Role of Opioids in the Management of Work Injuries – Part 1: Focused Literature Review

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The American College of Occupational and Environmental Medicine’s (ACOEM’s) Occupational Medicine Practice Guidelines, 2nd ed., states that “opioids appear to be no more effective than safer analgesics for managing most musculoskeletal and eye symptoms; they should be used only if needed for severe pain and only for a short time.¹ The Guidelines further indicate that pain medications (referring to opioids) are “typically not useful in the sub-acute and chronic phases,”² and, when used for the latter, should be taken with care because they are “easy” and as such may represent a path of little resistance, thus preventing both the patient and physician from vesting in a difficult and uncomfortable rehabilitation course.³

Opioid use is, in fact, described in the Guidelines as “the most important factor impeding recovery of function in patients referred to pain clinics,” which “may reflect failure of providers to set up the expectation of improved function as a [prerequisite] for prescribing them.”² Recommendations in the Guidelines regarding the management of specific musculoskeletal conditions clearly indicate that it is preferable to reserve opioid use solely for the short-term management of severe pain.

On the other hand, the Guidelines also state that, under certain circumstances, the long-term use of sustained-release opioid medications may be appropriate in the treatment of chronic musculoskeletal pain, with the requirement that the patient’s functional status be reassessed at every visit.⁴ However, since these circumstances are not specifically defined, clarification via APG Insights has been requested regarding:

- indications, and contra-indications, for the use of opioids;
- criteria with regard to choice of opiate type and dosing frequency;
- recommended duration of treatment by diagnosis;
- use of supplemental adjunctive medications as a means of circumventing increased dosage requirements;
- optimal ways to address concerns regarding dose escalation, tolerance, addiction, and potential drug diversion; and
- criteria for the discontinuation of opioid therapy, including management strategies for patients on high-dose opioids.

For this discussion, a search was done for systematic reviews or meta-analyses discussing the use of opioids in managing chronic non-cancer pain, and for individual randomized controlled trials (RCTs) published subsequently comparing opioid medication with non-opioids, other opioids, or placebo. Increased concerns about the escalating use of opioids for the management of chronic non-malignant (non-cancer) pain has also prompted publication of a number of recent guidelines and narrative reviews,⁵⁻¹² which were reviewed both for content and to cross check the completeness of the citations retrieved.

Seven systematic reviews focusing on the use of opioid medication in the management of chronic low back,¹³ chronic non-malignant,¹⁴⁻¹⁶ or neuropathic pain,¹⁷⁻¹⁹ were identified. An ongoing Cochrane review of the use of opioids for chronic low back pain (CLBP) is underway for which the protocol has been published,²⁰ but no results are yet available. An additional low-quality systematic review of opioid hyperalgesia was evaluated,²¹ as was a general review of opioid addic-
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Do Opioids Reduce Pain/Improve QoL? What Are the Adverse Effects?

The sole systematic review/meta-analysis of opioid medication use in patients with CLBP identified 15 studies comparing opioids with nonopioids, placebo, or opioid comparators, such as non-steroidal anti-inflammatory drugs (NSAIDs).13 While quality scores were considered excellent, heterogeneous designs made interpretation challenging. Eleven of the studies (four high quality) described the prevalence of opioid treatment for CLBP. The proportion of patients prescribed opiates ranged from 3% to 66%, with the highest numbers seen in specialty treatment centers for patients with impaired functional status. The studies varied markedly regarding the samples selected, purported causes of back pain, length of opioid treatment, type of opioid medication, use of adjunct medications during the trial, and primary outcome instruments. The review/meta-analysis concluded that while opioids are commonly prescribed for CLBP, they may only be efficacious for short-term treatment (<16 weeks), if that. Long-term trials of opioid efficacy for chronic back pain were described as lacking, with findings suggesting that “clinicians should reconsider treating chronic back pain patients with opioid medications, and consider other treatments with similar benefit and fewer long-term adverse effects.”13

An analysis was conducted in 2004 of available randomized, placebo-controlled trials of fentanyl, hydromorphone, methadone, morphine, and oxycodone – opioids advocated by the World Health Organization (WHO step 3 opioids) – for efficacy and safety in treating chronic non-cancer pain (CNCP) – also referred to in the literature as chronic non-malignant pain or CNMP.14 Fifteen trials were included – four studied intravenous opioid testing, while 11 compared oral oxycodone or morphine with placebo for 4 days to 8 weeks. Pain was neuropathic in six studies, due to osteoarthritis in three studies, musculoskeletal in one study, and mixed in the other. Only 674 of the 1,025 patients randomized completed the trial due to adverse effects or lack of efficacy, with the former more likely in the opioid groups and the latter more common with placebo. Six of the 15 included trials had an open-label follow-up of 6 to 24 months. Approximately 80% of these patients experienced at least one adverse event, with constipation (41%), nausea (32%), and somnolence (29%) being most common – only 44% were still on opioids after therapy of 7 to 24 months.

Mean decrease in pain intensity was about 30% for all 15 studies except the musculoskeletal pain study. Important clinical issues such as the effects of opioids on function or quality of life (QoL) were generally not addressed. When addressed, the methods used to assess functional improvement were inconsistent, with only three studies using a validated QoL questionnaire (e.g., SF-36 or Sickness Impact Profile). The musculoskeletal pain study claimed that improvement in pain-related disability was closely correlated with pain relief. Pain relief was however only 10% – well below the level (30%) usually considered as the minimum required for clinical significance.25-27 The efficacy of opioids as compared with treatments such as anti-depressant medications and/or anticonvulsants was not addressed. In addition, patient populations of the trials reviewed represented “ideal” patients for opioid treatment with generally identifiable sources of pain. Patients with histories of substance abuse, psychosis, or major depressive disorder were generally excluded, precluding any evaluation of the association between opioid use and addiction. The overall conclusion was that the role of opioids still needs to be assessed and that criteria for meaningful pain relief, tolerance, and addictive or problematic behavior must be more precisely defined.

