Adverse effects of chronic opioid therapy for chronic musculoskeletal pain

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Abstract | The use of opioids for the treatment of chronic pain has increased dramatically over the past decade. Whether these drugs provide considerable benefits in terms of pain reduction and improved function to balance the risks associated with their use, however, is unclear. Of particular importance to clinicians treating chronic musculoskeletal pain is opioid-induced hyperalgesia, the activation of pronociceptive pathways by exogenous opioids that results in central sensitization to pain. This phenomenon results in an increase in pain sensitivity and can potentially exacerbate pre-existing pain. Opioids also have powerful positive effects on the reward and reinforcing circuits of the brain that might lead to continued drug use, even if there is no abuse or misuse. The societal risk of increased opioid prescription is associated with increased nonmedical use, serious adverse events and death. Patients with chronic musculoskeletal pain should avoid the long-term use of opioids unless the benefits are determined to outweigh risks, in which case, the use of chronic opioids should be regularly re-evaluated.

Introduction

Clinicians who treat the chronic musculoskeletal pain that is associated with many rheumatic diseases are faced with the difficult task of improving the quality of life and physical function of their patients. It is clear that currently available treatment strategies are inadequate to the task. However, it is the responsibility of treating clinicians to assure, to the best of their ability, that the recommended treatment(s) provide the expected benefit and do not harm. Opioids have been used for centuries to treat pain, but few studies support a favorable risk:benefit ratio for their long-term use in patients with arthritis or other rheumatic diseases. Furthermore, growing evidence indicates that opioid-induced activation of pronociceptive pathways—termed 'opioid-induced hyperalgesia'—is a clinically important phenomenon that might facilitate the persistence of chronic pain or even enhance pre-existing pain. The use of opioids is also associated with powerful positively-reinforcing psychological effects that are typical of drugs that have considerable abuse liability. For this reason, patients who are prescribed opioids for the treatment of chronic musculoskeletal pain might have difficulty discontinuing the use of prescription opioids even if there is no evidence of abuse or misuse. Although surely not all patients are harmed by the long-term use of low-to-moderate doses of opioids, many patients will continue to take these medications despite experiencing neither a reduction in chronic pain nor improved function. The prescription of old and new forms of opioid analgesics has escalated dramatically in the past 5–10 years,[1,2] and clearly increases the societal risks associated with prescription drug abuse and diversion.

In this Review, I aim to outline the risks to patients and society of continuing to increase the use of opioids for the treatment of chronic, nonmalignant pain. The mechanisms that underlie the complex central changes associated with prolonged opioid use and that are responsible for some of these long-term risks will be described, as will strategies that clinicians can use to identify patients

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Key points

- Increased opioid prescription is associated with increased misuse, abuse and diversion
- Endogenous opioid peptides and receptors are involved in the reward and reinforcement circuitry in the brain, which is altered by taking exogenous opioid drugs
- In addition to providing antinociception or analgesia, opioids activate pronociceptive pathways resulting in central sensitization called opioid-induced hyperalgesia
- Opioid-induced hyperalgesia could lead to persistence or enhancement of chronic musculoskeletal pain
- Opioids have a poor benefit:risk ratio in chronic, nonmalignant pain states including osteoarthritis
- Long-term opioid use should be avoided in patients with chronic musculoskeletal pain; in cases where benefits are determined to outweigh risks, use of chronic opioids should be regularly re-evaluated
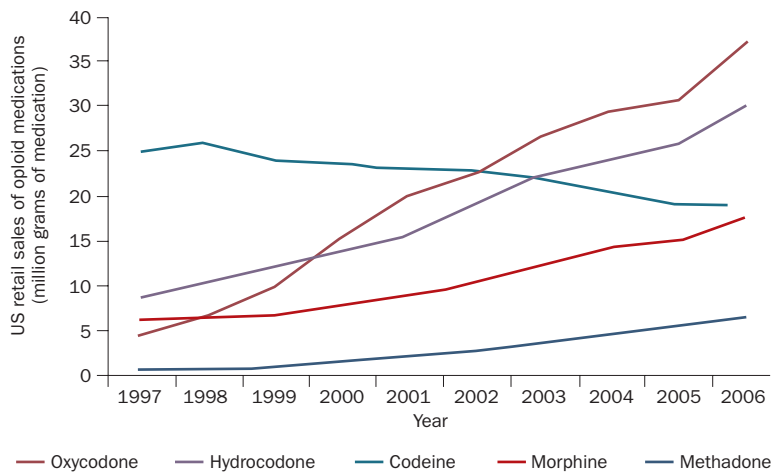

