate Medicine* 1983; **73**: 81–94.
91. Tennant F, Robinson D, Sagherian A, Seecof R. *Chronic Opioid Treatment of Intractable, Non-malignant Pain*. NIDA Research Monograph 1998; **81**: 174–180.
92. Twycross RG. Clinical experience with diamorphine in advanced malignant disease. *International Journal of Clinical Pharmacology* 1974; **9**: 184–198.
93. Urban BJ, France RD, Steinberger EK, Scott DL, Maltbie AA. Long-term use of narcotic/antidepressant medication in the management of phantom limb pain. *Pain* 1986; **24**: 191–196.
94. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer* 1987; **59**: 851–6.
95. Wall PD. Neuropathic pain. *Pain* 1990; **43**: 267–268.
96. Wallenstein SL, Houde RW, Portenoy R, Lapin J, Rogers A, Foley K. Clinical analgesic assay of repeated and single doses of heroin and hydromorphone. *Pain* 1990; **41**: 5–13.
97. Warncke T, Breivik H, Vainio A. Treatment of cancer pain in Norway. A questionnaire study. *Pain* 1994; **57**: 109–116.
98. Weissman DE, Haddox JD. Opioid pseudoaddiction: an iatrogenic syndrome. *Pain* 1989; **36**: 363–366.
99. Wood MM, Cousins MJ. Iatrogenic neurotoxicity in cancer patients. *Pain* 1989; **39**: 1–3.
100. World Health Organisation. *Cancer pain relief*. Geneva: WHO, 1986.
101. Yaster M, Maxwell LG. Opioid agonists and antagonists. In: Schechter NL, Berde CB, Yaster M, eds. *Pain in Infants, Children and Adolescents*. Baltimore: Williams and Wilkins, 1993; 145–171.
102. Yaksh TL. Tolerance: factors involved in changes in the dose–effect relationship with chronic drug exposure. In: Basbaum AI, Besson J-M, eds. *Towards a New Pharmacotherapy of Pain*. Chichester: John Wiley & Sons, 1991; 157–179.
103. Zech DFJ, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organisation guidelines for cancer pain relief. A 10 year prospective study. *Pain* 1995; **63**: 65–76.
104. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. *Journal of Pain and Symptom Management* 1992; 7: 69–77.
105. Zenz M. Morphine myths: sedation, tolerance and addiction. *Postgraduate Medical Journal* 1991; **67** (suppl 5): S100–S102.
106. Zenz M, Willweber-Strumpf A. Opiophobia and cancer pain in Europe. *Lancet* 1993; **341**: 1075–1076.