

Published in final edited form as:

Exp Clin Psychopharmacol. 2008 October ; 16(5): 405–416. doi:10.1037/a0013628.

Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions

Andrew Rosenblum^{1,*}, Lisa A. Marsch¹, Herman Joseph¹, and Russell K. Portenoy²

¹National Development and Research Institutes (NDRI); 71 West 23rd Street; 8th Floor; New York, NY 10010.

²Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, First Avenue at 16th Street, New York, NY 10003.

Abstract

Opioids have been regarded for millennia as among the most effective drugs for the treatment of pain. Their use in the management of acute severe pain and chronic pain related to advanced medical illness is considered the standard of care in most of the world. In contrast, the long-term administration of an opioid for the treatment of chronic non-cancer pain continues to be controversial. Concerns related to effectiveness, safety, and abuse liability have evolved over decades, sometimes driving a more restrictive perspective and sometimes leading to a greater willingness to endorse this treatment. The past several decades in the United States have been characterized by attitudes that have shifted repeatedly in response to clinical and epidemiological observations, and events in the legal and regulatory communities. The interface between the legitimate medical use of opioids to provide analgesia and the phenomena associated with abuse and addiction continues to challenge the clinical community, leading to uncertainty about the appropriate role of these drugs in the treatment of pain. This narrative review briefly describes the neurobiology of opioids and then focuses on the complex issues at this interface between analgesia and abuse, including terminology, clinical challenges, and the potential for new agents, such as buprenorphine, to influence practice.

Introduction

Opioids play a unique role in society. They are widely feared compounds, which are associated with abuse, addiction and the dire consequences of diversion; they are also essential medications, the most effective drugs for the relief of pain and suffering (Portenoy et al, 2004). Historically, concerns about addiction have apparently contributed to the undertreatment of disorders widely considered to be appropriate for opioid therapy, including cancer pain, pain at the end-of-life, and acute pain (Field and Cassel, 1997; Schnoll & Weaver, 2003; Portenoy & Lesage, 1999; Breitbart et al. 1998; Smith et al., 2008). The use of opioids for chronic non-malignant pain (CNMP) remains controversial (Manchikanti, 2008; McQuay, 1999). Following publication of reports on the safety and efficacy of opioids prescribed to small numbers of patients with CNMP (e.g., Portenoy and Foley, 1986; Nyswander and Dole, 1986) and the publication of a seminal article entitled “The Tragedy of Needless Pain”, (Melzack, 1990), the use of opioids to treat CNMP began to be more widely practiced and incorporated into clinical guidelines. Nevertheless, despite the advances in pain medicine and the wider use of opioids for various chronic pain conditions, there is still considerable controversy surrounding the type of conditions that should be treated, whether the treatment

*Corresponding author; E-mail: Rosenblum@ndri.org.

can be generally safe and effective in selected patients, and what the clinical goals should be (Ballantyne & Forge, 2007; Stretzler & Johansen, 2006; Stretzler & Kosten 2003).

History of Opioids

The Sumerians in Mesopotamia were among the first people identified to have cultivated the poppy plant around 3400 BC. They named it *Hul Gil*, the “joy plant” (Booth, 1986). It eventually spread throughout the ancient world to every major civilization in Europe and Asia and was used to treat pain and many other ailments (Schiff, 2002; Askitopoulou, Ramoutsaki, & Konsolaki, 2002; Booth, 1986; Dikotter, Laaman, & Xun, 2004).

Developments in the 19th century transformed the practice of medicine and initiated the tension between the desire to make available the medicinal benefits of these drugs and recognition that the development of abuse and addiction can lead to devastating consequences for individuals and for society at large (Booth, 1986; Musto, 1999):

- In 1803 morphine, an opioid analgesic, was extracted from opium by Friedrich Serturner of Germany;
- Dr. Charles Wood, a Scottish physician, invented the hypodermic needle and used it to inject morphine to relieve pain from neuralgia;
- Dr. Eduard Livenstein, a German physician, produced the first accurate and comprehensive description of addiction to morphine, including the withdrawal syndrome and relapse, and argued that craving for morphine was a physiological response.
- Diacetylmorphine (brand name heroin) was synthesized and briefly promoted as more effective and less addictive than morphine. In the early 20th century, when heroin was legally marketed in pill form, it was used by young Americans to elicit intense euphoria by crushing the heroin pills into powder for inhalation or injection (Katz et al., 2007, c.f. Meldrum, 2003; Hosztafi, 2001).

