# Opioids for chronic pain: promise and pitfalls

Catherine F. Stannard

Pain Clinic, Macmillan Centre, Frenchay Hospital, Bristol, UK

Correspondence to Dr Catherine F. Stannard, MB, ChB, FRCA, FFPMRCA, Consultant in Pain Medicine Pain Clinic Macmillan Centre, Frenchay Hospital, Bristol BS16 1LE, UK
Tel: +44 117 340 3119; e-mail: cfstannard@aol.com

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**Purpose of review**

The prescribing of opioid medicines is increasing progressively despite a substantial body of literature identifying potential limitations and harms of therapy. Production and dissemination of best practice guidance in relation to prescribing do not yet seem to have an impact on this trend. This article highlights updated concerns about and unanswered questions in relation to opioid treatment to provide focus for further scrutiny and evaluation of opioid treatment for pain.

**Recent findings**

The literature cited in this paper confirms that opioid prescribing is prevalent despite an established evidence base spanning a decade that indicates that efficacy of opioids in long-term pain management remains uncertain and that harms of therapy are well defined. In particular, problems with treatment are more likely to occur when high doses are used and in certain patient populations and many recent high-quality studies highlight these problems. Although much is to be learned regarding clinical decision making, it is clear that current prescribing activity does not reflect the existing knowledge base.

**Summary**

Authors are unanimously agreed that the literature answers some important questions about opioid therapy but there are substantial knowledge gaps, particularly in relation to benefits and harms of long-term therapy in day-to-day clinical practice. Evidence-derived guidance clearly identifies common and important pitfalls in relation to opioid use but promotion of adherence to guidance remains a substantial challenge.

**Keywords**

addiction, chronic pain, effectiveness, opioid dose, opioids, side-effects

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## Introduction

The historical use of opioids for therapeutic benefit, dating back to the third century B.C., and their more recent introduction into western medicine for the relief of pain have earned these drugs a unique place in medical and public perception. The widespread and unrestricted use of these drugs gave way to a culture of suspicion and regulation as they became recognised as drugs of addiction. The recognition that opioids are known to be the most potent analgesics available and an understanding of the imperative to treat severe pain and minimise suffering allowed physicians and patients together to overcome regulatory barriers and, in many but not all countries, have established opioids as the most important tool in the treatment of acute pain associated with trauma or surgery and pain associated with terminal illness. In these circumstances, the duration of symptoms is finite, the therapy is often delivered in the hospital setting and it can be monitored closely with side effects managed and optimal dose established.

Persistent noncancer pain is prevalent. Around 7.8 million people in the UK have moderate to severe pain that has lasted for more than 6 months. Pain is disabling for the individual and costly to society. Persistent pain is difficult to treat with interventions (pharmacological or otherwise) offering no more than modestly successful modification of symptoms. The use of opioids to treat persistent pain may seem rational given the utility of these drugs in the treatment of severe acute pain but early experience suggested that persistent pain may be inherently refractory to opioid therapy [1]. More recently, over the last two decades, the efficacy of opioids for the treatment of chronic pain has been studied extensively and evidence has emerged of modest benefit in relation to reduction in pain intensity in the medium and long term [2,3,4••,5]. Importantly, however, data demonstrating improvements in quality of life with opioid therapy are lacking, and concerns exist in relation to long-term safety and the propensity for problematic opioid use [6,7,8•].

There has been a marked and progressive rise in the prescription of opioid drugs in both the UK and the USA

over the last decade but the promise of reducing the burden of persistent pain has not been fulfilled [9,10,11•,12]. It may be that the increasing use of opioids for persistent pain imposes an additional set of harms for these patients and for society. Influences on prescribing are complex and include marketing by the pharmaceutical industry, regulatory change and availability of alternatives to treat persistent pain. Clinician beliefs regarding the effectiveness and potential harms of treatments have also been shown to influence the decision to prescribe opioids [13,14,15•,16•].

Data from the USA clearly demonstrate increase in prescription drug misuse and additional risk of overdose and death in parallel with the rise in prescription of opioids, and identification and management of patients who may misuse or divert opioid drugs has been an intense focus of research [17•,18–20]. Data regarding misuse and diversion of prescribed opioids are lacking in the UK, but concerns about long-term safety and efficacy have prompted clinicians to question whether the tempting option of strong opioid analgesia is always in the best interests of patients with pain.

