

Use of opioids in chronic noncancer pain

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Opioids play a much smaller role in the management of chronic noncancer pain than they do in that of severe acute pain and cancer pain. They are beneficial in a small subset of patients with chronic noncancer pain but there are pharmacological, psychological and societal concerns about their current widespread use for this indication.

Key points

- There are pharmacological, psychological and societal concerns about the current widespread use of opioids for chronic noncancer pain.
- Opioids should not be regarded as the sole approach to managing chronic noncancer pain but as one component of a multidisciplinary management plan.
- They should only be used for this type of pain after an initial trial with defined positive outcomes, in particular improvement of function.
- They are not intended as life-long treatment and should be discontinued by tapering the dose when treatment goals are reached (or aberrant drug-taking behaviour becomes obvious).



There has been a dramatic increase in recent years in the use of opioids to treat chronic noncancer pain, particularly in the USA but also in Australia. This has led to increasing concerns about the usefulness versus risks of this approach, both for the individual patient and society as a whole. This review article outlines the controversies surrounding their use for treating chronic noncancer pain and summarises their role in this setting, the risks and complications regarding their use for this type of pain and the goals of such treatment, and its initiation and long-term use.

Different pain states

Chronic noncancer pain is a heterogenous disorder, characterised by a wide spectrum of pain states ranging from physiological pain with nociceptive and inflammatory origin (e.g. osteoarthritis) to pathological pain states of either neuropathic origin (i.e. caused by damage or disease of the somatosensory system, e.g. diabetic polyneuropathy) or dysfunctional origin (i.e. no such damage/disease and no nociception but caused by central sensitisation/insufficient endogenous inhibition, e.g. fibromyalgia).¹ It is therefore not surprising that the role of opioids in these different pain states is not the same.

Some principles of opioid therapy in the acute pain and chronic cancer pain setting, where they have well accepted analgesic efficacy and a good safety profile, may be transferred to the setting of nociceptive and neuropathic pain, where their use can lead to improved function and reduced pain in some patients, although long-term outcome data are limited or even contradictory.^{2,3} Dysfunctional pain states on the other hand are characterised primarily by central sensitisation and limited endogenous inhibition, and seem to be poorly responsive to opioid therapy. Furthermore, chronic pain is characterised as a biopsychosocial phenomenon, and the wide array of psychosocial factors, such as catastrophising, anxiety, mood states including depression, suffering and dependence on the healthcare system, are not really responsive to opioids and need to be addressed by

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1. Opioid therapy: useful reference material

- For Quick Clinical Guidelines for the use on opioids in patients with chronic noncancer pain, see for example the West Australian guidelines at: www.dao.health.wa.gov.au/DesktopModules/Bring2mind/DMX/Download.aspx?Command=Core_Download&EntryId=168&PortalId=0&TabId=211
- For a more detailed Prescription Opioid Policy, agreed upon by the Faculty of Pain Medicine of ANZCA, the RACGP, RACP and RANZCP, see: www.fpm.anzca.edu.au/resources/professional-documents/documents/Prescription_Opioid_Policy.pdf
- For an example of a treatment contract for an opioid medicine, see: www.public.health.wa.gov.au/cproot/3590/2/Treatment_contract_for_opioid_medicine.pdf

multimodal, multidisciplinary interventions.⁴ Single modality opioid therapy in dysfunctional pain states is both less successful in improving analgesia and functional outcome and also carries a significant risk of aberrant drug-taking behaviour and abuse.

Efficacy

As indicated above, opioids might confer a benefit and have some demonstrated efficacy in well-defined chronic pain states such as osteoarthritis and neuropathic pain.⁵⁻⁸ Despite opioids showing effectiveness and published guidelines supporting their use in osteoarthritis-related pain, a 2009 Cochrane review on the efficacy of opioids in osteoarthritis of the knee or hip found only small to moderate beneficial effects of opioids and an increased risk of adverse effects.^{2,9,10} Similarly, opioids are viewed in guidelines for neuropathic pain treatment as second- or third-line treatments because of their risk-benefit profile,¹¹⁻¹³ and therefore should only be used if first-line drugs (such as anticonvulsants and antidepressants) fail or are contraindicated.

The overall evidence for efficacy of opioids in chronic noncancer pain is even more disappointing. A 2010 Cochrane review on long-term opioid management of chronic noncancer pain that included a total of 4893 patients found only weak evidence for sustainable pain relief and an inconclusive benefit on functional improvement or quality of life.¹⁴ A similar outcome in relation to lack of improved pain control, function or quality of life in chronic noncancer pain patients treated with opioids was reported in a large epidemiological study from Denmark.¹⁵

In summary, the evidence in favour of use of opioids in the chronic noncancer pain setting is at best weak. This statement is further confounded by most trials assessing only short-term benefits, having methodological flaws and describing heterogeneous outcomes.