Figure 1 | Increased prescription of opioids in million grams of medication between 1997 and 2006. Data taken from www.justice.gov/dea/index.htm.

in whom opioids might be contributing to maintenance of chronic pain.

Opioid addiction, misuse and diversion
Rise of prescription opioids

Over the past two decades, there has been a dramatic expansion in the use of prescribed opioid analgesics in the USA (Figure 1). A steep rise in opioid abuse, misuse and diversion has occurred in parallel, such that prescription opioid medications have now surpassed cocaine and heroin as the leading drugs of abuse.[1,2] In a cross-sectional survey of 91,823 respondents aged 18 or above,[3] the 2002–2004 National Survey on Drug Use and Health reported a prevalence of past-year nonmedical use of prescription opioids of 4.5%; of this figure, 12.9% met the criteria for abuse or dependence, or both.

Risk factors for nonmedical use included the occurrence of anxiety disorders, low self-rated health status and the use and/or misuse of other substances (tobacco, alcohol, other prescription drugs, illicit drugs).[3] In 2006, the number of emergency department admissions related to the use of opioids was approximately 250,000, compared with less than 50,000 for the use of NSAIDs or

acetaminophen-containing products.[4] In another report from the US Centers for Disease Control and Prevention, the number of deaths resulting from overdoses of opioids more than tripled to 13,800 between 1999 and 2006.[3]

Diversion of prescription opioids

Prescription opioids can be obtained in two ways—legitimately, from the treating clinician, or through illicit sources. Of course, the increase in the number of prescriptions increases the potential for diversion. Internet prescriptions are widely available, and the shift in prescribing behavior away from pain specialists towards primary care physicians is also likely to contribute to increased use.[2]

Diversion can occur by multiple routes, including inappropriate physician prescribing and theft or loss. Most cases of theft or loss are from pharmacies (89.3%) and the US Drug Enforcement Agency has reported that supply chain losses of prescription drugs totaled more than 7 million doses in 2003, of which 24% were commonly prescribed opioids (oxycodone, morphine, methadone, hydromorphone, meperidine and fentanyl).[5] Diversion between household members and through drug sharing or selling might also occur. Although these actions might be done in ignorance of the potential dangers, they represent a significant additional cause of drug diversion outside of normal prescribing.[6,7]

Opioid misuse in patients with chronic pain

As the statistics indicate, the amount of prescription opioids that ultimately circulate in the community has increased considerably. The literature is sparse with respect to opioid abuse and misuse in patients with chronic, nonmalignant pain who are prescribed opioids for therapeutic purposes, and the prevalence rates vary widely depending on the definitions applied to the problem.[8] A 2008 structured review indicates that opioid abuse or addiction will occur in only a small percentage of patients, but that adverse drug-related behaviors and the use of other illicit drugs occurs in a larger percentage.[8] In studies carried out over the past decade, the prevalence of substance use and misuse in patients with chronic pain has ranged from 20% to 40%.[9,10] In a prospective study of 196 patients with chronic, nonmalignant pain who signed a contract as part of the study, 32% misused opioids in violation of the contract. This misuse was defined on the basis of: negative urine toxicology screens on at least two occasions despite the patient reporting taking the medication (an indication of possible diversion); inconsistent urine toxicology screens defined as positive on at least two occasions for opioids or controlled substances not prescribed by the practice or investigators; evidence of concurrent procurement from multiple providers; diversion of opioids or controlled substances; prescription forgery; or positive urine toxicology screening for stimulants (cocaine or amphetamine).[1] The strongest predictor of misuse was a self-reported history of previous alcohol or cocaine abuse, or a previous criminal drug-related or alcohol-related conviction. Younger age was also associated with misuse, but the effect was minimal.