This review will explore the effectiveness of opioid therapy for long-term pain and the evidence for short-term and long-term harm. Most of the literature on long-term opioid therapy relates to patients with noncancer pain but the weighing up of potential benefits and harms for the patient if opioids are being considered for prolonged periods should be consistently rigorous whatever the diagnosis. The important and clinically challenging issue of pain management in patients with a past or current history of substance misuse is outwith the scope of the review.

## Evidence for benefits of opioid treatment for persistent pain

Over the past decade, increasing evidence has indicated a moderate efficacy of opioids in the management of long-term pain. Two decades ago, use of opioids for persistent pain was thought to be of limited benefit but from the 1990s onward many studies suggested that, for the duration of the clinical trial, opioids are moderately effective in the treatment of pain of both neuropathic and nociceptive origin. There are now a number of high-quality systematic reviews that confirm the findings of these individual trials demonstrating effectiveness of opioids (usually compared with placebo) in reducing pain intensity [2,3,4••,5,21]. An early important systematic review demonstrated a mean decrease in pain intensity of 30% in a variety of common pain conditions [2]. Data on longer term use are lacking. A Cochrane review of opioids for neuropathic pain demonstrated equivocal efficacy of opioids in the short term (<24 h) but modest benefit in the intermediate term (8–70 days) with a mean post-treatment reduction of 13 points on a 100-point visual analogue scale [5]. A more recent review of data to May 2009 evaluated longer term use of opioids (over 6 months) administered by a variety of routes and found modest evidence of efficacy although around half of patients given opioids for persistent pain will discontinue therapy in the long term because of lack of efficacy or adverse effects (see below) [4••]. There are few head-to-head trials of opioids compared with other drugs. A systematic review in 2006 demonstrated superiority of opioids to naproxen and nortriptyline and an evidence-derived algorithm for the management of neuropathic pain found opioids to be as effective as other commonly used classes of drug including gabapentinoids [3,22]. There is to date no high-quality evidence to suggest superior efficacy of any specific opioid preparation or formulation [23].

**Key points**

- The prescribing of opioids continues to increase despite cautionary guidance in relation to prescribing.
- Opioids may be effective in reducing long-term pain but side effects of therapy are common and may limit compliance with treatment.
- Opioid therapy is associated with a number of long-term harms but there are insufficient data to quantify risk.
- There is good evidence that the likelihood of harm is greater when high doses of opioids are prescribed.

Although the published data demonstrate that opioids reduce pain intensity in the context of clinical trials, and, for those patients who can tolerate the drugs, some benefit in the longer term, all systematic reviews note that data relating to improved functional outcomes and quality of life are sparse. Furthermore, patients included in clinical trials may not be representative of the population for whom opioids are usually prescribed with respect to discrete pain diagnoses and medical and mental health comorbidities. Certainly, epidemiological data suggest that when comparing opioid users with nonopioid users, opioid use appears to be associated with poorer self-related quality of life and employment status, increased healthcare use, and worse pain [24]. These data are concerning as opioids are prescribed with the purpose of improving pain and function, and these goals may not be met.

## Harms of opioid treatment

Clinician concerns regarding opioid therapy relate to effectiveness when therapy is prolonged, adverse effects that may limit acceptability of treatment, opioid-induced

endocrine and immune dysfunction, hyperalgesia and effect on quality of life. Tolerance is an expected effect of opioid use but risk factors for addiction and problematic use including diversion are now emerging. Harms of therapy are related to drug dose and firm recommendations are available to guide prescribers in determining appropriate dose of opioid to improve safety. Patients being considered for treatment need to understand the potential complications of therapy but may also express additional concerns not usually addressed by prescribers [25••].

### Adverse effects of opioids

The clinical utility of opioids is limited frequently by adverse effects. Side-effects are burdensome to the patient and are a common contributor to noncompliance with therapy. Additionally, the management of opioid side effects is costly in terms of specific therapies to attenuate side effects and healthcare visits as well as the indirect costs associated with impairment of function [26•].

One systematic review exploring the efficacy of oral, transdermal and intravenous opioids for chronic pain identified that, in the analysis of placebo-controlled trial data relating to 1025 patients, 80% of patients taking opioids compared with 56% given placebo report adverse effects of therapy with a number needed to harm of 4.2 (3.1–6.4) [2]. In this review the commonest adverse effects were constipation (41%), somnolence (29%), and nausea (32%) with frequent reporting of vomiting (15%), dizziness (20%), and itching (15%). A later systematic review of adverse effects of oral opioids analysed data from 4212 patients [27]. Trials of weaker opioids, for example codeine and dextropropoxyphene, were included as were trials that were not placebo controlled. The authors found that dry mouth (affecting 25% of patients), nausea (21%), and constipation (15%) were the most common adverse events. In this latter review, 22% of patients withdrew from trials because of adverse effects, a figure comparable with that derived for treatment withdrawals (22.9%) in a recent Cochrane review [4••].

