Review Article

The Role of Opioids in Managing Chronic Non-cancer Pain

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Abstract

The use of opioids for the treatment of chronic non-cancer pain has become more widespread recently. Available data support the short-term use of opioids in clearly defined nociceptive and neuropathic pain states. Their use in 'pathological' pain states without a clear diagnosis, such as chronic low back pain, is more contentious. A decision to initiate opioid treatment in these conditions requires careful consideration of benefits and risks; the latter include not only commonly considered adverse effects such as constipation, but also opioid-induced hyperalgesia, abuse, addiction and diversion. Ideally, treatment goals should not only be relief of pain, but also improvement of function. Opioid treatment of chronic non-cancer pain requires informed consent by, and preferably a treatment contract with, the patient. Treatment should be initiated by a trial period with defined endpoints using slow-release or transdermal opioids. Ongoing management of the patient requires ideally a multi-disciplinary setting. Treatment should not be regarded as life-long and can be discontinued by tapering the dose.

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Introduction

"*For all the happiness Mankind can gain;*
is not in pleasure, but in rest from pain".

John Dryden, 1631-1701

The past half-century has seen a revolution in how we approach pain with the rethinking of the organisation of pain management. This began when John Bonica recognised the fragmentation of care that existed for many pain sufferers.[1] He initiated the first interdisciplinary clinic for the assessment and treatment of patients with persistent pain. This was followed by Wall's and Melzack's description of the gate control theory of pain.[2] Their theory linked the neurophysiological mechanisms of peripheral stimulation as well as the internal psychological activity. A surge of research followed which elucidated among others the mechanisms of opioid analgesia. Now it is understood that opioids such as morphine act by replacing a natural, endogenous substance (endorphins and enkephalins) in the descending pathways from brain to spinal cord that control the intensity of nociceptive tissue injury signals reaching the brain from the periphery.[3]

Issues of addiction and dependence have always hindered the use of opioids in the treatment of pain. Up until the 1980s, opioid phobia has been fuelled by irrational and undocumented fear that appropriate use of opioids will lead to patients becoming addicts.[4] This irrational fear has influenced the prescribing behaviours of doctors, even in cancer pain. In the mid-1980s however, first publications appeared on the use of opioids in chronic non-cancer pain.[5] Since the 1990s, there has been a swing of the opioid pendulum to more liberal and widespread prescription of opioids. Today, opioids are second only to non-steroidal anti-inflammatory agents in terms of prescription frequency for chronic pain. This significant increase in opioid use has been the result of clinical requirements, recommendations from pain physicians and also sale promotion activities from pharmaceutical companies.[6]

Opioids in Chronic Non-cancer Pain – What Are the Issues?

The use of opioids in the treatment of moderate to severe acute pain and cancer-related pain is well-established. It provides effective pain control and does not usually lead to tolerance, obvious physical dependence and/or psychological addiction. The role of opioids in chronic non-cancer pain, however, is somewhat poorly defined, more contentious and the subject of this review; the simple

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transfer of concepts and findings in acute or cancer pain treatment to the chronic pain setting might be flawed.

Chronic pain is commonly defined as pain lasting longer than 3 to 6 months and/or pain that persists beyond the normal time of tissue healing.[1,7] Chronic pain is a generic term summarising many different conditions; chronic non-cancer pain patients are not a homogeneous group. The foundation of the argument for use of opioids in these conditions is their unique analgesic efficacy and the experience in acute and cancer pain treatment. The argument to apply the same knowledge to chronic pain patients seemed to be reasonable.[5] On the basis of these concepts and some limited surveys, case series and open label follow-up studies, opioid usage in chronic pain states has recently become more widespread.