Given the societal risk of increased abuse, misuse and diversion of prescription opioids, prescribing physicians must critically evaluate the role of these drugs in the overall pain management strategy. Furthermore, the prescribing physician should understand the factors related to opioid biology associated with adverse outcomes and reduced effectiveness of opioids for patients with chronic musculoskeletal pain, which are outlined below.

Supraspinal effects of opioids
Activation of the reward response
The biologic effects of opioids are mediated by receptors expressed in the central nervous system (brain and spinal cord) and in the periphery.[11] These receptors are associated with a range of psychological and physiological responses to endogenous and exogenous ligands (Table 1). The opioid system mediates hedonic evaluation of natural rewards, such as food and sexual pleasure.[11] Opioid peptides and receptors are also known to be involved in the brain network that mediates the reward and reinforcing properties of essentially all drugs with significant abuse liability.[11,12] Neural effects shared by drugs of abuse include stimulation of dopaminergic neurons in the ventral tegmental area and increased release of dopamine in the nucleus accumbens. A complex relationship exists between endogenous opioid peptides and mesolimbic dopamine, which is the principal mediator of reward and reinforcement. In general, enkephalin enhances dopaminergic activity via μ-opioid receptors whereas dynorphin inhibits dopaminergic activity via κ-opioid receptors.[11] Genetic studies have been particularly useful in understanding this complex pathway and have identified some potential risk factors for drug abuse. For example, high levels of prodynorphin are seen in mouse strains that are resistant to the rewarding effects of morphine.[13] It is proposed that these high levels might protect against drug abuse by limiting the drug-produced reward owing to dynorphin-mediated modulation of the release of dopamine.

Chronic administration of exogenous opioids seems to alter the expression of endogenous opioid peptides and opioid receptors mainly in the reinforcement circuit.[11,14] Opioid administration is also associated with alterations of other main neurotransmitter systems, other signaling pathways, and can markedly alter gene expression in many regions of the brain.[14] It is likely that chronic opioid administration in patients with musculoskeletal pain is associated with neuroplastic changes in the brain. Taken together, these central adaptations might result in the clinical picture of dependence, opioid-seeking behaviors and difficulty in weaning patients off opioid medications, whether or not there is true addiction or abuse.

Conditioned opioid responses
Perhaps the best evidence that conditioned or learned responses are important in the response to analgesic medications is the efficacy of placebo therapy in studies of chronic pain. Placebo-induced analgesic effects have long been known to be inhibited by μ-opioid receptor antagonists. Within the past 5 years, it was demonstrated

Table 1	Opioids and opioid receptors		
Receptor class	**Mu (μ)**	**Delta (δ)**	**Kappa (κ)**
Activity	Mu-1: analgesia Mu-2: sedation, vomiting, respiratory depression, pruritis, euphoria, anorexia, urinary retention, physical dependence	Analgesia, spinal analgesia	Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria
Endogenous peptides			
Encephalins	Agonist	Agonist	NA
Endorphins	Agonist	Agonist	NA
Dynorphins	Agonist	NA	Agonist
Endomorphins	Agonist	NA	NA
Exogenous agonist			
Morphine	Agonist	NA	Weak agonist
Hydromorphone	Agonist	NA	NA
Codeine	Weak agonist	Weak agonist	NA
Fentanyl	Agonist	NA	NA
Meperidine	Agonist	Agonist	NA
Methadone	Agonist	NA	Weak agonist
Hydrocodone	Agonist	NA	NA
Oxycodone	Agonist	NA	NA
Exogenous agonist–antagonist			
Buprenorphine	Partial agonist	NA	Antagonist
Pentazocine	Weak antagonist	NA	Weak agonist
Nalorphine	Antagonist	NA	Agonist
Exogenous antagonist			
Naloxone	Antagonist	Weak antagonist	Antagonist
Naltrexone	Antagonist	Weak antagonist	Antagonist