A later review including data from 6019 patients which also included trials of weaker opioid preparations (e.g. codeine) and trials comparing opioids with NSAIDs or antidepressants, reported that only constipation and nausea were statistically more frequently reported with opioids compared with placebo or other comparator drugs [3]. A comprehensive review comparing safety and efficacy profiles of different long-acting opioids suggested that there was insufficient evidence to suggest that there are insufficient data from head-to-head trials of long-acting opioids, and trials of long-acting opioids compared with other drug classes or placebo, to suggest that any one long-acting opioid is associated with fewer adverse effects than another. Similarly there is no evidence that use of long-acting opioids for persistent pain is associated with fewer adverse effects than the use of short-acting drugs [23].

All reviewers agree that these figures need to be interpreted with caution. The duration of trials included in the reviews was mostly of less than 8 weeks and patients included in the trials had often been selected having demonstrated ability to tolerate opioid therapy. In clinical practice, patients are usually unselected particularly with respect to medical and psychiatric comorbidity, previous experience of weak or strong opioids and coprescription of other drug classes. The dose of opioid is usually titrated depending on analgesic effectiveness and side effects compared to the usually more fixed regimens found in clinical trials. Patients will usually become tolerant to opioid side-effects although constipation tends to persist and patients should be offered appropriate adjunctive therapy.

It is established clinical practice to offer patients an alternative opioid prescription if the first prescribed drug is ineffective or if continued treatment is limited by side effects (opioid switching). There are a number of reasons why an individual patient may respond to one opioid more favourably than another. These include differences in pharmacokinetics and pharmacodynamics of opioid drugs between patients. The genetic basis of this variability has now been well researched and reported [28,29]. A recent review of the evidence concluded that although change to an alternative opioid might be a pragmatic option to improve control of symptoms the evidence for this practice is derived from uncontrolled and anecdotal studies only [30].

### Opioids and cognitive function

The potential for opioid treatment to impair concentration and memory are commonly expressed concerns for patients considering this treatment. A recent systematic review concludes that high-quality evidence suggests that opioids used for long periods do not impair cognitive function but points out that analysis of studies that may be methodologically somewhat flawed suggest a degree of uncertainty regarding firm conclusions in relation to cognitive effects [31••].

Patients with pain may have mobility problems and driving is important in enhancing social and vocational function. Pain and associated fatigue can impair concentration and ability to drive [32,33]. Individual differences in pharmacokinetics and pharmacodynamics, coprescription of other drugs and associated medical and mental health morbidity also make it difficult to predict the degree to which a patient may be impaired. Systematic reviews have concluded that there is insufficient

evidence to make firm comment about the effects of opioids on cognition in relation to driving and advice to patients should be individualized [34,35]. Patients are usually advised to avoid driving when first starting on opioids or immediately following dose change [36•].

### Endocrine effects of opioids

The use of long-term opioids is associated with hormonal disturbance in both men and women. The effects are most prominent on the hypothalamic–pituitary–gonadal axis but adrenal insufficiency may also occur [37–40]. Both endogenous and exogenous opioids inhibit the release of hypothalamic gonadotrophic releasing hormone (GnRH) with consequent decrease in pituitary production of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Opioids may also act directly on the pituitary to impair LH and FSH release with consequent inhibition of gonadal production of testosterone and oestradiol. Adrenal cortisol and androgen production (particularly dehydroepiandrosterone sulphate, DHEAS) may also be suppressed and this has been demonstrated following use of transdermal and oral opioids [41–43]. Clinical features of hypogonadism include depression, fatigue, weight gain, osteoporosis and loss of libido and menstrual irregularities in women and erectile dysfunction in men. Some of these symptoms also occur in association with persistent pain so opioid-induced endocrinopathy may be difficult to diagnose [44]. The endocrine consequences of long-term opioid therapy should be discussed with patients and if symptoms potentially attributable to endocrinopathy are identified patients should be evaluated by an endocrinologist.