The use of opioids in physiological pain (well-defined nociceptive or neuropathic origin) can be effective; opioids have been shown to reduce pain and improve functional outcomes better than placebo in both neuropathic and musculoskeletal conditions.[8,9] Such conditions include long-term post-trauma pain, osteoarthritis, rheumatoid arthritis and osteoporosis; here opioid administration may be justified irrespective of the duration of pain. Opioids have been commonly underutilised in this setting due to unfounded fears, but could be used to replace more harmful [e.g. non-steroidal anti-inflammatory drugs (NSAIDs)] or less effective (e.g. paracetamol alone) therapies.

However, the issue is the use of opioids in pathological pain when patients develop physiological (central sensitisation) and behavioural responses that sustain a pain state without ongoing nociception. These patients may demonstrate a wide range of biological, psychological and social symptoms often complicated by depression, anxiety, somatoform disorders and substance abuse disorders. In such "pathological pain states", nociception is not the sole target, but also suffering, dysfunction, mood states, psychosocial factors and dependence on the health system.[10] Then opioid use is less likely to improve analgesia and even less to yield psychological or functional improvement.

Use of Opioids in Osteoarthritis as an Example of Nociceptive Pain

Osteoarthritis can be a progressive disease of the synovial joints associated with significant pain and dysfunction. Osteoarthritis of the hip and knees often respond well to operative treatment. However, when symptoms of osteoarthritis involve joints not amenable to surgery or where patient comorbidities preclude surgery, the treatment is palliative. Opioids may form part of the symptomatic medical treatment. The underutilisation of opioids is a major contributor to poor pain management in the elderly population,[11] despite evidence for the effectiveness of opioids and published guidelines recommending their usage.[12] Reasons for underutilisation include poor assessment of pain, fear of polypharmacy, opiophobia and concerns of tolerance, physical dependence, addiction and adverse effects.

In the treatment of hip osteoarthritis, opioid analgesics with or without paracetamol are regarded by current guidelines as useful alternatives in patients in whom NSAIDs and COX-2 selective inhibitors are contraindicated, ineffective or poorly tolerated.[13] Opioids are devoid of the organ toxicity of NSAIDs and COX-2 selective inhibitors, a risk which is increased in the elderly.

Controlled-release oxycodone therapy has been shown to be safe and effective for patients with chronic, moderate to severe, osteoarthritis-related pain.[14] The treatment resulted in reduction in interference of pain with mood, sleep and enjoyment of life; analgesia was maintained with long-term therapy and daily doses remained stable after titration. Typical opioid side effects occurred and generally decreased over time. Similar outcomes have been shown with sustained-release morphine.[15] Cepeda et al[16] evaluated the role of tramadol for osteoarthritis in a systematic review of 11 randomised controlled trials to determine the analgesic effectiveness, effect on physical function, duration of benefit and safety of oral tramadol with or without paracetamol in patients with osteoarthritis. Patients who received tramadol reported less pain and improved function, even though these benefits were small.

There has been concern of opioid consumption in elderly patients with impaired hepatic and renal function, since impairment of end organs is common in the elderly, especially with respect to renal function. It is, therefore, recommended that doses be reduced, a longer time interval be used between doses, and renal function be monitored. Slow-dose titration helps to reduce the incidence of typical initial adverse events such as nausea and vomiting. Sustained-release preparations, including transdermal formulations, may also increase patient compliance. Given that osteoarthritis presents in the elderly population, in whom opioid side effects can be expected to be more severe, a careful assessment needs to be made of the potential benefits and risks prior to starting a trial of opioids; this needs then to be weighed against the risks of organ toxicity with other analgesics.