In 2005, Devulder reviewed 11 studies evaluating QoL in a low-quality systematic review of patients receiving long-term treatment with opioids.15 Six of the studies were randomized trials and their quality was mixed, with long-term use defined as more than 4-6 weeks in only one study (described as high quality) evaluating tramadol use for osteoarthritis of the knee. The
remaining trials were of moderate or low quality; the five observational trials reviewed were all low quality. Although the conclusion was that there “is both moderate/high- and low-quality evidence suggesting that long-term treatment with opioids can lead to significant improvements in functional outcomes, including QoL, in patients with chronic, non-malignant pain,” the methodological short-comings of this review were such as to support only the recommendation for further more rigorous investigations.

Furlan performed a high-quality meta-analysis of narcotic use for CNCP in 2006, with the objective of comparing the efficacy of opioids for chronic non-cancer pain with other drugs and placebo; identifying types of CNCP that respond better to opioids; and determining the most common side effects of opioids, including incidences of opioid addiction and sexual dysfunction.16 Pain had to be present for more than 6 months and could include neuropathic pain, osteoarthritis, rheumatoid arthritis, fibromyalgia, and back and musculoskeletal pain. While interventions could be any opioid administered via an oral, transdermal, or rectal route for 7 days or more, comparisons of different opioids were excluded. Opioids were classified as weak (propoxyphene, codeine, tramadol) or strong (oxycodeone, morphine). Data quantifying pain (intensity or relief), function, and side effects was abstracted. Forty-one (41) randomized trials were included: 80% of the patients had nociceptive pain (osteoarthritis, rheumatoid arthritis, or back pain); 12% had neuropathic pain (postherpetic neuralgia, diabetic neuropathy, or phantom limb pain); 7% suffered from fibromyalgia; and 1% had mixed pain. The methodological quality of 87% of the studies was high. Average duration of treatment was 5 weeks (range 1-16). Dropout rates averaged 33% in the opioid groups and 38% in the placebo groups.

Meta-analysis of the 28 trials comparing opioids to placebo indicated that the former were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia.16 Eight trials comparing opioids and other analgesics did not find opioids statistically significant for pain relief, a finding that was not influenced by either the type of drug used in comparison (e.g., NSAIDs or antidepressants) or the study’s methodological quality. Sensitivity analysis revealed the strong opioids to be significantly more effective than the other drugs for pain relief; with the addition of codeine to acetaminophen in one trial not included in the meta-analysis also indicating that the combination was superior to acetaminophen at 7 days of follow-up, but not afterward. Opioids were inferior, however, with regard to functional outcomes, although this in part reflected results from one study comparing a weak opioid with diclofenac. Compared with other drugs, use of opioids led to significantly higher incidence of nausea (14%; 95% CI 4-25%), constipation (9%; 95% CI 1-17%), and somnolence or drowsiness (6%; 95% CI 0-11%). Patients with a history of addiction were excluded from 25 trials; only three trials asked about signs or symptoms of addiction with 8.7% of patients in the morphine group and 4.3% in the placebo group reporting “drug craving.” An improvement in sexual function was found in those four studies that questioned it. The overall conclusions were that while weak and strong opioids outperformed placebo for pain and function in all types of CNCP, other drugs produced better functional outcomes than opioids, and were outperformed only by strong opioids for pain relief. Despite the relative shortness of the trials, more than one-third of the participants abandoned treatment, with constipation and nausea the only clinically and statistically significant opioid side effects.

The remaining reviews evaluated the use of opioid therapy in neuropathic pain. Discussion of neuropathic pain is often included in general guidelines regarding the management of CNMP, however it is physiologically distinct from nonspecific musculoskeletal pain states. It would appear logical to base management options for CNMP on the pathophysiology of the condition being treated. Guidelines often fail to do so. Instead, they tend to either apply principles regarding the management of patients with objective evidence of disease generally associated with intractable pain states (such as cancer, sickle cell disease, etc.) to CNMP, and/or apply information from studies regarding the management of one type of CNMP to the management of all patients who fall into this category. Discussion of systematic reviews regarding the management of neuropathic pain states should therefore not be interpreted as suggesting that the results of studies evaluating treatment options for these disorders be extrapolated to the management of other types of pain. On the other hand, failure of review articles to strongly support the use of opioids in the management of neuropathic pain should lead one to question the basis for their use in other clinical conditions where the pain generator is less well-defined.

The most recent review of opioid therapy for neuropathic pain is Eisenberg/Carr’s 2006 Cochrane Collaboration.18 Twenty-three of 46 articles identified met inclusion criteria. Outcomes reviewed were pain intensity using a visual analog scale (VAS); type/amount of opioid and control use; and incidence of adverse effects during treatment with opioid or control. Fourteen of the trials were classified as short-term (<24 hours), in which opioids were administered mostly as brief intravenous infusion and divided as follows: 3 with postherpetic neuralgia; 2 with post-traumatic neuralgia; 5 with mixed neuropathies; 2 with central pain, 1 with secondary trigeminal neuropathy; and 1 with post-amputation stump and phantom pain. Results regarding the effectiveness of short-term use of opioids were mixed. Six trials showed efficacy, 5 showed equivalent efficacy, and 2 demonstrated partial efficacy.