Abbreviation: NA, not applicable. Permission obtained from American Society of Interventional Pain Physicians © Trescot, A. M. *et al. Pain Physician* **11**, S5–S62 (2008).[40]

that placebo administration increases endogenous opioids in many brain regions and dopamine in the nucleus accumbens.[15,16] These central effects are translated to the earliest pain-processing pathways in the spinal cord by engaging subcortical pathways that activate descending antinociceptive pathways.[17,18]

Hyperalgesia and tolerance
Opioid tolerance
Some patients receiving chronic opioid medication might need to increase their dose to maintain analgesia.[19] Physicians typically attribute the development of inadequate analgesia over time to the pharmacologic phenomenon of tolerance. This form of tolerance is related to adaptive cellular changes associated with a reduction in the turnover rate and number of opioid receptors, or desensitization of opioid receptors to ligand, or both.[20,21] The mechanism for these adaptive changes might also involve pronociceptive pathways that are dependent on the N-methyl-ᴅ-aspartate (NMDA) receptor.[22,23] In
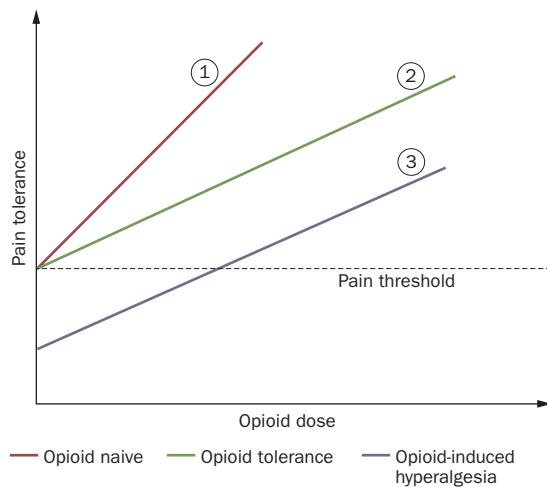
Figure 2 | Tolerance versus opioid-induced hyperalgesia. In the idealized curves, the normal response of opioid-naive individuals to an increasing dose of drug is associated with an increasing analgesic effect (1). If adaptive tolerance is present, the baseline pain tolerance is unchanged, but an increased opioid dose is required for equivalent analgesic effect, as indicated (2). If opioid-induced hyperalgesia occurs (3), baseline pain tolerance is reduced, pain tolerance is lower at each dose level, and maximum analgesic effect is not reached.

animals, inhibition of the NMDA receptor at spinal levels enhances opioid efficacy and reverses apparent tolerance.[24] In clinical settings, NMDA receptor antagonists such as dextromephorthan have been proposed to reduce tolerance, but results overall have been mixed.[25,26]

Opioid-induced hyperalgesia

Studies in animal models have indicated that opioid exposure can induce a paradoxical increase in pain sensitivity and potentially exacerbate pre-existing pain.[22,23] The phenomenon of opioid-induced hyperalgesia is thought to be predominantly the result of central sensitization of pronociceptive pathways and is associated with reduced nociceptive threshold.[19,20] In contrasting opioid-induced hyperalgesia with tolerance, patients who are tolerant have no increase in baseline pain sensitivity, but require increased doses of opioids over time to achieve a level of analgesia previously reached using a lower dose. Patients with opioid-induced hyperalgesia exhibit an increase in pain sensitivity defined by lower nociceptive threshold and an increase in pain perception at all levels of sensory stimulation (Figure 2). Distinguishing opioid-induced hyperalgesia from tolerance in an individual patient might require clinical demonstration of reduced pain sensitivity after opioid detoxification.[27]

A major role for the spinal glutaminergic NMDA-dependent pronociceptive pathway has been proposed for the central sensitization involved in opioid-induced hyperalgesia, suggesting an overlapping cellular mechanism with adaptive tolerance.[22] In fact, apparent tolerance might instead, or additionally, be related to opioid-induced hyperalgesia.[28] Signaling through protein kinase C has also been shown to be critical for the development of opioid-induced hyperalgesia in mice by use of gene knockout and pharmacologic methodologies.[22] Opioid-induced hyperalgesia is seen with administration of κ-opioid receptor agonists and may be triggered by increased spinal dynorphin resulting from exposure to μ-opioid receptor agonists.[22] However, other mechanisms are also likely: a study in mice lacking the three classical opioid receptors (μ, κ and δ) showed a marked and immediate decrease in nociceptive threshold associated with infusion of opioids, which was not inhibited by NMDA receptor antagonists.[29]

