Efficacy of Opioids for Chronic Pain

A Review of the Evidence

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Abstract: Opioid therapy for chronic pain has been popularized over the past few decades, and a concern has arisen that the analgesic efficacy of opioids is not always maintained over prolonged courses of treatment despite dose escalation and stable pain. Considering the potentially serious adverse effects of opioids, the idea that pain relief could diminish over time may have a significant impact on the decision to embark on this therapy, especially in vulnerable individuals. Possible loss of analgesic efficacy is especially concerning, considering that dependence may make it hard to withdraw opioid therapy even in the face of poor analgesia. This article first reviews the evidence on opioid efficacy when used for the treatment of chronic pain, and concludes that existing evidence suggests that analgesic efficacy, although initially good, is not always sustained during continuous and long-term opioid therapy (months to years). The theoretical basis for loss of analgesic efficacy over time is then examined. Mechanisms for loss of analgesic efficacy proposed are pharmacologic tolerance, opioid-induced hyperalgesia, subtle and intermittent withdrawal, and a number of psychologic factors including loss of the placebo component.

Key Words: opioids, chronic pain

(*Clin J Pain* 2008;24:469–478)

Opioids were used to treat pain to the limits of their availability until the introduction of regulations put the brakes on opioid use and physicians' opioid prescribing. In the United States and other industrial nations, this happened at the beginning of the 20th century. Active lobbying eventually reestablished opioid treatment for acute and terminal cancer pain, and evidence was quickly gathered supporting not only opioids' unique analgesic efficacy, but also very low risks of addiction in these populations.[1–3] The reestablishment of opioid treatment for chronic pain was delayed partly by the belief that chronic pain conditions were not responsive to opioids; this was also a convenient reason to deny opioid treatment to patients with chronic pain conditions. This reasoning allowed physicians to avoid the much more difficult issue of whether, in the case of long-term outpatient pain treatment, opioid dependence and abuse would interfere to the extent that the treatment would make lives worse rather than better.

During the past 20 years or so, opioids have been used increasingly to treat chronic pain; currently an unprecedented number of patients are receiving long-term opioids. Some are clearly doing well with improvements in both pain and quality of life (QOL). But there are also patients in this population failing the treatment. There are many unanswered questions about who should be selected for treatment, how the treatment should be structured, which drugs, formulations, and doses are optimal, whether analgesic efficacy is maintained, or whether function and QOL overall are improved, and if so, by what exact regime.

Today's expectation is that there will be evidence to support treatments, whether this consists of known historic success, the consensus of experts, or evidence from trials. In terms of historic accounts, although few early accounts could be called "scientific," many descriptions can be found in the general literature of the addiction of Victorian laudanum users (especially middle-class women with neither a domestic or social role, who used laudanum to treat their minor aches and pain), descriptions that must inevitably have influenced medical practice and caution regarding opioid treatment of chronic pain. In terms of expert opinion, there are deep rifts on the matter of whether and how opioids should be used to treat chronic pain. Because there is neither a strong history of success of opioids for chronic pain nor strong unchallenged expert opinion supporting the therapy, there is a clear need for trials. Thus, when opioid treatment of chronic pain became popular during the closing decades of the 20th century, this triggered a huge increase in the number of randomized trials of opioids for chronic pain conditions.[4]

Despite the clear and urgent need to find evidence to validate opioid treatment of chronic pain, assimilating this evidence has proved difficult. First, there is no agreement as to primary outcome—should this simply be pain relief, or is function more important, or QOL, or patient satisfaction? As it has become obvious clinically that short-term analgesic efficacy does not necessarily predict long-term analgesic efficacy, this presents difficulties in terms of what form of evidence can be used to assess long-term effects given the practical constraints on

Received for publication January 27, 2008; accepted January 28, 2008.
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TABLE 1. Controlled Studies: Summary of Results