The second group of studies consisted of 9 intermediate-term trials in which opioids were administered orally or for longer periods of between 8 and 70 days (median 28 days). These trials tested morphine, oxycodeone, methadone, and levorphanol with three including, for comparison, additional study groups in which participants were administered non-opioid active drugs: carbamazepine, the tricyclic antidepressants, nortriptyline and desipramine; and gabapentin. Five enrolled patients with diabetic neuropathy, while the
other four enrolled people with neuropathic pain and diverse etiologies. The intermediate-term trials demonstrated that opioids were effective when compared to placebo for neuropathic pain over the relatively short duration of the studies. Side effects such as nausea (33% vs 9%), constipation (33% vs 10%), drowsiness (29% vs 12%), and dizziness (21% vs 6%) were common, but not life threatening. The conclusion was that intermediate-term opioid treatment has a beneficial effect over placebo for spontaneous neuropathic pain for up to 8 weeks of treatment, with the magnitude of this opioid effect a 13-point difference in pain intensity at study end (similar to that achieved by other commonly used treatments for neuropathic pain) compared with placebo. As this effect was achieved by a low-to moderate-dose of opioids, the question is whether higher doses of opioids have the potential to produce a greater magnitude of pain reduction in people with neuropathic pain. The 2003 randomized comparative efficacy trial by Rowbothan28 comparing patients who received either high (0.75 mg) or low (0.15 mg) strength capsules of levorphanol was cited. Of relevance is that although the high-dosage regimen did indeed describe a 36% reduction in pain (as compared to 21% in the low-dose group), higher doses produced more side effects without significant additional benefit in terms of other outcome measures such as affective distress, sleep, and interference with functioning. This raises the question of whether an average decline of 13 points on a scale of 0 to 100, corresponding (based on initial reports of pain intensity) to a 20-30% greater reduction of neuropathic pain with opioids than with placebo is clinically meaningful for people with pain. Prior analyses of data from large randomized clinical trials were noted to have shown a 30% reduction in pain intensity to be the threshold for describing a reduction in chronic pain as meaningful.26,27,29 Consequently, further analysis of data to assess the characteristics of those who benefited most or least from therapy was recommended.

Another main caveat was with regard to study duration. Since this was at most 10 weeks, there was no data on the efficacy or adverse event rate of opioids in the treatment of neuropathic pain over months to years. As a corollary, the available RCTs did not clearly address the issues of addiction and abuse, with it likely that pre-screening of participants most likely eliminated those at highest risk for addiction. Other lower-quality review articles have raised similar concerns.10 Finally, it was noted that the management of any form of chronic pain requires not only a reduction in pain intensity but also in improved quality of life in dimensions such as sleep, mood, work, social and recreational capacities.30 The use of a large number of measurement tools in the included trials made it impossible to demonstrate any consistent improvement in quality of life as these results could not be quantitatively combined. Recommendations were for further RCTs assessing longer-term efficacy, safety (including addiction potential), and improved quality of life prior to establishing the value of opioids for management of neuropathic pain.

There was also a 2005 version17 of Eisenberg and Carr’s 2006 review.18 It differed in that only 22 articles met inclusion criteria, but led to similar conclusions. The addition of one intermediate trial to the 2006 review had no significant effect, although the median change in VAS scores was diminished from 14 (2005 review) to 13. An additional 2006 review18 by Eisenberg focused solely on the use of mu-opioid agonists in the treatment of evoked neuropathic pain. While the relevance of this analysis of only two intermediate 4-week trials (7 short-term) to discussion on the role of opioids in managing CNMP is unclear, the failure to show reduction in anything but the intensity of dynamic mechanical alldynia and, perhaps, cold allodynia in peripheral neuropathic pain is worth noting. The authors also noted that the identification of variable responsiveness of different types of evoked pain to opioids reflected the complexity of opioid responsiveness of neuropathic pain. One might also reasonably assume that this complexity pertains to CNMP as well.

Two observational studies evaluating long-term effects of opioids were done in Denmark, where opioid consumption is higher than the rest of the world.31 Eriksen noted the failure of most long-term reviews to investigate opiate use in excess of 4 to 8 weeks, and choose instead to evaluate long-term effects on pain relief, quality of life, and functional capacity in long-term CNCP via a cross-sectional study.23 A random sample of 16,684 individuals (>16 years of age) were selected from the general population. Only non-cancer patients who took part in an interview and completed a self-administered questionnaire (including questions on chronic/long-lasting pain of > 6 months, satisfaction with medical pain treatment, etc.) were included. Those reporting pain were divided into opioid and non-opioid users. Logistic regression analyses indicated an association between opioid use (as a dependent variable) and reporting of moderate/severe or very severe pain (90% of opioids vs 46% of non-opioid users in the pain group), poor self-rated health, living alone, and a lower health-related quality of life as registered in all SF-36 items. Opioid use (as an independent variable) was significantly associated with inactivity in leisure time, not being employed, and higher use of the health care system, with results adjusted for age, gender, comorbid use of anxiolytics and antidepressants, and pain intensity. Although the cross-sectional nature of the study did not allow causative relationships to be ascertained, it was considered remarkable that opioid treatment of long-term/chronic non-cancer pain “did not seem to fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity.”