Use of Opioids in Neuropathic Pain

In the United States, an estimated 2 million people are diagnosed with neuropathic pain.[17] This may result from central or peripheral mechanisms, including trauma, inflammation, ischaemia, metabolic and neoplastic disorders. Common examples of peripheral neuropathic pain include diabetic neuropathy, postherpetic neuralgia and trigeminal neuralgia. Central neuropathic pain includes central poststroke pain, pain associated with multiple sclerosis and spinal cord injury pain. Pharmacological treatment usually

involves antidepressants or anticonvulsants; however, effective analgesia is achieved in less than half the patients.[18] The role of opioids in neuropathic pain has been under debate in the past, but is nowadays more widely accepted.[19]

Numerous clinical trials have been conducted to assess the efficacy of opioids in neuropathic pain states. Unfortunately, there is great variability in the trials in terms of neuropathic pain syndrome treated, type of opioid administered and the duration of treatment, leading to conflicting and often confusing results. A recent systematic review by Eisenberg et al[20] showed that short-term trials for neuropathic pain yield mixed results with respect to the analgesic efficacy of opioids. Intermediate term trials demonstrated consistent opioid analgesic efficacy in reducing spontaneous neuropathic pain that was statistically significant up to 8 weeks of treatment. Overall, higher opioid doses are often needed for treatment of neuropathic pain than for nociceptive pain.[21] There is limited data on the use of opioids in central versus peripheral neuropathic pain; however, the review quoted above showed similar opioid responsiveness for pain of central and peripheral mechanisms.[20]

Oral and transdermal opioids have proven efficacy in neuropathic pain that is similar to that of the tricyclic antidepressants and gabapentinoids. However, as opioids result in more adverse effects, they are commonly regarded as second-line treatments for neuropathic pain.[22,23] Opioids should, therefore, be used in patients who have failed to respond to respond to one of the first-line treatments, or have shown intolerance to first-line treatments. Again, dose titration of opioids should be performed to achieve efficacy with minimal adverse effects.

A substance that might be specifically interesting in this group is the atypical centrally-acting analgesic tramadol, which is a weak opioid agonist but also a selective noradrenergic and serotoninergic receptor inhibitor. It has shown efficacy in a variety of neuropathic pain settings, with an NNT of 3.8.[24] Further advantages are the low abuse potential, non-controlled drug status, as well as a reduced rate and severity of constipation.

Buprenorphine also shows a potential benefit in improving neuropathic pain symptoms, possibly due to its specific pharmacological profile.[25]

Methadone is a viable choice in treatment of neuropathic pain even in the ambulatory setting. In a study of 50 subjects with intractable neuropathic pain (previous failed treatment or side effects from treatments), methadone was used in an initial dose of 20 mg per day with a maximum dose of 160 mg per day.[26] Concomitant treatments were continued and these included tricyclic antidepressants, non-steroidal anti-inflammatory agents, selective serotonin reuptake inhibitor, benzodiazepines and anticonvulsants. Over a mean duration of treatment of 17 months, 52% of the subjects improved in pain relief and 32% of the subjects improved in function.

Use of Opioids in Chronic Back Pain

Chronic musculoskeletal pain is a common cause of disability and low back pain is the most common painful musculoskeletal condition. The lifetime prevalence is estimated to be between 50% and 80% and point prevalence is between 12% and 35%. A systematic review of opioid treatment for chronic back pain by Martell et al[27] showed variable prescribing patterns for opioids ranging from 3% to 66%. The prevalence estimates of opioid prescribing were highest in the specialty treatment centres, ranging from 11% to 66%, and lowest in the primary care settings, ranging from 3% to 31%.[28,29] The authors conclude that *'opioids seem to have limited, if any, short-term value in chronic low back pain. … long-term efficacy (>16 weeks) is unclear.'*[27] The meta-analysis identifies also a number of relevant issues; patients were more likely to be prescribed opioids if they reported greater distress and suffering. The prevalence of substance abuse disorders was in the range of 40% to 50% in these patients and up to 24% showed aberrant medication-taking behaviour.[27]

A more rigorous Cochrane review of opioids in chronic low back pain included only 4 trials with duration of treatment longer than 4 weeks.[30] Three trials compared tramadol to placebo. Pooled results supported that tramadol was more effective than placebo for pain relief and improvement of function.[31-33] One trial comparing morphine or oxycodone to the NSAID naproxen showed no significant benefit either for relieving pain or improving function.