Beginning in the twentieth century, there were many research advances and major changes in the way opioids were used for the treatment of pain and addiction (Ballantyne, 2006; Corbett et al., 2006). These included attempts among several nations and international organizations to control the distribution and use of opioids (Musto, 1999); the introduction of opioid maintenance therapy for the treatment of opioid addiction (first with morphine and later with methadone, LAAM (levo-alpha acetyl methadol) and sublingual buprenorphine) (Courtwright, Joseph & Des Jarlais, 1989; Strain & Stitzer, 2006); the discovery of the endogenous opioids (Hughes, Smith, Kosterlitz, Fothergill, Morgan & Morris, 1975); and the recognition that pain is a debilitating and destructive disease and that opioids are essential for the treatment of many forms of acute and chronic pain.

During most of the twentieth century, the widely held perception among professionals in the United States was that the long-term use of opioid therapy to treat chronic pain was contraindicated by the risk of addiction, increased disability and lack of efficacy over time. During the 1990's, a major change occurred, driven by a variety of medical and nonmedical factors (see below). The use of opioids for chronic pain began to increase, showing a substantial year-to-year rise that continues today. This increased use of opioids for legitimate medical purposes has been accompanied by a substantial increase in the prevalence of nonmedical use of prescription opioids (Zacny, et al., 2003). The National Survey on Drug Use and Health reported that the number of first time abusers of prescription opioids increased from 628,000 in 1990 to 2.4 million in 2004, that emergency room visits involving prescription opioid abuse increased by 45% from 2000 to 2002, and that treatment admissions for primary abuse of prescription opioids increased by 186% between 1997 and 2002 (SAMHSA, 2004a, 2004b).

Opioid abuse indices rose most for two frequently prescribed opioids, hydrocodone and controlled-release (CR) oxycodone (Cicero, Inciardi, Munoz, 2005). Although the increase in prescription drug abuse is likely to be multifactorial, it is likely to reflect, in part, changes in available drug formulations and prescribing practices of opioid medication (Compton and Volkow, 2006). This link between increased medical use and increased abuse has driven some of the re-examination of the medical role of these drugs. The challenge, of course, is to reduce the likelihood of opioid misuse while not imposing barriers on the legitimate use of opioid medications, acknowledging both that increased abuse is probably inevitable when a psychoactive drug becomes more accessible and that attempts to control abuse can have the unintentional effects of discouraging treatment and placing severe restrictions on the medical profession.

Brief Overview of Opioids: Neurobiology and Mechanism of Action

The term *opioid* refers to all compounds that bind to opiate receptors. Conventionally, the term *opiate* can be used to describe those opioids that are alkaloids, derived from the opium poppy; these include morphine and codeine. Opioids include semi-synthetic opiates, i.e., drugs that are synthesized from naturally occurring opiates (such as heroin from morphine and oxycodone from thebaine), as well as synthetic opioids such as methadone, fentanyl, and propoxyphene. The term *narcotic* is a legal designation and should not be used in the clinical setting; it refers to opioids and a few other drugs that are grouped with the opioids by law enforcement.

In the United States, numerous opioids have been commercialized for oral, transdermal and intravenous administration. Oral and transdermal formulations are usually administered for pain in the ambulatory setting. These include combination products, such as those containing hydrocodone and acetaminophen (Vicodin®, Lorset®) or ibuprofen (Vicoprofen®), tramadol and acetaminophen (Ultracet®), oxycodone and acetaminophen or aspirin (Percocet® or Percodan®), and those containing codeine and acetaminophen or aspirin. The single entity formulations on the market include those containing morphine (Avinza®, Kadian®, MS Contin®, MSIR®), oxycodone (OxyContin®), fentanyl (Duragesic®, Actiq®, Fentora®), hydromorphone (Dilaudid®), oxymorphone (Opana®), and methadone.

Opioids act by binding to specific proteins, called opioid receptors. Receptors are widely distributed. Those involved in pain modulation are situated in both the central nervous system and the peripheral nervous system. These receptors also bind endogenous opioid peptides (endorphins), which are involved in pain modulation and numerous other functions in the body. Among these functions are those mediated by deep structures of the brain, which are involved in the modulation of reinforcement and reward mechanisms, mood and stress. Opioid receptors are also found on cells from the immune system (Bidlack, 2000). In studies with rats, activation of these receptors with morphine is associated with varied effects, including sensitization of afferent nerves to noxious stimuli (Raghavendra, Rutkowski, & DeLeo, 2002).