There are at least 5 identified opioid receptors with exogenous narcotics affecting at least 3 of them. This is part of the underlying reason why opioid-induced hyperalgesia occurs. Morphine acts on the µ receptor; however, exogenous opiates do not affect the opioid receptors in the same way as do endogenous opioids. For example, prolonged use can result in excess dynorphin expression. Details of receptor physiology have not been fully clarified, and are incompletely understood; an accurate explanation of how they act as agonists or antagonists at CNS receptor sites is hence impossible. A complete discussion of this topic is beyond the scope of the article.

Pain resulting from stimuli that were previously innocuous.
Jensen also studied the long-term consequences of opioid use in Denmark, evaluating adherence to medical treatment, opioid dose escalation, health-related quality of life, anxiety, depression, coping strategies, and health care utilization in chronic pain patients 10 years after treatment in a multidisciplinary pain center. Information was gathered from medical records, postal questionnaires, and a central hospital register. While opioid dose escalation had occurred in only a few patients, 60% of those discharged on long-acting opioids were still on that treatment at follow-up; another 28% had initiated opioid treatment after discharge. Forty-seven percent of those available to the job market at discharge remained in this category; the remainder had retired or were on a disability pension. Increasing age and economic support by transfer income were identified as independent risk factors for using opioids 10 years after discharge from the multidisciplinary pain program, with opioid users having a lower health-related quality of life (as measured by the SF-36), higher occurrence of depression, and more frequent use of coping strategies such as “catastrophizing” and “hoping and praying.” Adjuvant analgesics were generally discontinued; the reason was unknown. Given the study design, no conclusions could be reached regarding causation; however, it was recommended that future research on opioid treatment focus not only on biological issues, but on the effect of opioids on consequences such as health-related quality of life, depression, and the use of coping strategies.

**Does Opioid Use Lead to Addiction?**

There has been considerable concern regarding the potential for the development of tolerance and addiction in patients on opioids. A descriptive analysis of trends in the medical use and abuse of 5 opioid analgesics (fentanyl, hydromorphone, meperidine, morphine, and oxycodone) from 1990 to 1996, suggested a low and steady rate of abuse despite increased medical use. An updated study using data from 1997 to 2002, noted that the frequency of abuse in association with opioid analgesic use had increased from 5.75% to 9.85% during this period. A significant increase in opioid diversion was also described; with the amount of diverted oxycodin noted to have increased from 218,339 dosage units in 2000 to 506,711 units in 2002.

Though not specifically addiction, the abuse of opioids is evidenced even in drug company-sponsored research. Given increased concern regarding opioid abuse, Martell addressed the prevalence of substance use disorders in conjunction with opioid use for CLBP in his previously cited review. Relevant studies were generally of low quality, and while the current prevalence of aberrant medication-taking behaviors ranged from 5% to 24%, the highest quality study did not indicate a difference between current and lifetime prevalence estimates of substance use disorders in patients who were or were not receiving opioids for CLBP (23% for both groups current; lifetime 54% vs 52%).

Hojsted performed a literature search for reports of addiction, dependence, aberrant drug-taking, abuse, misuse, and problematic opioid use among patients with cancer and those with CNMP. Twenty-five reports of CNMP patients were identified, with the prevalence of addiction varying from 0% to 50% depending on the subpopulation studied and criteria used. Variation in screening tools used made it difficult to assess the accuracy of the diagnosis of addiction among chronic pain patients treated with opioids. Although the Portenoy and ICD-10 criteria were felt to be the most appropriate for diagnosing addiction, only one study used the former while none used ICD-10. Available screening tools for drug dependency and/or addiction were described in depth; the heterogeneity of tools used in the 25 articles reviewed made it difficult to draw conclusions about the true prevalence of addiction. However, when estimates of addiction in non-malignant pain patients were based on criteria defined by the authors, the prevalence varied from 24-27.6%. The conclusion of patients with a history of alcohol, drug, and/or substance abuse from four of the studies, even though these are the patients at greatest risk of developing addiction when opioids are prescribed, likely resulted in a substantial underestimation of the population-based risk of addiction. Conversely, including abuse of other drugs in determining addiction may have overestimated the problems attributed to opioids per se. While prospective studies using appropriate criteria were recommended in order to make firm conclusions, it was held appropriate and necessary to be aware of potential problems associated with addiction during long-term opioid treatment.

**Are Additional Adverse Effects of Opioids Associated with Long-term Use?**

While additional adverse effects of opioid use (other than tolerance and addiction) such as osteoporosis, hypogonadism, and decreases in cortisol and DHEA-S levels have been described, opioid-induced hyperalgesia (OIH) is of critical significance as it represents the proposed mechanism through which, paradoxically, opioid therapy aiming at alleviating pain may aggravate or increase sensitivity to it. OIH development has been closely linked to the development of pharmacologically mediated opioid tolerance via mechanisms which include increased spinal dynorphin activity, and activation of N-methyl D aspartate and NK-1 receptors. Given its importance, OIH was evaluated in a comprehensive 2005 narrative review which discussed it in the context of both human and animal studies as related to: 1) maintenance dosing and withdrawal; 2) very high or escalating doses; and 3) ultra-low doses. A complex search strategy was used, resulting in 139 articles supplemented by an additional 41 publications. Evidence suggested that OIH does develop in humans based on data collected in three distinct experimental settings: 1) in former opioid addicts maintained on a stable dose of methadone; 2) in patients undergoing surgery receiving a high rather than low intra-operative dose of narcotics; and 3) in...
human volunteers tested in experimental pain paradigms that involved short-term administration of opioids followed by demonstration of secondary hyperalgesia and cold pressor pain. Data revealed increased sensitivity to acute experimental pain in patients receiving methadone maintenance therapy, increased postoperative pain and opioid consumption in patients receiving a high rather than low intra-operative dose, and exacerbation of secondary hyperalgesia after short-term administration of short-acting opioids. Additional animal studies indicating that administration of a high opioid dose can evoke an allodynic/hyperalgesic state were also described.