Reference	Study Type	Type of Pain	n/N	Drug	Daily Dose (mg)	Follow-up	Pain Relief	Level of Function
Kjaersgaard et al[7]	RCT	Osteoarthritis of the hip, in elderly patients	83/75	Codeine with acetaminophen vs. acetaminophen	180	4 wk	+	
Moran et al[8]	RCT, crossover	Rheumatoid arthritis	20	CR morphine vs. placebo	Up to 120	10 wk	+	0
Arkinstall et al[9]	RCT	Musculoskeletal in most patients	46	CR codeine vs. placebo	200-400	1 wk	+	+
Moulin et al[10]	RCT, crossover	Musculoskeletal or soft tissue	46	CR morphine vs. active placebo (benztropine)	Up to 120	11 wk	+	0
Jamison et al[11]	RCT	Back pain	24/12	Oxycodone or CR morphine plus oxycodone vs. naproxen	Up to 130 mg (morphine equivalent)	16-32 wk	+	+
Sheather-Reid et al[12]	RCT, crossover	Cervicobrachial syndrome, fibromyalgia	6	Codeine vs. ibuprofen or placebo	120 mg	12 wk	0	0
Watson and Babul[13]	RCT, crossover	Postherpetic neuralgia	38	CR oxycodone vs. placebo	28-62 mg	8 wk	+	+
Caldwell et al[14]	RCT	Osteoarthritis	71/36	CR oxycodone or oxycodone with acetaminophen vs. placebo	Up to 60 mg	8 wk	+	+
Peloso et al[15]	RCT	Osteoarthritis hip and knee	31/35	CR codeine vs. placebo	Up to 400 mg	4 wk	+	+
Roth et al[16]	RCT	Osteoarthritis	44/(44)/45	CR oxycodone, high dose (or low dose) vs. placebo	Up to 40 mg	14 wk	+ (0)	+ (0)
Huse et al[17]	RCT, crossover	Phantom limb pain	12/12	CR morphine vs. placebo	70-160 mg (300 mg in one patient)	4 wk	+	0
Caldwell et al[18]	RCT	Osteoarthritis	73/73/76/73	CR morphine (24 h) or CR morphine (12 h) vs. placebo	30 mg	4 wk	+	0
Maier et al[19]	RCT, crossover	Mixed	49	CR morphine vs. placebo	Up to 180 mg	2wk	+	+
Raja et al[20]	RCT, crossover	Postherpetic neuralgia	76/44	CR morphine or methadone vs. placebo (or tricyclic antidepressant)	15-225 mg morphine, 40-140 mg methadone	8-24 wk	+ (0)	0
Gimbel [21]	RCT	Diabetic neuropathy	63/52	CR oxycodone vs. placebo	20-120 mg	6 wk	+	+
Morley et al[22]	RCT, crossover	Mixed neuropathic	11/(18)	Methadone high dose (or low dose) vs. placebo	20 mg (10 mg)	20 d	+ (0)	
Rowbotham et al[23]	RCT	Peripheral and central neuropathic pain	43/38	High-dose levorphanol vs. low-dose levorphanol	Up to 11.8 mg (approximately 60 mg morphine equivalent)	8 wk	+	0
Watson et al[24]	RCT, crossover	Diabetic neuropathy	35/36	CR oxycodone vs. active placebo (benztropine)	10-40 mg	4 wk	+	+
Hale et al[25]	RCT	Chronic low back pain	71/75/67	CR oxymorphone or oxycodone vs. placebo	20-220 mg (oxymorphone), 40-440 mg (oxycodone)	3 wk	+	+
Markenson et al[26]	RCT	Osteoarthritis	56/51	CR oxycodone vs. placebo	20-120 mg	13 wk	+	+

Matsumoto [27]	RCT	Osteoarthritis	114/(114)/120/119	CR oxymorphone high dose (or low dose) or CR oxycodone vs. placebo	40-80 mg (20-40 mg) oxymorphone, 20-40 mg oxycodone	3 wk	+(+)0	+(+)0
Kivitz et al[28]	RCT	Osteoarthritis of hip and knee	87/91/92/87	CR oxymorphone high dose or (low dose 1) or low dose 2 vs. placebo	40-100 mg (40-80 mg) 20 mg	2 wk	+(+)0	+(+)+
Webster et al[29]	RCT	Chronic low back pain	199/(204)/205/101	Oxytrex q.i.d. (or b.i.d.) or oxycodone vs. placebo	10-80 mg (10-80 mg) Oxytrex, 10-80 mg oxycodone	12 wk	+(+)+	+(+)+
Hale et al[30]	RCT	Chronic low back pain	70/72	CR oxymorphone vs. placebo	30-100 mg	12 wk	+	
Katz[4]	RCT	Chronic low back pain	100/106	CR oxymorphone vs. placebo	10-140 mg	12 wk	+	
Portenoy et al[31]	RCT, crossover	Chronic low back pain	77/77	Fentanyl buccal tablet vs. placebo	0.1-0.8 mg	2 h	+	+