### Effects of opioids on the immune system

Opioids have been known to have an effect on the immune system for 100 years. Immunity may be impaired by effects on natural killer cell activity, T-cell proliferation, antibody production, phagocyte function and production of cytokines in addition to effects on the neuroendocrine system described above [45]. Much of the literature relates to immune-compromised patients with HIV and the relevance of suppressed immunity in immunocompetent patients is unclear particularly because persistent pain also impairs natural killer cell activity [46–49]. Heroin abusers and chronic users of opioids may be more susceptible to bacterial infection and demonstrate delayed wound healing and the mechanisms of this latter have been well demonstrated *in vitro* [50]. There is an emerging literature on the role of perioperative opioids in influencing tumour spread related to their effects on natural killer cells, which play an important role in cell-mediated antitumour immunity although studies show conflicting results [51–54]. Both in-vitro and in-vivo studies have suggested that tumour growth may be influenced by opioids [55,56•]. Although the influences of opioids on tumour growth are understood mechanistically the clinical significance in relation to routine opioid prescribing needs much more investigation. Preclinical studies demonstrate that opioids vary in their immunomodulatory effects with morphine having more profound effects than methadone: buprenorphine does not seem to be associated with immune suppression [57].

### Opioid-induced hyperalgesia

There is now experimental and clinical evidence that use of opioids can be associated with development of a state in which patients become more sensitive to pain despite continuing opioid treatment although the clinical significance is debated and more evidence is needed [58]. This has been termed opioid-induced hyperalgesia (OIH). This sensitivity had previously been attributed to opioid withdrawal but is now thought to be a consequence of central glutamatergic activation, elaboration of spinal dynorphins and descending facilitation of spinal nociceptive transmission via the rostroventral medulla [59]. Mechanistically, OIH has commonality with opioid tolerance and OIH does not occur in the absence of observed tolerance. Studies in the acute pain literature of intensification of postoperative pain and apparent resistance to increasing opioid therapy [60–62]. Hypersensitivity to experimental pain has also been shown in healthy volunteers following short opioid infusion [63]. Relating to long-term use, studies of former heroin addicts receiving methadone maintenance have shown reduced tolerance to a number of experimental pain modalities [64–66].

Hyperalgesia in patients receiving long-term opioid therapy for pain is now recognised as a complication of treatment but may be difficult to diagnose. Increased pain in this context may relate to underlying disease progression, pain resulting from increased activity because of (previously) effective opioid therapy, opioid tolerance or hyperalgesia. The pain of OIH is usually qualitatively different and more widespread than the pre-existing pain although this latter is usually intensified. Development of allodynia is also reported [60]. The mainstay of treatment of OIH is opioid detoxification or rotation to an alternative opioid, particularly methadone, which because of its *N*-methyl-D-aspartate antagonist properties is effective in reversal of tolerance and hyperalgesia. The unique properties of this drug make it a useful tool in the management of persistent pain, but recognition of its established role in the management of heroin addiction confers on it a social stigma that acts as a barrier to prescribing [67•].

### Addiction and problematic drug use

Data from the USA and from Australia demonstrate that the steady increase in the prescription of opioids for pain

relief is paralleled by an increase in the misuse of these drugs [8•,20]. Although the prescription of strong opioids in the UK has increased markedly over the past decade there are no data regarding misuse of the drugs and this is an urgent research priority. Risk of addiction is a much feared complication of opioid therapy and acts as a barrier to prescribing and a concern for patients [16•]. Identifying risk factors for addiction and development of screening tools to support opioid therapy has become an intense focus of research [68]. Attempts to define the prevalence of addiction to prescribed opioids have yielded diverse results because of heterogeneity in study populations and lack of agreement about definitions of misuse and addiction. The most commonly used criteria for substance dependence are the International Classification of Diseases Tenth Revision (ICD-10) and the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association, but these may have poor applicability when describing addiction to medication used for pain relief [69,70]. Portenoy [71,72] has developed some pragmatic criteria for defining addiction in relation to prescribed drugs. One review indicated a prevalence of addiction of between 0 and 50% of patients using opioids for noncancer pain and 0–7.7% in cancer pain patients [73]. A recent study of 253 patients presenting to a tertiary pain centre showed that addiction prevalence was 14.4% using ICD-10 criteria and 19.9% using Portenoy's criteria. The two diagnostic criteria indicated different risk factors for addiction [74••]. The strongest predictors for opioid misuse are pre-existing or current substance misuse disorders and comorbid mental health diagnoses. A systematic review of risk of addiction showed that studies that preselected patients for no history of substance misuse suggested that the abuse addiction rate is 0.19% [75]. Despite consistent identification of risk factors for problematic use, prescription rates for opioids to treat noncancer pain are much higher and increasing faster in patients with a history of substance misuse or mental health disorder [76••–78••]. Patients with these comorbidities present some of the most formidable challenges in providing safe and effective opioid therapy.