A role for the opioid-receptor system in mediating this allodynic/hyperalgesic state was deemed unlikely because the phenomenon was: 1) not reversed by opioid-receptor antagonists; 2) not produced by all opioid agonists tested at a high dose; 3) evoked in a non-stereospecific fashion by various enantiomers; and 4) not cross-tolerant with effects known to be mediated by opioid receptors. It was instead noted that “recent evidence suggests that the excitatory phenomena observed in conjunction with a high opioid dose are most likely mediated by the NMDA receptor system,”21 with recommendations that dose reduction of the causative agent and/or substitution with an opioid agonist or to another class of opioids medication be considered an appropriate next step. Recommendations were for clinicians to be aware of the possibility that opioid therapy, particularly if aggressive in nature, may cause heightened pain sensitivity and may aggravate pre-existing pain, with the disappearance of opioid treatment effects, particularly if coupled with the unexplained expansion of pain complaints, potentially signaling the expression of OIH. Similar statements have been made in other narrative reviews regarding OIH.39,42 There are also additional RCTs regarding this topic; space constraints preclude their inclusion.

Conclusions

The literature regarding the use of opioids in the management of CNMP does not indicate that they consistently and reliably relieve pain. It also overall demonstrates a decrease rather than increase in quality of life and functional status in conjunction with opioid use, especially over the long-run and when opioids are compared to active, non-opioid alternatives. All of the reviews cited have found side-effects such as constipation, nausea, and somnolence to be common; similar complaints (25% dry mouth, 21% nausea, and 15% constipation) were found in a recent systematic review focusing solely on the prevalence of opioid adverse events in chronic pain.43 Given the failure of most studies to follow patients longer than 4 to 8 weeks, the degree to which these particular adverse effects persist subsequently is unclear. Conversely, other adverse effects such as hypogonadism and alterations in cortisol and DHEA levels are more likely to be seen with long-term use. The literature regarding the contribution of opioid-related hyperalgesia to dose escalation and the development of increased, non-localized pain is conflicting; it is likely that genetic and perhaps psychological factors, as well as the nature, dose and chemical structure of the opioid used, all play a role. Adverse effects of opioids when used long-term may explain the overall lack of functional benefit associated with their use.

The prevalence and incidence of tolerance/dependency and addiction solely as a consequence of opioid use cannot be determined, as the quality of the literature is poor with no uniform diagnostic criteria. While selection bias may have excluded patients at risk of dependency or addiction from many opioid trials, it is also possible that any association between these conditions and opioid use reflects the baseline characteristics of patients that develop CNMP, and does not result from opioid use per se. Difficulty in differentiating analgesia due to pharmacodynamic effects of drugs on pain pathways from effects on expectation pathways has been demonstrated,44 while a recent double-blind placebo controlled crossover trial revealed high and moderate levels of psycho-pathology to be associated with heightened placebo analgesia in chronic low back pain patients.45

Gatchell has commented eloquently on the role of psychosocial factors in the genesis of chronic pain.46,47 Turk in discussing the treatment of chronic pain, has stressed the need to pay greater attention to “the important role of pain sufferers’ appraisals, beliefs and expectations” … noting that “enthusiasm for new and innovative pharmacological and physical treatment modalities, and the focus on anatomical and physiological perturbations, often overshadow consideration of the patient within his or her social context.”48 It is therefore possible that the “response” to opioids in certain CNMP patients is predominantly mediated through expectation pathways; concerns regarding the adverse effects of opioids, would clearly be heightened if this were indeed the case. Other functional approaches, as suitable for specific cases, would appear more appropriate.

Given the uncertainty regarding the balance between benefit and risk when opioids are used in managing CNMP and, in particular, in association with their use for chronic musculoskeletal pain, the use of opioids during the sub-acute and chronic phases of an injury, especially in the absence of an objectively identifiable pain generator, cannot be recommended. There is no high-quality scientific evidence that allows for definitive answers to the questions posed at the beginning of this review regarding indications and contra-indications for the use of opioids; criteria with regard to choice of opiate type and dosing frequency; recommended duration of treatment by diagnosis; use of supplemental adjunctive medications as a means of circumventing increased dosage requirements; optimal ways to address concerns regarding dose escalation, tolerance, addiction, and potential drug diversion; or criteria for the discontinuation of opioid therapy, including management strategies for patients on high-dose opioids. Consensus-based answers to these questions are provided in the following Recommendations.
REFERENCES