A plus sign denotes a statistically significant positive difference, and 0 no statistically significant difference compared with placebo. Where 2 numbers are given, the first is the number of patients in the experimental group and the second is the number in the control group.
Parentheses link treatment with outcome when more than 2 treatment groups are included in the study.
CR indicates controlled release. Study drugs not labeled CR are immediate-release preparations; Oxytrex, oxycodone with ultra low-dose naltrexone; RCT, randomized-controlled trial.

conducting long-term randomized trials. The complexities of pain and opioids, and the significant biopsychosocial influences on pain and pain relief, make assessments on the basis of simple pain measures less useful for predicting overall treatment success. Analgesic efficacy, as demonstrated in randomized trials, does not necessarily predict effectiveness in terms of the larger real-life goal of providing helpful pain relief that is not compromised by adverse drug effects. Differences in handling opioids between patients often confound opioid trials.[4] These factors are not fully understood, but could be related to pharmacogenetic effects, sex effects, concomitant medications, or the opioid responsiveness of the underlying pain conditions. Finally, one must ask if the randomized trial really is the best form of evidence for assessing opioid treatment of chronic pain given the artificiality of the trial setting, the tendency of trials to select "ideal" patients, and the lack of generalizability to the wider population that is being treated outside trials.[5,6]

EVIDENCE

Randomized-controlled Trials

The randomized-controlled trials (RCTs) that began coming out in the literature in the 1990s were conducted to test the analgesic efficacy of opioids for various chronic pain conditions, including the arthritides and various neuropathic pain conditions. This was with the background that there had long been a sense (unproven) that chronic pain conditions, notably neuropathic pain conditions, were not sensitive to opioids. The suitability of opioids, compared with nonsteroidal anti-inflammatory drug treatment for arthritic pain, was also under question. Table 1 lists these trials and summarizes their results.[7–31] Measured pain scales from the RCTs show a statistically significant improvement across all the studies, both in the case of painful arthritides and neuropathic pain. The randomized studies also make it clear that contrary to traditional belief, neuropathic pain is opioid responsive, although larger doses are required than those needed to treat nociceptive pain.[13,17,20–24,32] It should be noted that the randomized trials are conducted only over the short-term (usually weeks, although 1 trial reached 32 wk),[11,33] and that the doses used in these trials are generally moderate (up to 180 mg morphine or morphine equivalent per day).[34–37]

The RCTs provide mixed results on function (Table 1); some find improvement, others do not. The focus of the functional testing in studies varies with the primary interest of the investigators—for example, physical function (Fries index), joint tenderness (Ritchie score), activity levels and grip strength for arthritis patients (Grip Strength Score), sleep, anxiety, psychomotor function, and disability scores for back pain patients (Oswestry Low Back Disability Score, Brief Pain Inventory). The findings on function from the RCTs are therefore limited because they assess only short-term (initial) effects on function, with a focus on specific functional goals, not necessarily extended to general functionality.

To provide an overview of the RCTs, some authors have conducted meta-analyses and systematic reviews. The earliest of these by Kalso et al[35] analyzed RCTs conducted for up to 8 weeks. Short-term analgesic efficacy was good in both neuropathic and musculoskeletal pain groups, but only a minority of the patients in the studies chose to continue opioid therapy. Eisenberg et al[38] specifically studied trials of opioids for neuropathic pain, finding significant analgesic benefit overall in 8 trials assessing nonparenteral therapy used for up to 28 days, thus substantiating the efficacy of opioids for neuropathic pain. Devulder et al[34] conducted a systematic review with the primary goal of assessing function and QOL. Open-label observational studies were included with RCTs in this systematic review, with the blinded RCTs (5/11 studies) being conducted for up to 12 weeks, others up to 48 months. Conclusions about analgesic efficacy cannot be derived from these analyses, but function and QOL showed improvement overall. However, the authors allow that the quality of many of the trials contributing to these analyses is low. In 2006, Furlan et al[36] published a meta-analysis assessing effectiveness and side effects of opioid for chronic pain. They included 41 RCTs and 6019 patients, treated for up to 16 weeks. Interestingly, they were able to show that pain relief overall was improved by strong opioids but not by weak opioids or nonopioids, whereas function was improved by weak opioids and nonopioids, but not by strong opioids. The latest systematic review by Martell et al,[37] which assessed opioid therapy for chronic back pain, included 6 RCTs comparing opioids to placebo or nonopioid control, 4 of which were used in a meta-analysis that found no reduction in pain with opioids. No study in this systematic review was conducted beyond 16 weeks.