In randomised controlled trials of shorter duration, opioids were found unlikely to yield psychological or functional improvement.[29,34] Another showed only an insignificant improvement of quality of life and the opioid treatment was termed palliative and without long-term benefits.[35]

Overall, the benefit of opioids for long-term management of chronic low back pain remains currently questionable at best.

Risk of Opioid Abuse

Several investigations have identified drug abuse in 18% to 41% of patients receiving opioids for chronic pain.[36-40] The prevalence of lifetime substance use disorders range from 36% to 56%, with an estimate of 43% current substance use disorders and 5% to 24% of the patients with aberrant medication taking behaviours. Furthermore, patients on chronic opioid therapy have been shown to also abuse illicit drugs.

Risk factors for opioid abuse and dependence include history of substance abuse, mental disorders, male gender, younger adults and those with longer prescription days of opioids.[41] Hence, clinicians need to screen for substance

abuse and mental disorders when prescribing opioids and facilitate appropriate treatment for these disorders. Also, a subset of the population may be at higher risk of opioid abuse and dependence requiring greater vigilance.[41]

One screening tool that might be useful for patient selection and risk stratification is the opioid risk tool.[42] One of the briefest measures available in risk stratification, it consists of 5 yes-or-no self-report items to predict the probability of a patient displaying aberrant behaviour when prescribed opioids for chronic pain. Items covered include family and personal history of substance abuse, age, history of preadolescent sexual abuse, and psychological disease. The tool is specifically designed to predict problematic behaviour in people prescribed opioids for pain.The opioid risk tool exhibited a high degree of sensitivity and specificity for determining which individuals are at risk for opioid-related, aberrant behaviours.[43] The critics of this tool may find it too concise and may want something more detailed and comprehensive; however, it can be a useful tool in a busy pain clinic setting.[44]Prescription opioid abuse has harmful ramifications for the legitimate and appropriate use of opioids, including stigmatisation, opiophobia, and undertreatment of pain.[45] However, one should note that in a prospective study of 15,000 veterans, who were initiated on opioids based on medical grounds and were supplied with at least 3 months of opioid medication for pain, only 2% developed an opioid abuse diagnosis.[41] The second most commonly used opioid, hydrocodone, was studied for its side effects. Adams et al[46] evaluated a comparison of the abuse liability of tramadol, NSAIDS and hydrocodone in 11352 patients with chronic pain. The abuse liability of hydrocodone was 4.9%, compared to 2.7% for tramadol and 2.5% for NSAIDS.

Clearly, a more balanced approach would be that if mental disorders are important risk factors for opioid abuse, there should be careful screening and facilitation of appropriate mental health treatment as part of chronic opioid therapy.[47] This may also facilitate adequate pain relief, since there is evidence that appropriate treatment of mental disorders helps with pain management.[48]

Opioid-induced Hyperalgesia

Opioid-induced hyperalgesia describes the paradoxical phenomenon whereby a patient receiving opioids for the treatment of pain may actually become more sensitive to certain painful stimuli.[49] Such a phenomenon might default the therapeutic intentions of long-term opioid treatment by rendering patients more sensitive to painful stimuli.

Opioids provide analgesic and antihyperalgesic effects initially. Subsequently, there is upregulation of compensatory pronociceptive pathways, leading to hyperalgesia.[50] Such hyperalgesia results from neuroplastic changes within the spinal cord in response to repeated exposure to opioids.[51] It has been generally acknowledged that the activation of N-methyl-D-aspartate (NMDA) receptors plays a pivotal role in the development of neuroplastic changes following repeated opioid exposure. Moreover, interactions between NMDA and opioid receptors can lead to potentially irreversible degenerative neuronal changes in the spinal cord in association with the development of opioid tolerance. Hence, there is induction of pain facilitation by sustained opioid exposure.[52]

Clinically, opioid-induced hyperalgesia may be characterised by pain that has become more diffuse and less defined in quality and has a wider spatial distribution than the pre-existing pain state. There is emerging evidence that some opioids have different profiles with regard to analgesia and hyperalgesia.[53] The pure μ-agonists may be less effective at attenuating secondary hyperalgesia than mixed opioid agonists-antagonists such as buprenorphine. Similar suggestion can be made for methadone due to its NMDA antagonist actions that may render it more effective in the treatment of sensitisation.[54] However, these suggestions would need validation from clinical trials.