3. IBID p. 106.


Role of Opioids in the Management of Work Injuries – Part 2: Recommendations

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The preceding summary of high-quality systematic reviews and descriptive epidemiologic studies stated that the use of opioids for subacute and chronic non-cancer pain cannot be routinely recommended unless there is an objectively identifiable pain generator. This judgment reflects a key principle of evidence-based medicine – to refrain from recommending treatment that has not been clearly demonstrated to improve on the natural history of a disorder, especially if potential harms are personally or socially significant. The background prevalence of musculoskeletal pain is estimated at 50% of the U.S. population – chronic pain is estimated to range from 7% to 42%. Routine use of opioids for anyone who reports chronic pain, as recommended by some pain management groups, would lead to opioid use by a large percentage of the adult population. Management of a person presenting with prolonged pain requires understanding and careful consideration. If a chronic pain problem is confirmed, and there is no specific intervention that will cure the problem, then management should be substantially different than for an acute-pain problem. Care of a patient with chronic pain should emphasize functional status and goals, and the means to increase the functional status to meet the patients’ goals. The initial evaluation should ascertain:

- Activity level and abilities, including exercise types and levels.
- Work status or disability in the patient and the family as appropriate.
- Worksite issues contributing to absence from work or limited duty.
- Avocational activities, as well as limitations.
- Treatment goals, including desired functional goals that the patient has currently not met.
- Unreasonable barriers that inhibit the patient from setting higher functional goals.
- Prior musculoskeletal disorders, opioid use and treatment expectations.
- Pain triggers and relievers.
- Quantified current and prior pain and psychoactive medication use.
- Adverse effects of any prescribed medications and review of the impact of these effects on quality of life vs positive effects of prescribed medications on functional status.
- Relationship to stress and other circumstances at home and at work.
- Prior and current alcohol, substance and tobacco use, abuse and dependence.
- Mental illness, including “mild” states of depression that are often only detected on screening questionnaires. This also includes consideration of other relatively common conditions including somatization disorder and anxiety disorders.

The role of the clinician treating a patient with persistent pain complaints should include:

- Understanding and interpreting the pain complaint in the context of the whole person.
- Full discussion/disclosure of: 1) the need to work toward improving the patient’s functional status to meet their avocational and vocational goals; 2) the benefits of all evidence-based therapeutic alternatives designed to improve function, particularly graded aerobic exercise, stretching, and graded strength building in appropriate muscle groups; 3) the presence and adverse effects of catastrophizing; and 4) the role of relaxation techniques.
- Meeting with the patient frequently to encourage increasing levels of physical activity. Setting benchmarks for activities, instead of pain-limited activities.
- Discussion and instruction to the patient concerning the importance and therapeutic benefit of return to work/stay at work in the improvement and maintenance of functional improvement and restoration.
- Coordinating with other providers treating patient, including mental health and family counselors, regarding communicating messages about activity/functional levels, and optimizing the use of medications and other treatments to maximize functional gains.

Subsequent visits should include an update of relevant components from the initial visit with a focus upon:

- Current activities, focusing on objective evidence of improvement/lack of improvement in physical function, since the last visit.
- Current work status, including objectively measurable citations to patient’s level of physical activity at work.
- Medication use (type, dose, route, frequency).
- Adverse effects of medications.
The patient should be informed of logical and consensus recommendations for and against opioid use in the management of acute, subacute, and chronic musculoskeletal pain. Other treatments, management of associated behaviors, and medication discontinuation should also be described. Some summary points from the literature review and supplementary sources deserve reiteration for consideration in the rational clinical decision process:

- There is no high-quality scientific evidence that supports definitive answers to the questions posed at the beginning of the review regarding indications and contra-indications for the use of opioids in musculoskeletal pain beyond acute trauma, or acute post-operative pain.
- In the studies reviewed, the magnitude of pain relief often did not reach clinical significance. Studies of efficacy were generally quite short, making extrapolation to long-term use of opioids impossible.
- Similarly, a review of the literature regarding opioids in the BMJ Clinical Evidence series did not find them more effective than NSAIDs in acute low back pain, and only single studies sponsored by pharmaceutical firms showed slightly better RTW and reduced pain for tramadol (classified as a weak opioid) at 7 weeks and at 3 months. This same series did not find sufficient evidence to assess the efficacy of opioids in neck pain or shoulder pain.
- Patients who complain of musculoskeletal pain beyond the expected period of tissue healing have a high prevalence of concurrent depression, anxiety, personality disorders, somatization, and psychological distress, which affect pain perception and medication use in chronic pain patients, and confuse symptom interpretation and the appropriateness of using opioids.
- Patients with chronic pain tend to catastrophize and typically focus on pain and perceived poor health.
- Chronic pain patients do not have an appreciable rate of return to work. This is not improved by opioid use, and the presence of persistent debilitating musculoskeletal pain has been correlated with compensability and litigation.
- Chronic pain patients exhibit high rates of substance abuse or misuse.
- While observed clinically, there is a lack of epidemiological or prospective cohort information about the prevalence of cognitive disorders, negative effects on exercise adherence, and the extent of addiction and failure to take medications as prescribed.
- The use of opioids in sub-acute and chronic musculoskeletal pain seems less appropriate than cognitive-behavioral therapy (CBT), family therapy, exercise, treatment of psychiatric co-morbidity, and weight loss.
- While the American Heart Association has taken a position against use of NSAIDs and in favor of acetoaminophen, aspirin, and opioids for management of musculoskeletal disorders, this is predominantly with regards to the use of COX-2 inhibitors in patients with, or at risk of, heart disease, as more data were “needed on cardiovascular safety of conventional NSAIDs.” Review of discussion regarding the AHA position paper clearly indicates that it was not to be seen as endorsing indiscriminate use of opioids.