The dorsal horn of the spinal cord is central to many of the mechanisms that converge to support opioid-induced hyperalgesia. In addition to the actions of opioids on neurons and other cells via classical opioid receptors, opioids might act on spinal glia via opioid-receptor-independent pathways. It has become increasingly recognized that sensitization of pain-transmission pathways involves activating microglia and astrocytes to exhibit a proinflammatory phenotype and that this activation can be induced by opioids.[30] The mechanism underlying this phenomenon seems to involve opioid-induced signaling through Toll-like receptor 4 (TLR4), an effect that has been proposed to oppose opioid analgesia. In support of this concept, morphine induces TLR4 signaling and *Tlr4*-knockout mice have considerably enhanced morphine-induced analgesia and attenuated development of opioid-induced hyperalgesia.[31]

Clinical evidence for opioid-induced hyperalgesia

Evidence that opioid-induced hyperalgesia occurs in humans has been shown in clinical studies, although the concept has been present in the medical literature since 1870, when Clifford Albutt observed "I have much reason to suspect that reliance on hypodermic morphia only ended in that curious state of perpetuated pain."[32] Opioid-induced hyperalgesia in humans has been detected as hyperalgesia to cold pressor testing in opioid addicts or in patients treated with oral morphine.[33] In chronic opioid addicts, pain perception does not return to normal levels for at least 1 month following detoxification.[34]

Two prospective studies have examined the issue of opioid-induced hyperalgesia in patients receiving opioids for pain. Chu *et al.*[35] prospectively assessed analgesic tolerance and hyperalgesia in patients with moderate to severe chronic low back pain before, and 1 month after, treatment with oral morphine. The authors used the tonic cold and phasic heat experimental pain models and found that opioid treatment was associated with significant hyperalgesia using cold models, but not heat pain models. A cross-sectional study by Chen *et al.*[33] examined three groups of individuals: those who had no pain and were not receiving opiate treatment; those suffering from chronic pain but receiving no opiates; and those in chronic pain receiving opiates. Quantitative sensory testing, including cold and heat detection, pain threshold, tolerance, and temporal summation of second pain using a heat stimulus, was carried out. The authors also evaluated mechanical pain using von Frey filaments and pinprick testing. A number of parameters

differed between patients with or without chronic pain, but those of hyperalgesia that were strongly associated with opioid use were heat pain threshold and temporal summation of second pain. Chen *et al.*[33] suggested that these parameters might be useful in detecting opioid-induced hyperalgesia clinically. One further finding was a considerable association between the daily use of high levels of opioids and altered quantitative sensory responses, which, again, suggests that tolerance and opioid-induced hyperalgesia share at least some basic cellular mechanisms in humans, as has been demonstrated in animal models.[22]

Pharmacologic considerations

As previously noted, clinical studies suggest that opioid-induced hyperalgesia occurs more frequently in patients receiving high doses of drug than in those receiving lower doses or no opioid treatment. The various exogenous opioids, however, might have pharmacologic properties that influence their propensity to cause hyperalgesia based on the receptor profile and other factors. For example, methadone is a μ-opioid receptor antagonist but might also function as an NMDA receptor antagonist. Buprenorphine is a partial μ-opioid receptor agonist but also acts as a κ-opioid receptor antagonist. As the endogenous κ-opioid receptor ligand dynorphin has been implicated in the development of opioid-induced hyperalgesia, buprenorphine may be useful in patients with hyperalgesia.[23]

Endogenous opioids in chronic pain

Studies in patients with rheumatoid arthritis or fibromyalgia have suggested that opioidergic pathways could be dysregulated. The finding that low μ-opioid receptor binding activity is present in these conditions suggests that either there is an increase in μ-opioid ligands or that receptor numbers are reduced.[36,37] Other studies in patients with fibromyalgia using the opioid receptor antagonist naltrexone have yielded conflicting results. One mechanistic study revealed no evidence of a dysregulated endogenous opioid system by clinical change after acute administration of naltrexone.[38] However, a pilot treatment study demonstrated a reduction in pain following treatment with naltrexone, raising the possibility that at least some of these patients might have hyperalgesia related to the dysfunction of opioidergic pathways.[39] Larger studies exploring these findings should be conducted before any definitive conclusions can be drawn.