Risks and complications of opioid therapy

The most serious complication of opioid use is opioid-induced ventilatory impairment leading to death. Although this is unlikely to occur

in patients who are taking a stable dose of opioid for long-term treatment, statistics for the USA and Australia show a dramatic increase in mortality linked to prescription opioids.^{16,17} Reasons for this increased mortality include incorrect opioid prescribing by doctors and incorrect intake by patients, and also diversion with use by others and co-administration with sedatives such as alcohol and benzodiazepines.¹⁸

Constipation is a major adverse effect of the long-term use of opioids and seriously affects patients' quality of life. Patients do not develop tolerance to opioid-induced constipation and need co-medication with appropriate laxatives. Opioid preparations with a reduced risk of constipation are transdermal patches or combinations with naloxone.¹⁹ Nausea, vomiting, sedation and cognitive impairment are often only short-term adverse effects; tolerance to these can develop and therefore interference with work or driving as well as the increased risk of falls occur primarily in periods of dose titration or dose escalation.^{20,21} Opioids, via direct effects on the μ -receptor, also cause significant impairments of immune and endocrine functions, particularly with long-term use. Impairment of endocrine function can lead to opioid-induced androgen deficiency requiring testosterone substitution.¹⁸

The phenomenon of opioid-induced hyperalgesia, a paradoxical increase in sensitivity to pain in patients on long-term opioid therapy, should also be mentioned.²² Attempts to treat this with increasing opioid doses can result in escalation of opioid doses without benefit for the patient.¹⁸ This therefore needs to be differentiated from development of tolerance to opioids.²³ Physiological dependence will also develop, but it and the potential withdrawal reactions can be overcome by tapering opioid doses slowly instead of discontinuing abruptly.

There are rather contradictory and inconsistent data on the prevalence of opioid abuse in patients using opioids for chronic noncancer pain. Addiction ('psychological dependence') is a behavioural pattern of drug use, characterised by overwhelming involvement with the use ('compulsive use') of a drug leading to physical, social and psychological harm.²⁴ A systematic review of trials of opioid therapy for chronic back pain showed a prevalence of lifetime substance abuse in the order of 36 to 56% and of current aberrant medication use of 5 to 24% in these patients.²⁵ Similarly, in a recent study, one in three patients undergoing long-term treatment with opioids for chronic pain met DSM-IV criteria for addiction.²⁶ On the other hand, a Cochrane review from 2010 reported an addiction rate of only 0.27% in patients undergoing long-term opioid therapy for chronic noncancer pain.¹⁴ Risk factors for the development of addiction are male gender, younger age, history of substance abuse disorder, mental health problems and use of higher doses of opioids.^{26,27}

Finally, there is a risk that long-term opioid therapy might contradict the goals of chronic pain management. These goals are not only pain reduction but also reduced pain behaviour, improved function and increased self-efficacy. Current data suggest that opioids are used particularly to treat patients who describe greater disability, distress and suffering and poorer functioning, which might set up a vicious cycle.²⁵ Rather than promoting self-efficacy and an internalised locus of control, opioid therapy leads to an externalised locus of control with increased dependence on the healthcare system, encouragement of

passivity and reinforcement of pain behaviour proven to be counterproductive in patients with chronic pain.²⁸

Implementation of opioid therapy

The basis of good chronic pain management is a multidisciplinary and multimodal approach. Psychological therapy with emphasis on cognitive behavioural strategies to enhance coping mechanisms and reduce psychological stressors and physical therapy that includes exercise programs and physiotherapy form integral components of such an approach. Pharmacological therapy should be initiated according to well-established guidelines, with paracetamol and NSAIDs/COX-2 inhibitors (coxibs) being used in nociceptive pain states and anticonvulsants and/or antidepressants in neuropathic pain states. As a small subgroup of patients with chronic pain may benefit from opioid use, this treatment should not be denied. However, in view of the risks described above, the introduction of opioids to treat chronic noncancer pain requires strict adherence to well-established guidelines.^{29,30} Details of examples of a quick clinical guideline for the use of opioids in patients with chronic noncancer pain, a prescription opioid policy and a treatment contract for an opioid medicine are given in Box 1.

Opioids should not be considered as a first-line treatment or a single treatment modality but as one component of multidisciplinary pain treatment. They should only be trialed after reasonable attempts at multidisciplinary pain management, including other pharmacological options, have failed. Their introduction requires a diagnosis of persistent nociceptive-inflammatory pain (e.g. osteoarthritis) or neuropathic pain, and even then they should only be considered second- or third-line treatment.^{18,31} They should not be used in dysfunctional pain states, including fibromyalgia, visceral and pelvic pain syndromes, headaches and nonspecific chronic low back pain. Factors to be taken into account before initiation of opioid therapy are listed in Box 2.