As a result, the treatment of chronic non-cancer pain, and chronic musculoskeletal pain in particular, remains controversial. Given the information summarized above, which is derived from the previous literature review and other well accepted expert sources, and the “first principles” upon which the ACOEM Practice Guidelines are based, we recommend the following:

**Indications for the use of opioids in musculoskeletal pain**

There should be a clear diagnosis supported by objective findings. Low back pain, neck pain, and chronic pain syndrome, to name a few, are not diagnoses per se. Before embarking on any course of treatment that in itself has the potential to become chronic (e.g., narcotic prescribing) for a chronic or persistent pain complaint, the physical and emotional root causes of the complaint should be clearly identified. Given the balance between benefits and harms, the lack of improved efficacy of opioids over NSAIDs in acute low back pain, and the lack of information with regards to other musculoskeletal complaints, opioids should be used in acute musculoskeletal pain only for:

- injuries accompanied by objective findings significant enough to warrant treatment with opioids;
- painful conditions where other medications such as NSAIDs and acetoaminophen are contraindicated in a patient (for example with fractures, post-operatively, with a history of a bleeding diathesis or concomitant anticoagulation); or
- the first 2 weeks following injury/surgery if other medications have failed to control pain.

Infrequently, in chronic pain settings, short-term use of an opioid may occasionally be helpful to facilitate initiation of an active physical rehabilitation plan in patients with objective evidence of deconditioning, increased pain with exercise, and (fear avoidant) chronic pain behavior if other means of temporary reduction in the musculoskeletal pain that increases with exercise, such as heat,

acetaminophen or NSAIDs, are ineffective. In that setting, the judicious, short term use of one non-combination short-acting narcotic like oxycodone or codeine may be indicated. A maximum duration of four weeks is suggested. In the absence of significant progress in rehabilitation, measured objectively by improvements in muscle girth, strength and endurance, and advancement of modified duty, opioids are not indicated. The fear of potential adverse effects from discontinuing opioids in those who clearly do not demonstrate improvements in function or reported pain is not a reason to keep prescribing. Rather, fear of what might be is a clear indication that opioid prescribing is leading to addiction and must be discontinued. The rare situation where a patient derives clear functional benefit from opioid use was the basis for the patient management suggestions contained in the ACOEM Indication that opioid prescribing is leading to addiction and must be discontinued. The rare situation where a patient derives clear functional benefit from opioid use was the basis for the patient management suggestions contained in the ACOEM Practice Guidelines.15 These are elements of a standard pain management contract.

Contraindications for the use of opioids in musculoskeletal pain
Contraindications to the use of opioids include concurrent psychiatric illness and personality disorders.7,16 They are also contraindicated in those with prior history of abuse or dependency. Opioid use in those with psychiatric illness may confound the treatment of the psychiatric disorder, with a low benefit and high risk. If the patient is already using interacting medications (such as antidepressants and other psychiatric medications), opioids should be judiciously considered and used only in the acute phase; they are not advised for use beyond 2 weeks. Clinicians should avoid opioid use in patients with other underlying chronic pain disorders (e.g., fibromyalgia, pelvic pain, myofascial pain, etc.). These disorders are often associated with psychiatric co-morbidity.13 There is no evidence of isolated long-term benefit of opioids in these conditions absent the investment of considerable time and effort in encouraging activity, CBT, and relaxation-based pain management – opioid use may also undo beneficial but hard-won lifestyle changes. High levels of ongoing opioid use without functional improvement represent a treatment failure in the context of functional restoration. There is therefore no benefit and significant risk. In such cases adding other opioids or escalating the dose is not advised.

There are administrative contraindications to opioid use in chronic pain patients who have safety sensitive jobs. Several federally mandated and/or state mandated programs govern certain job circumstances where an employee/patient is precluded from using narcotic preparations while performing job duties. Additionally, companies may, as a matter of policy, preclude employees from using these medications while working, particularly in safety sensitive positions (e.g., operating motor vehicles, operating forklifts or other modes of transportation, operation of overhead cranes, or working in elevated or suspended circumstances with potential of falls.) This may extend to operation of all machinery. Drug diversion is an absolute contra-indication for opioid use. Recommendations regarding the management of patients suspected of drug diversion or misuse are subsequently provided.

Criteria for choice of opiate type and dosing frequency
In circumstances with acute musculoskeletal pain, oxycodone 5 mg or codeine 30 mg every 4 to 6 hours may be used as needed for pain relief. In the infrequent circumstances described above (during active functional and physical restoration of the deconditioned chronic pain patient who has increased pain with activity), one may use oxycodone 5 mg or codeine 30 mg every 4 to 6 hours as needed for musculoskeletal pain following recovery from a period of increased exercise. This should only be done after taking a careful history of prior use of opioids and other psychoactive medications, as well as assessing the patient’s psychiatric co-morbidity and functional status. Most of the time patients decline these medications in favor of NSAIDs and mobilization after an informed discussion. Use of more than one opioid at a time is not indicated. Appropriate follow up for drug response should be frequent. A response in terms of increased function should be seen in a few days.

Stronger medications or higher doses, multiple opioids, combinations with benzodiazepines, ultra-short and long-acting opioid medications are not recommended. The ultra-short-acting narcotics are clearly not indicated. These drugs were approved ONLY for use in patients with cancer pain on high dose around-the-clock narcotics because of their potential to cause a terminal event. They cause almost immediate “highs” which predispose to abuse and are thought to increase the probability of impairments.