## Appropriate opioid dosing

The effectiveness data inform us that doses of opioid averaging 120 mg morphine equivalent/day may be helpful in the management of persistent pain [79•,80••]. In practice, the doses of opioids used often far exceed those known to be safe and effective in the context of clinical trials. Long-term harm of opioids as described above, particularly endocrine and immune disturbance and also cognitive impairment are dose related. Data published in 2005 noted that an upward trend in opioid dosing was paralleled by an increase in opioid overdose and a recent cohort study has demonstrated that the risks of overdose increase nine-fold when daily opioid dose exceeds 100 mg morphine equivalent/24 h [17•,81]. A further study showed that use of more than 120 mg morphine equivalent/24 h was associated with more emergency department visits and alcohol and drug-related encounters [82•]. The risks of falls and fractures are also dose related [83•]. One large-scale study of patients taking at least 90 days of continuous opioid therapy showed that use of more than 120 mg morphine equivalent/24 h increased the likelihood of drug misuse [84••]. Recommendations now state that patients whose pain is not controlled on 120 mg morphine equivalent, or who do not at this dose demonstrate improvement in function should be referred for specialist advice [36•,79•,80••]. This situation does not mean that doses more than 120 mg morphine equivalent/day should never be prescribed, rather they should be limited to patients who demonstrate clear improvements in function and quality of life from therapy and in whom pain is usefully attenuated. Despite clear guidance many patients are being prescribed high-dose opioids and the determinants of this are complex but include physician factors and patient factors [85]. In a recent study, high-dose opioid use (>190 mg morphine equivalent/day) occurred in 2.4% chronic pain patients and 8.4% patients prescribed long-term opioids [86••]. High-dose users were more likely to have multiple pain diagnoses and a higher incidence of medical and mental health comorbidity including substance misuse disorder and were frequently taking additional medications such as benzodiazepines likely to increase overdose risk. The findings of this study were interesting as these groups are those about whom there are fewest data as they are often excluded from clinical trials [87]. These patients might be at risk of more harm from high-dose opioid prescribing and therapy would need to be monitored more closely than was indicated by the reviewed records. A prospective cohort study of patients with low back pain demonstrated that opioid dose escalation was related to time of opioid prescription following onset of symptoms and to a lesser extent initial dose prescribed. Dose escalation was also more frequent when 'pure' opioids were used rather than combination preparations of opioids with other drugs. An unintuitive finding was that dose escalation did not relate to severity of symptoms, which highlights the complexity of the decision making in relation to dose determination [88•].

## Conclusion

The early enthusiasm for the use of opioids for persistent pain was in part supported by the emerging evidence for their potential utility. The more recent literature is overwhelmingly cautionary but data demonstrate

unequivocally that opioid drugs are being increasingly prescribed. Because of their unique position in medical and public perception, the potential for abuse and the legislative framework surrounding their use, opioids are scrutinized more closely than any other analgesic drug. The promise of opioid therapy is the potential for the drugs to support patients in managing their pain and achieving the goals that have been barred by pain. There is an interesting ethical debate about the important but difficult balance between the patient's desire for relief of symptoms and the clinician's role in providing safe and effective therapy [89••].

Best practice guidance in relation to opioid prescribing for persistent pain has been produced in many countries. UK prescribing guidance was first published in 2004 and has recently been revised [67•,90]. Guidance aims to promote safe practice in opioid prescribing which is underpinned by collaboration between prescriber and patient and a mutual understanding of goals of treatment and burdens of therapy. Updated guidelines in the USA are published with a supporting evidence review and research gaps have been identified including improved strategies for identifying which patients are at risk of problems and how to monitor therapy to improve safety [36•,91••].

Research into the effective implementation of prescribing guidance is a priority. There is consensus between all guidelines regarding the most problematic issues in relation to clinical opioid use yet many of the studies cited in this review suggest that guidance is not being followed. Epidemiological studies give insight into the experience of opioid use in the long term but more prospective data are needed to clarify clinical decision making in relation to opioid therapy and the benefits and burdens of opioid treatment in unselected patients who use opioids for months and years.

Opioid therapy can be both the most challenging and also the most rewarding of activities in clinical practice. Clinician adherence to simple guidance in relation to opioid prescribing will ensure that patients who benefit from therapy will be exposed to fewer risks of long-term harm. In addition, promulgation of good practice will ensure that prescribers who are reluctant to prescribe opioids to patients who might benefit are well informed about how to prescribe opioids safely.

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## References and recommended reading

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- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 180–182).

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