Patient data have not provided an unequivocal demonstration that opioid-induced hyperalgesia is a clinically meaningful phenomenon. A pilot study investigated patients with axial back pain before and after a 1-month course of opioids.[55] This showed the development of both hyperalgesia and tolerance to the cold pressor test after 1 month of opioid administration, while the patients showed improvements in their pain scores when commenced on the opioids; this leaves open the question of whether opioid-induced hyperalgesia is clinically significant. However, in an interesting study, patients' pain and unpleasantness rating of a standardised stimulus were directly correlated to opioid dose and duration of opioid treatment.[56] These findings have been supported by other studies.[57]

Opioid tolerance and opioid-induced hyperalgesia may appear similar, but require entirely opposite treatment. Increasing the dose of opioids would treat opioid tolerance, whereas the same course of action would exacerbate opioid-induced hyperalgesia.[58]

Practice and Complications of Opioid Use in Chronic Pain

The challenge of patients with chronic non-cancer pain to their treating physicians is whether to use opioids in their treatment plan. The combination of poorly defined pathology, significant psychosocial factors, manipulative behaviour, dependence, tolerance and legal regulations are important considerations here. In recent years, multiple reviews have been published to evaluate the effectiveness of opioid therapy.

Chou et al[59] performed the first systematic review of comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain. The investigators concluded that there was insufficient evidence to prove that different long-acting opioids are associated with different efficacy or safety profiles. Further, they concluded that there was also insufficient evidence to determine whether long-acting opioids as a class were more effective or safer than short-acting opioids.

Nevertheless, there is evidence that an increasing number of Australian patients are receiving prescribed oral opioids for both cancer and non-cancer pain.[60] This may be filling a previously unmet need. It is, however, unclear if the increasing use is appropriate and whether this has lead to an improvement in function, reduction of pain and suffering or possibly diversion to the illicit market. In Denmark, a country with liberal use of opioids, an epidemiological study showed worse pain, higher healthcare utilisation and lower activity levels in opioid-treated patients compared to a matched cohort of chronic pain patients not using opioids.[6] This suggests that when opioids are prescribed, even if a small number of patients benefit, the overall population does not. The increased awareness and treatment of chronic pain has also fuelled the availability of opioids in the past few decades.[61]

Kalso et al[62] showed a mean decrease in pain intensity of at least 30% with long-term opioids; however, about 80% of the patients experienced at least 1 adverse event. Only 44% of the 388 patients in the open label treatment arms were still on opioids after 7 months to 24 months.

Opioid treatment does have inherent risks, particularly in a long-term perspective. These include physical dependence, tolerance development, opioid-induced hyperalgesia, addiction, abuse and cognitive impairment. Thus, opioids may give rise to serious problems and may be even responsible for maintaining or worsening the pain condition.

Additionally, there is increasing evidence that long-term opioid treatment may have harmful effects on the immune system and the reproductive system. Morphine can decrease the effectiveness of several functions of both natural and adaptive immunity, and significantly reduces cellular immunity.[63] Acute and chronic opioid administration is known to have inhibitory effects on humoral and cellular immune responses including antibody production, natural killer cell activity, cytokine expression, and phagocytic activity. Opioids behave like cytokines, modulating the immune response by interaction with their receptors in the central nervous system and in the periphery. Potential mechanisms by which central opioids modulate peripheral immune functions may involve both the hypothalamic-pituitary-adrenal axis and the autonomic nervous system.[64] Survivors of cancer who chronically consumed opioids may experience symptomatic hypogonadism with significantly higher levels of depression, fatigue, and sexual dysfunction.[65]