Recognizing opioid-induced hyperalgesia

Although no literature specifically addresses recognition of opioid-induced hyperalgesia, it seems prudent to develop an understanding of the clinical features that might be associated with this phenomenon. Some observations that, in the absence of disease progression, might indicate the occurrence of opioid-induced hyperalgesia are outlined in Box 1. Of particular relevance might be the development of fibromyalgia-like central pain features. It is unclear whether using clinical

Box 1 | Recognizing opioid-induced hyperalgesia

- Pain persists or increases with increased opioid dose
- Pain increases with constant opioid dose
- Pain worse on opioid treatment than before treatment with opioids
- Duration of analgesia decreases with duration of therapy
- Pain becomes increasingly diffuse and less-well defined in character with increased dose or duration of treatment

Box 2 | Adverse effects of opioids

Neuropsychiatric
- Sedation, mental clouding, euphoria, sleep disorder, hyperalgesia

Cardiopulmonary
- Respiratory depression, bronchoconstriction (high doses), orthostatic hypotension, bradycardia (high doses)

Gastrointestinal
- Nausea, vomiting, constipation, gastrointestinal or biliary spasm

Urinary
- Urinary retention

Endocrine
- Reduced testosterone, menstrual irregularities

Allergic or immunologic
- Pruritis, immunosuppression

measures, such as pain maps or tender point counts, would identify the development of central sensitization owing to opioids. Opioid use in patients with arthritis or other types of regional musculoskeletal disorder could potentially even facilitate the development of fibromyalgia in these patients.

Other adverse effects of opioids

Opioids can adversely affect many physiological and psychological processes (outlined in Box 2). Several of these adverse effects should be highlighted as relevant to patients with chronic musculoskeletal pain.

Gastrointestinal effects

Adverse gastrointestinal effects can include constipation, delayed gastric emptying, nausea and vomiting. These adverse effects can be considered important complications for many patients with chronic musculoskeletal pain.[40]

Sleep problems

Sleep disturbance, which is common in patients with chronic musculoskeletal pain, might also be an adverse effect of opioid use. Obstructive sleep apnea, central sleep apnea, sleep-related hypoventilation, Biot or ataxic breathing, and cluster breathing are among the commonly described sleep disorders in patients who are undergoing long-term opioid treatment.[41] In one

report,[42] sleep-disordered breathing was resolved after discontinuation of opioids after their long-term use.

Hormone systems

Opioids also influence hormone systems, including the hypothalamic–pituitary–adrenal (HPA) and hypothalamic–pituitary–gonadal (HPG) axes.[20] It is not completely clear if altered HPA axis activity results in mood disorders as seen in patients using chronic opioids and in patients with painful rheumatic conditions. Changes in the responsiveness of the HPA axis could also potentially adversely affect patients with inflammatory rheumatic conditions as there is evidence that HPA axis dysfunction resulting in altered endogenous glucocorticoid activity is itself associated with autoimmunity and inflammation.[43]

Opioids clearly reduce the release of hormones, including prolactin, follicle-stimulating hormone, luteinizing hormone, testosterone and estrogen. Clinically relevant reductions in testosterone levels might lead to reduced libido and increased aggression and drive. In women, amenorrhea or irregular menses may occur.[20] The effects could increase the risk of osteoporosis in patients with rheumatic diseases.