The RCTs provide strong evidence that opioids provide initial relief for chronic pain conditions. However, because RCTs cannot be conducted over prolonged periods, this methodology is not useful for assessing long-term effects of the treatment. Open-label follow-up studies in association with some RCTs provide some insight into longer-term opioid utility.[35,39] These report satisfactory analgesia for all patients who stay on the treatment. Reviews of the open-label follow-up studies, however, have shown that up to 56% of patients abandon the treatment because of lack of analgesic efficacy or side effects.[35,36]

Observational Studies

Before the recent increase in the conduct and publication of RCTs of opioids for chronic pain, the literature that was used to provide support for the treatment consisted of surveys and uncontrolled case series, and was generally positive.[40–50] The most common finding of these reports is that patients with chronic pain achieve satisfactory analgesia using a stable (nonescalating) dose of opioids, with minimal risk of developing addiction. Reported length of treatment is up to 6 years. In most cases, doses fall into a "moderate" range (up to 195 mg morphine or morphine equivalent per day). A more recent prospective observational study (open-label follow-up to prior controlled trials) conducted for up to 3 years finds sustained opioid analgesic efficacy with only modest dose escalation in the minority of patients (39/174) who choose to continue opioid therapy.[51] Whether long-term opioid treatment can improve patients' function or QOL is clearly a broader issue than whether opioids can reduce a pain score. Surprisingly, only a few of the early reports focus on this issue. The few that do assess functionality through patients' self-report, most reporting improvement.[42,44,48] Several more recent, prospective case series report on function, and are conducted for up to 48 months. These studies predominantly report improvement, although the quality of the studies is low.[34,52–55]

The majority of observational studies used to support opioid treatment of chronic pain have been reports of practice from single practice settings. This type of study clearly has a tendency to be biased. Bias may be a particular problem in reports of opioid treatment for chronic pain because the authors are strong advocates of the treatment, and by their own reports, provide the treatment in a careful and structured manner, not often reproduced in busy nonspecialist practice settings. At the same time, devotion and attentiveness to these patients may do as much to help them through their painful existence as any drug. As Portenoy and Foley,[40] authors of an early and influential report themselves say: "*It must be recognized, therefore, that the efficacy of this therapy and its successful management may relate as much to the quality of the personal relationship between physician and patient as to the characteristics of the patient, drug, or dosing regime*." Larger, carefully planned, population-based observational studies, preferably with controls, are needed to help identify the true incidence of both favorable and unfavorable outcomes in a broader population than can be included in RCTs and single practice case series, yet in a more controlled situation that can be assumed by epidemiologic studies.[56]

Epidemiologic Studies

Seeing the need to supplement the information from their own prospective cross-sectional studies,[57–59] a Danish group of investigators recently published one of the first population-wide epidemiologic studies to assess outcomes of opioid therapy for chronic pain compared with a matched cohort of patients with chronic pain not receiving opioids.[60] A total of 1906 patients were included in this study. Denmark is among the most liberal in prescribing opioids for chronic pain, and has the highest per capita usage of prescription opioids in the world, most being used for chronic (noncancer) pain.[60,61] The findings of this study are at once surprising and worrying. Opioid users reported significantly more moderate to severe or very severe pain, poorer self-rated health, and lower QOL scores than nonusers. There were also significant associations between opioid use and low levels of physical activity and employment, and high levels of healthcare utilization. Even after controlling for pain

severity, most of these associations persisted. Epidemiologic studies can only identify associations and cannot assess causation. Nevertheless, this study suggests that when opioids are widely used to treat chronic pain, as they are in Denmark, a substantial number of patients do not achieve the chief goals of the treatment to improve pain, function, and QOL. More large and population-based studies are currently in progress and under review, and are likely to add to the work of Eriksen et al.[60] Although epidemiologic studies do not help in identifying which patients benefit from opioid treatment or how the treatment should be structured to achieve the best outcomes, they do suggest that not all patients benefit, and that therefore patients should be selected and managed carefully.