Initiation of opioid therapy for chronic noncancer pain should be in the form of a closely monitored trial period of around four weeks' duration of a transdermal or slow-release oral opioid. Definitive endpoints such as improvement in quality of life and function, including mood, sleep, occupational and recreational activities, should be as important as simple pain reduction. Such endpoints along with risks, benefits and rules on supply should ideally be formulated as an opioid contract between the patient and the provider. Failure to achieve these treatment goals on reasonable opioid doses (less than 100 mg daily oral morphine equivalent) deems the patient's pain as not responsive to opioids and should lead to an agreed termination

2. Opioid therapy: factors to consider prior to initiation*

- Pain diagnosis/psychological assessment
- Multidisciplinary pain treatment
- Assess baseline function and severity of pain
- Screen for addiction risk
- Determine treatment goals (focus on functional and quality of life improvement)
- Explain risks and benefits of opioid therapy
- Opioid treatment contract with patient: informed consent, rules for treatment and cessation, consequences of aberrant drug-taking behaviour

* Modified from multiple sources including references 3, 18 and 30.

of opioid treatment via tapering doses. An approach to the initiation of opioid therapy is summarised in Figure 1.

If the agreed endpoints were reached, the patient should qualify for long-term treatment with opioids; however, this should not be seen as a decision for life-long treatment. Long-term treatment requires

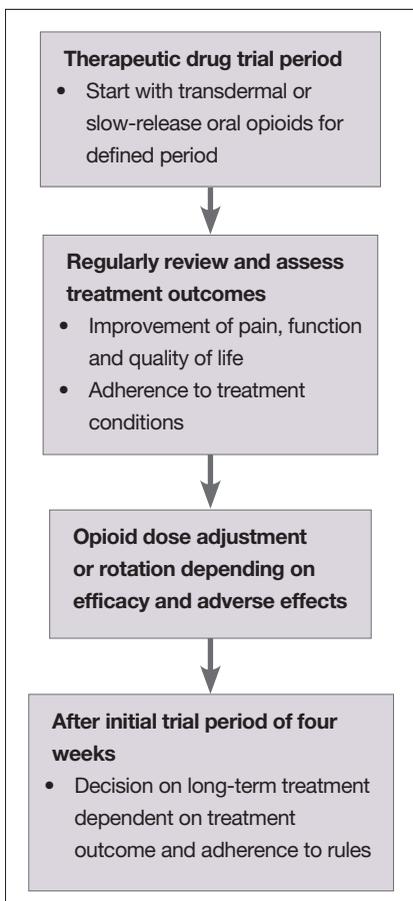


Figure 1. Initiation of opioid therapy.

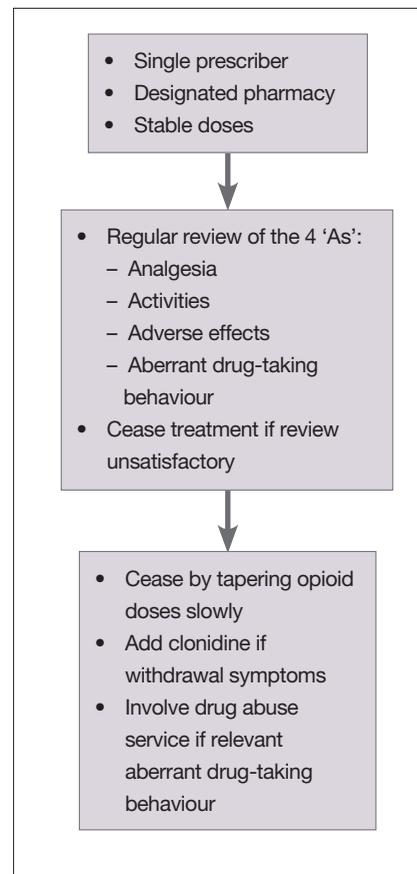


Figure 2. Long-term treatment/maintenance opioid therapy.

adherence to the opioid contract, including a single prescriber, a designated pharmacy and no unauthorised escalation of doses. Regular monitoring of the patient should assess the four 'As' of pain treatment outcomes: Analgesia, Activities of daily living, Adverse effects and Aberrant drug-taking behaviour. An approach to long-term opioid therapy is summarised in Figure 2.

Indications for cessation of long-term opioid therapy are lack of improvement in function, lack of analgesia and aberrant drug-taking behaviour.^{18,31}

Conclusion

Opioids play a much lesser role in the management of chronic non-cancer pain than they do in the management of severe acute pain and cancer pain. Although they may be beneficial in a small subset of patients with chronic noncancer pain, who should not be denied treatment of their chronic condition, there are pharmacological, psychological and societal concerns about their current widespread use for this indication. In the management of chronic noncancer pain, opioids should therefore only be used after an initial trial with defined positive outcomes, in particular improvement of function. Their use requires an established pain diagnosis, screening for increased risk of abuse, a good doctor-patient relationship and adherence to agreed rules, ideally formulated in a treatment contract.

Opioids should not be regarded as the sole approach to chronic noncancer pain but as one component of a multidisciplinary management plan. They are not intended as life-long treatment and should be discontinued by tapering the dose when treatment goals are reached (or aberrant drug-taking behaviour becomes obvious). This might be a particular challenge in the many patients who have been started on opioids inappropriately in the past.

PMT

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A list of references is included in the website version (www.medicinetoday.com.au) of this article.

Further reading

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Cohen ML, Wodak AD. Opioid prescribing in general practice: a proposed approach. *Med Today* 2012; 13(1): 24-32.

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