Immunity

The effects of opioids that are mediated by the neuroendocrine system and perhaps direct effects on of opioids on cells of the immune system lead to altered innate and adaptive immunity. Leukocytes and other cells of the immune system express opioid receptors and release opioid peptides. Chronic inflammation in patients with rheumatoid arthritis is associated with increased levels of β-endorphin, Met-enkephalin and opioid receptors in synovial tissues compared to patients with osteoarthritis or joint trauma.[44] In animals, prolonged exposure to opioids is more likely to be immunosuppressive than short-term exposure. Furthermore, different opioids might have different effects on the immune system: morphine is well-known to affect the immune response, whereas methadone or buprenorphine might have fewer immunosuppressive effects.[45] A robust literature regarding the immunosuppressive effects of acute morphine administration exists, but the effects of chronic opioid administration or opioid withdrawal on the immune system remain somewhat unclear, particularly in humans.[46] Improved understanding of these issues, particularly in elderly patients or other patients at risk of infection owing to underlying disease or its treatment, is critically important and further investigation is clearly needed.

Long-term treatment for chronic pain

Given the prevalence of opioid use for the treatment of chronic musculoskeletal pain, it is surprising how few data address the safety and efficacy of these analgesic drugs. Furthermore, patients are commonly prescribed doses that are much higher than those studied for safety and efficacy based on the principle espoused by some authors that doses should be escalated to attain maximal analgesia with minimal side effects.[20] In view of the important dose-related adverse effects, such as opioid-induced hyperalgesia, it would seem prudent to limit the dose of opioids in patients with chronic musculoskeletal pain. Daily doses above 180 mg of morphine or its equivalent have not been validated in clinical trials.

The American Society of Interventional Pain Physicians (ASIPP) guidelines for management of noncancer pain has concluded that only weak evidence exists to support the effectiveness of long-term opioid use in reducing pain and improving functional status.[40] After a systematic review of the literature, ASIPP reported considerable evidence of misuse and abuse of opioids, and stated that any benefits were closely balanced with risks and burdens for monitoring compliance.[40,47] Furthermore, there was limited or no evidence to support the long-term efficacy of the most commonly prescribed opioid analgesics, oxycodone and hydrocodone.[47]

A review from the Cochrane Collaboration specifically addressing the use of opioids to treat osteoarthritis of the knee or hip concluded that these drugs were more effective than control interventions, in terms of pain relief and improvement of function, without substantial differences in effects according to the type or potency of opioids or the duration of treatment.[48] However, the authors also found an increase in adverse events, which led them to conclude that "The small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events. Non-tramadol opioids should therefore not be routinely used, even if osteoarthritic pain is severe."[48] (Tramadol comprises a combination of μ-opioid agonist–antagonist and serotonin–norepinephrine reuptake inhibitor activities). There are few studies on the use of non-tramadol opioids in fibromyalgia and no meta-analyses with high numbers of patients have been performed. There is no evidence of long-term efficacy for non-tramadol opioids in patients with fibromyalgia.[49]

Conclusions

Effective treatment of chronic musculoskeletal pain is difficult to achieve and often inadequate using currently available strategies. Opioids are used, although evidence for their effectiveness in improving pain and function is scarce and weak. Any benefits of reduced pain and improved function are closely counterbalanced by the risk of adverse events. Opioid-induced hyperalgesia has been understudied in patients with chronic musculoskeletal pain and, on the basis that the bulk of evidence supports the conclusion that opioids can enhance pain sensitivity, the phenomenon of opioid-induced hyperalgesia should be understood by physicians. If the characteristics of pain change in a way that suggests central sensitization in patients undergoing long-term opioid treatment, clinicians should consider the possibility that their pain might be maintained or enhanced by these drugs.

The adverse effects and reinforcing properties of opioids might be particularly relevant for patients with fibromyalgia, whose physiology is characterized by activation of central pain-processing pathways. Opioids

are widely used in the fibromyalgia population and have not been shown to be effective.[49] Clinicians should make it a priority to consider strategies to reduce or eliminate opioid use in this group of patients. The long-term use of opioids should be avoided in patients with chronic musculoskeletal pain. In cases where benefits are determined to outweigh risks, the use of chronic opioids should be regularly re-evaluated.

Review criteria

English-language articles from PubMed were identified by use of the following search terms, alone and in combination: "opioid", "abuse", "diversion", "chronic pain", "osteoarthritis", "fibromyalgia", "hyperalgesia" and "mechanism". No date restrictions were placed on the search.

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