Summary and Limitations of the Evidence

The question of whether opioids are efficacious for the treatment of chronic pain is not simple, and presents many challenges in terms of providing an evidence base to support the treatment. Is the primary concern that opioids should provide adequate analgesia? If so, how can studies be designed to test the ability of opioids to provide good long-term relief from chronic pain? RCTs are considered "best evidence," yet in the case of assessing the effectiveness and suitability of long-term opioid therapy, they play only a limited role. Because of the impracticalities of conducting randomized trials over prolonged periods, they test only short-term effects, or the initiation of therapy. In general, RCTs are setup to test specific drugs in specific disease states. Outcomes measured by RCTs tend to be outcomes that lend themselves to metric measurement, primarily pain or pain relief scores, sometimes function scores or QOL scores. Often factors that could confound the results of trials assessing effectiveness, such as addiction, serve as exclusion criteria, although they are part of the reality of long-term opioid pain treatment. There are tremendous difficulties assessing addiction risk because there is little agreement about what constitutes iatrogenic opioid addiction,[62] and the occurrence is possibly rare enough that it may only be determined in large population-based studies, where there has been no exclusion of patients at risk.[6] Enrichment protocols used to increase trial sensitivity, also reduce the internal validity of trials, making them less generalizable.[4] Randomized trials, because of the limitations imposed on them by trial methodology, can both underestimate and overestimate the benefit of opioid treatment.[4] In the end, RCTs tend to be useful only for showing efficacy for certain pain conditions, only for the length of the trial which tends to be short (up to 8 mo), and only in terms of the metrics of the trials.

Much more difficult is the question of whether analgesic efficacy is satisfactorily maintained over the long term, and if long-term treatment achieves the overarching goal of effectiveness-improving lives, whether by improving pain or function or well-being or QOL. For the reasons outlined above, RCTs have a limited role in making these assessments. Existing observational studies, which, with the exception of a few recent larger multicenter trials,[51,53,54] have tended to be case reports and case series, provide evidence that in structured treatment settings, the treatment can be effective, with patients reporting good pain relief and good function.[33,63] In fact, the medical community was encouraged to pursue opioid therapy for chronic pain largely on the basis of early favorable reports, which predated both the RCTs, and recent larger observational and epidemiologic studies. Yet a recent large community-wide epidemiologic study, in a population in which opioids are widely prescribed for chronic pain, suggests that in a large proportion of treated patients, opioid effectiveness is not maintained over time and goals of treatment are not met. This, and other accumulated evidence about loss of analgesic efficacy over time,[64–68] opioid refractoriness in opioid treated patients and failure to overcome tolerance with dose escalation,[69–73] suggests a need to try and understand why analgesic efficacy may not be maintained, how it can best be preserved, and what exact circumstances predict successful treatment.

THEORETICAL BASIS FOR ANALGESIC FAILURE

Whatever one's belief concerning the underlying purpose of opioid pain treatment—to improve pain, to improve function, to improve QOL, or to produce patients who are content with their treatment—the underlying premise of opioid treatment of pain is that it will improve pain. As can be seen from a review of trials and studies, improvements in pain are not necessarily accompanied by improvements in function,[33] just as improvements in patients' well-being and satisfaction are not necessarily accompanied by improvements in pain.[74] One could argue that as long as the opioid treatment improves lives, as it does for the treatment of established opioid addiction—a fact that is based on 30 years experience of opioid maintenance for the treatment of addiction and is well documented[75,76]—pain relief per se is not important. However, as long as the basic premise of opioid treatment for pain is that it relieves pain, it is important to establish that analgesic efficacy is maintained during long-term treatment. Analgesic tolerance is a well-recognized phenomenon known to reduce analgesic efficacy unless compensated for by increasing dose. Although dose escalation works well in the short term, several lines of evidence suggest that during long-term treatment, opioid analgesic efficacy is not always satisfactory. This prompts the question why would analgesic efficacy decline?