We recommend against using any long-acting narcotic formulations for chronic musculoskeletal pain. The literature does not support the long-term use of sustained-release opioid medications for CNMP as there are no long-term studies that show they are safe or effective. We do not know of any studies showing that the use of long-term sustained-release opioids consistently increases function or is associated with return to work in this population. Long acting opioids are also more difficult to medically manage than short-acting opioids. Statements made regarding the lower abuse potential of long-acting vs short-acting narcotics have not been based on comparative studies. Weaning patients from the physical effects of long-acting opioids is more difficult. They may elevate the pain threshold as a result of opioid induced hyperalgesia and increase the peaks of breakthrough pain. There is no research-based pharmacological or clinical reason to prescribe sustained release oxycodone (Oxycontin), methadone, trans-dermal fentanyl (Duragesic), sustained release morphine sulfate (Avinza, Kadian), and similar medications for patients with CNMP.

Having noted the management and medical problems with long-acting opioids, we should also note that many ultra-short and short

acting opioids are psychoactive. Fentanyl citrate (Actiq), hydrocodone (Vicodin, Norco), hydromorphone (Dilaudid), meperidine hydrochloride (Demerol), and several others, act as mood elevators as well as analgesics, and produce a “high” that can result in drug-seeking behavior. Empirically, this may account for intermittent or recurrent use by many patients, as stated in their histories to the authors and others. These patients often request favored narcotic by name and may report “allergies” to generics or other opiate formulations. Other patients have said that these medications calm them. The low following the high from use accounts for continued use in some patients. There are more appropriate medications for depression, anxiety, and lack of energy.

Recommended duration of treatment by diagnosis
There are no data relating specific opioids to specific diagnoses. Given that the objective signs of most acute disorders generally resolve within 1-2 weeks that would ordinarily be the maximal duration of a tapering regimen in conjunction with NSAIDs, heat, mobilization exercises done at home, and graded aerobic exercise done at home. The rare situations in which opioid use may be warranted in patients with chronic pain have already been discussed.

Use of supplemental adjunctive medications
Other medications that are indicated for chronic musculoskeletal pain, as distinguished from neuropathic pain, are intermittent NSAIDs and acetaminophen. It is not clear that the addition of the opioid confers more benefit than the increased risk of inactivity and other problems. Cardiovascular events or hypertension may be associated with use of certain NSAIDs. Therefore blood pressure should be monitored while prescribing these medications, and prolonged or high dose use is best avoided.

Optimal ways to address concerns regarding dose escalation, tolerance, addiction, and potential drug diversion
The patient’s treatment expectations are best set in advance of an abrupt change. For example, the clinician should develop a plan to taper and stop the narcotic. This is done by informing the patient of the rationale, time line, and agreeing on the equivalent of a contract from Day 1 of therapy, indicating that he or she will give prescribe opioids for “X days” only and then will NOT prescribe any more.

Clinicians are cautioned not to agree to requests to extend courses of narcotics unless OBJECTIVE evidence of pathology suggests that the condition is severe enough to warrant such use (i.e. would cause pain severe enough to warrant narcotics in most individuals) and narcotic use clearly leads to increased function. In our experience, “flares” of pain in patients already on opioids represent escalations in use. Escalations are indications for detoxification, as they likely indicate the development of opioid-induced hyperalgesia.

If drug diversion or misuse is suspected, it can be detected in patients receiving prescriptions for chronic opioids therapy by frequent, unannounced urine drug screens using an “expanded panel” drug test which is capable of detecting the presence of the opioids prescribed, and capable of detecting common drugs of abuse. The right of the physician to obtain these drug tests should be agreed to by the patient in the formal, written chronic opioid prescribing contract. If the drug being prescribed does not appear in the patient’s urine, no further prescriptions are indicated. If use of illegal drugs, or sedating/psychoactive drugs not prescribed by the opioid prescribing doctor are detected, further opioid prescriptions are contraindicated.

Criteria for the discontinuation of opioid therapy, including management strategies for patients on high-dose opioids
In the workers’ compensation context, failure to return to work in a timely manner or demonstrate an unequivocal increase in function should be an absolute reason for discontinuation (if the medications were used despite the above recommendations). If a patient is using opioids when he or she enters one’s practice, the overall consensus recommendation was for initiation of a program of CBT coupled with carefully managed functional restoration if specific work-related functional deficits are noted. The patient should concurrently be weaned from the use of opioids. Weaning is best accomplished by immediate conversion to a short-acting narcotic such as oxycodone 5 mg or codeine 30 mg (see above) regardless of dose equivalency per se. Instead we suggest giving patients a reasonable amount of medication to last 2 weeks with instructions to use the medication only for withdrawal symptoms. The process can take several weeks and is initially very labor intensive as all the behavior around drug acquisition is extinguished. Since most people with chronic pain also have depression, the judicious use of an antidepressant is useful during the weaning process, and may also be useful during the active rehabilitation of deconditioning associated with chronic pain. (The choice on an antidepressant may be a bit challenging as tricyclics appear to have activity to decrease pain, but selective serotonin reuptake inhibitors do not have similar activity but have lower side effect profiles.)

A subgroup of patients who have been on long-term high-dose long-acting narcotics will refuse to be weaned. When asked, these patients will acknowledge unwanted adverse effects and admit to the harmful effects of continuing to utilize narcotics, yet remain convinced that they cannot live without them. Consideration may be given to referral to a methadone clinic, where the addiction can be managed in a manner most likely to result in some return to a productive life. In summary, the scientific evidence supports the ACOEM Practice Guidelines’ recommendations against the routine use of opioids in the management of CNMP.

REFERENCES


ADDITIONAL REFERENCES


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