Prescribing guidelines have been developed to assist practitioners in selecting the appropriate patients and ensuring an acceptable risk and benefit ratio of opioid therapy.[9,66-68] The management of chronic pain should be directed by the underlying cause of the pain. It is essential that all reasonable attempts be made to achieve a diagnosis for the cause of the presenting pain including the nociceptive, neuropathic and psychological contributions. The patient should be managed in the context of a multidisciplinary pain approach. This would include medical management, physical therapies and cognitive behavioural therapies.

Conservative therapies would include exercise programmes, psychological therapy, attention to improving coping skills, multidisciplinary pain management programme, reducing psychological stressors and appropriate physiotherapy. Opioids should not be the first-line therapy for non-cancer pain expected to last more than a short-term period; patients should be initiated on opioids after an adequate trial of paracetamol or non-steroidal anti-inflammatory agents for nociceptive pain and tricyclic antidepressants or anticonvulsants for neuropathic pain.

Opioid treatment should be considered for both continuous neuropathic and nociceptive pain if other reasonable therapies fail to provide adequate analgesia within a reasonable timeframe. The aim of opioid treatment is to relieve pain and improve the patient's quality of life and function.[69] Both of these should be assessed during a trial period. The prescribing physician should be familiar with the patient's psychosocial status. The selected patients should be psychologically stable, although it is recognised that this may be difficult to define.

Before committing a patient to long-term therapy, full disclosure of both the uncertain benefit and possible harm is essential. Added caution in the use of opioids is justified if there is past history of substance abuse or mental illness. The physician should also be aware of the associated potential abuse, misuse, addiction, diversion and all other associated complications including increasing disability.[61] A screening tool such as the opioid risk tool may be useful to screen for aberrant drug behaviour.[43] Patients should sign an opioid treatment agreement and provide informed consent to treatment. The informed consent should include discussion on likelihood of dependence and risk of addictive behaviour, lack of long-term outcomes, potential for cognitive impairment and physical dependence.[70] A contract setting out the patient's rights and responsibilities may help to emphasise the importance of patient involvement.[71] The indications for cessation of treatment with opioids should be outlined, including the consequences of aberrant pain or drug use behaviour.

The therapeutic trial period should consist of oral slow-release or transdermal therapy for a defined period with sustainable effects. The outcomes should not concentrate solely on reduction of pain intensity. The functional outcomes of improved quality of life in dimensions such as sleep, mood, work, social and recreational activities play a significant part in patient management.

For long-term maintenance on opioids, the physician must have defined rules in prescribing, have regular review of relief, function, mood, usage and adverse effects. The use of sustained-release opioids administered at regular intervals is recommended. Opioid treatment should not be considered a lifelong treatment.[9] If there is a need for termination of opioids, the dosage should be tapered off. In this way, opioids can be made available to the patient who may benefit from treatment, whilst minimising the risk of abuse and addiction.

Conclusion

Chronic non-cancer pain affects a significant portion of the population and opioid use for chronic non-cancer pain has increased substantially. However, there is at best weak evidence for long-term opioid therapy of chronic pain states. The applicability of existing studies to chronic non-cancer pain in the real world is also unclear.

The goals of pain management should not only be just removal or alleviation of pain; there should also be emphasis on overall functioning and self-management. However, these 2 goals may not be necessarily achievable in parallel.[69] Opioids may be counterproductive if they increase dependence on healthcare, reinforcement of pain behaviour, encouragement of passivity, loss of autonomy and possibly opioid-induced hyperalgesia.

Overall, long-term opioid treatment of chronic non-cancer pain should be used with caution; further research is required.

> "… *The patient uses opioids to relieve pain and maintain a normal relationship with the real world; the addict takes opioids to escape from reality*."
>
> **R. Melzack**[72]

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