Pharmacologic Tolerance

It has long been observed that marked tolerance develops to the hedonistic (euphoric) effects of opioids. In fact, tolerance, and the need to take increasing doses to achieve intoxication or the desired effect, characterizes opioid addiction (and addiction to several other substances).[77] Tolerance to the analgesic effects of opioids is far less obvious, to the extent that some clinicians argue

that there is no pharmacologic tolerance to the analgesic effects of opioids. This is on the grounds that after initial titration, there may be stable analgesia with no need for dose escalation. Yet the need for escalating doses in the absence of disease progression is also observed,[64,65] as is the need for higher than usual doses when acute pain arises in patients receiving chronic opioid treatment.[69–73] Supporting a pharmacologic mechanism for opioid analgesic tolerance, animal studies of reflex pain responses (absence of influence from higher centers) show marked analgesic tolerance[78–80]; classic studies in humans also show the effect[66]; and it is known that opioid-induced adaptations occurs at multiple locations and at multiple levels in the nervous system including pain-related areas, and involve direct drug effects (pharmacologic component) as well as a psychologic (associative or learned) effects.[78,81,82] This is a clinical controversy that is not resolved.[83–85]

The underlying mechanisms of tolerance remain elusive, despite intensive efforts to understand the phenomenon, given its implications in pain management. Cellular and molecular mechanisms of pharmacologic (physiologic) tolerance to opioids have not been fully elucidated but may involve receptor internalization, recycling, desensitization, or down-regulation.[86–89] Many studies have implicated the *N*-methyl-D-aspartate–receptor in opioid tolerance, although other receptors and systems could also be involved.[86,90–93] Spinal dynorphin mechanisms have also been implicated in the development of opioid analgesia tolerance.[94,95] Several endogenous peptides oppose the analgesic effects of opioids, and are therefore termed *antiopioid peptides*. These include vasopressin, oxytocin, nociceptin, and cholecystokinin.[96–98]

Opioid-induced Hyperalgesia

Withdrawal hyperalgesia—that is hyperalgesia arising during withdrawal from opioids—has long been recognized as part of the constellation of symptoms of the opioid withdrawal syndrome.[99] More recently, though, there has been renewed interest in the phenomenon of opioid-induced hyperalgesia, as the phenomenon has been observed not only during withdrawal, but also during opioid treatment.[67,68,70,100–103] This was first observed in methadone maintained addicts,[101,104–106] but more recently it has been recognized as a phenomenon with potential clinical implications during the treatment of pain with opioids. For example, patients treated with potent or high-dose opioid infusions display hyperalgesia with characteristic skin sensitivity (allodynia) that resolves once the infusion is weaned.[107–109]

It is seen, then, that repeated opioid administration results not only in the development of tolerance (a desensitization process), but also a pronociceptive process (a sensitization process). Although the relative contribution of each is not yet clear from animal or human studies, the latter may exacerbate and confound pharmacologic tolerance. Collectively, both desensitization and sensitization from prolonged opioid therapy may contribute to an apparent decrease in analgesic efficacy, regardless of the progression of the pain.[110] Hyperalgesia is a testable phenomenon (eg, using quantitative sensory testing), but clinically is not always easy to distinguish from pharmacologic tolerance. Thus, a decrease in analgesic efficacy, that is, the development of *apparent opioid tolerance,* could be the result of pharmacologic opioid tolerance, opioid-induced abnormal pain sensitivity and disease progression.[33,102,110–112] Much work needs to be done to elucidate the mechanisms and circumstances of opioid-induced hyperalgesia. It is already clear, though, that hyperalgesia represents part of the spectrum of neuroadaptations that arise during opioid use, and that the phenomenon may interfere with opioid efficacy under some circumstances.

Withdrawal

The opioids are one of several classes of drugs that produce a characteristic withdrawal syndrome. Opioid withdrawal is unpleasant, and produces both physical and psychologic symptoms that are seen as powerful drivers of opioid-seeking behaviors.[113–115] *Dependence* is the term used for the state of habitual use that will result in a withdrawal syndrome upon withdrawal of the drug. Physical dependence is the manifestation of compensatory adaptations in brain regions that control somatic functions: in the case of opioids an important region affected is the noradrenergic nucleus the locus coeruleus.[113,116] Symptoms of opioid withdrawal include central neurologic arousal and sleeplessness, irritability, psychomotor agitation, diarrhea, rhinorrhea, and piloerection, and seem to result, at least in part, from an up-regulation of cyclic adenosine monophosphate and noradrenergic mechanisms in the locus coeruleus or other brain regions.[117,118] Hyperalgesia is another component of the physical withdrawal syndrome, but this may not be related to noradrenergic mechanisms.[99]

Psychologic dependence must be distinguished from *physical dependence*. Psychologic dependence is manifest as the psychologic component of withdrawal, which comprises both unpleasant emotional effects (withdrawal anhedonia and dysphoria)[82,114,115,119] and motivational effects (craving during withdrawal), the latter being partly mediated by physical withdrawal.

The symptoms of withdrawal, whether physical or psychologic, are powerful drivers of opioid-seeking and *apparent opioid tolerance*.[113–115] The symptoms that accompany withdrawal and drive up opioid doses can easily be interpreted as inadequacy of pain relief. In fact, it is probable, as it is well established that symptoms such as depression, dysphoria, and hyperalgesia, can worsen the underlying pain syndrome,[120–124] that these symptoms have an effect also on measured pain scores. These effects might be particularly noticed after prolonged opioid therapy, when, as is well established in the addiction population, the positive reinforcing effects of opioids such as euphoria (and possibly analgesia) diminish, so opioid seeking become largely driven by the negative reinforcing effects of withdrawal.[114,115,125–128]

Psychologic Factors

It is important also, to remember the powerful effect of placebo during pain treatment, estimated to contribute approximately 15% to 53% of the analgesic effect of most pain treatments.[129] This placebo component likely diminishes over time, particularly as pain becomes more difficult to treat, higher doses are needed because of the development of dependence and tolerance, and patients lose confidence in the ability of their treatment to relieve them of their pain.[130,131] Part of this effect will be attributable to *associative* or *learned* drug tolerance. In addition to the pharmacologic (*nonassociative* or *physiologic*) tolerance described above, there is also a psychologic (*associative* or *learned)* component to drug tolerance. In the case of opioids, tolerance develops to the drugs' analgesic and hedonistic effects, as well as to their side effects, and each component is likely to arise through distinct mechanisms related to the anatomic or neuroanatomic substrate of the different effects.[82,117,119] *Associative tolerance* (which can arise in the case of all the central effects of opioid including euphoria and dysphoria, sedation, analgesia, and nausea) involves learning, and its development is linked to environmental or contextual cues.[132,133] Thus, opioid analgesia can change according to powerful psychologic drivers, learned behaviors, circumstances, and environment. For example, dangerous respiratory depression may arise if habitual heroin users are given equivalent opioid doses to treat acute surgical pain; the different circumstance produces a different level of tolerance.

CONCLUSIONS

Opioid drugs commandeer an endogenous system that is integral and vital to the body's responses to stressful and painful situations. It is not surprising, then, that both opioid drugs and endogenous opioids produce complex effects that are enmeshed with emotional, affective, and psychophysical function, and therefore difficult to understand. These complexities are particularly obvious during long-term treatment with opioids, when neuroadaptations alter normal homeostasis. The "experiment" of extending opioid treatment to patients with chronic pain during the last 2 decades has revealed many unanswered questions about whether and how this treatment should be provided. There are many issues such as whether the risk of developing aberrant and destructive behaviors is acceptable, whether treatment goals are likely to be met, whether it is advisable to exclude certain patients from chronic opioid treatment, whether the development of opioid analgesic refractoriness is clinically important, and whether analgesic efficacy is maintained over time. Many of these issues are explored in this edition of the *Clinical Journal of Pain*, whereas the present article has focused specifically on the issue of the effectiveness of opioids for chronic pain, whether effectiveness is maintained, the evidence supporting effectiveness and in particular, maintenance of analgesic efficacy, and evidence for mechanisms whereby opioid analgesic efficacy might decline. It can be concluded from this review that there is strong evidence to support the initial effectiveness of opioids for the treatment of chronic pain, with much less clarity about long-term effectiveness. There is much left to be learned about the mechanisms of analgesic decline, the specific treatment paradigms and drugs that might preserve analgesic efficacy, and the role of psychosocial factors in changing analgesic efficacy. This knowledge will come from the combined efforts of basic scientists and clinical researchers, with an emphasis on unraveling basic mechanisms and genetic contributions, whereas on the clinical side, conducting careful population-based studies to assess the true impact and sustainability of chronic opioid treatment.

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