When an opioid given for pain binds to receptors, analgesia may be accompanied by any of a diverse array of side effects related to the activation of receptors involved in other functions. These may include effects mediated by peripheral or by peripheral and central mechanisms, such as reduced peristalsis (leading to constipation) and itch, or primary central nervous system effects, such as miosis, (pupillary constriction) somnolence, mental clouding, and respiratory depression (Jaffe & Jaffe, 2004; Jaffe & Martin, 1990). Central mechanisms also lead to changes associated with hyperalgesia and decreased responsiveness to opioids (tolerance) and it has been speculated that opioid-induced hyperalgesia may be a clinically-relevant phenomenon leading to increased pain in some situations (Deleo, Tanga, & Tawfik, 2004). Activation of other central nervous system pathways by opioids also may produce mood effects, either dysphoria or euphoria.

Presumably, binding to those receptors involved in reinforcement and reward also occurs whenever an opioid is taken. In most individuals, when opioids are taken to treat pain, there appears to be no overt effect from change in these systems. In some cases, however, powerful reinforcement occurs, expressed as efforts to repeat the administration and these reinforcing outcomes may be associated with craving and with positive mood effects such as euphorogenic or pleasurable effects (Di Chiara, 2002; Koob & Bloom, 1988). These outcomes, which are uncommon but potentially serious when they occur (driving the development of an addictive pattern of use), can occur in the presence or absence of pain. Although these effects could be associated with iatrogenic addiction, they appear to be rare in patients who do not have risk factors suggesting the existence of the biological substrate for opioid-induced craving (see below).

Although several types of opioid receptors exist (e.g., mu, kappa and delta), opioid drugs largely produce their analgesic and reinforcing effects via activation of the mu opioid receptor; thus, opioids used for pain are often described as, “mu agonists”. Mu drugs that have the ability to fully activate opioid receptors (e.g., higher doses produce greater receptor activation in a dose-dependent manner) are referred to as opioid agonists or full mu agonists (such as morphine, oxycodone and methadone). Those opioids that occupy, but do not activate, receptors are referred to as opioid antagonists (e.g., naltrexone, naloxone); they can reverse the effects of mu opioid agonists. Those opioids that either have a low intrinsic activity at the mu receptor, or are agonists at another receptor and antagonists at the mu receptor are called agonist-antagonist drugs. Those with a low intrinsic activity are called partial opioid agonists and are characterized by a ceiling on most agonist activity, such that increases in dose will increase the drug’s physiological and subjective effects only to a certain level and further dose increases produce no additional effects (Jaffe & Martin, 1990).

These differences in mu receptor interactions are clearly related to the clinical use of opioid drugs and their abuse liability. Agonist-antagonist drugs are less attractive than pure mu agonists to individuals with addiction and no pain. Although other biochemical and molecular processes are presumably relevant to variation in these effects, relatively little is known about the interactions among these processes in humans.

The clinical use of opioid drugs is influenced by a variety of other characteristics, including pharmacokinetics. With the notable exception of methadone and buprenorphine, most opioids have relatively short half-lives and this has necessitated the development of new delivery systems designed to provide prolonged effects and a longer dosing interval.

Clinically-relevant physical dependence and tolerance (see below) may occur with short-term or long-term use of an opioid compound, particularly a pure mu agonist. These phenomena, which vary greatly in the clinical setting, represent neuroadaptational processes. The neurophysiology of physical dependence and tolerance are closely related to each other and to the phenomenon of opioid-induced hyperalgesia (Mao, 2002). The possibility that opioid administration, particularly at relatively high doses, may lead to increased pain has contributed to the controversy about opioid therapy for non-cancer pain, notwithstanding the limited evidence that this phenomenon occurs in clinical settings.

Brief Overview of Chronic Pain

Chronic pain has been described as pain that has persisted for at least 1 month following the usual healing time of an acute injury, pain that occurs in association with a nonhealing lesion, or pain that recurs frequently over a period of months. In most clinical and research reports, chronic pain is typically defined as pain that has persisted for at least 3 months (Verhaak, Kerssens, Dekker, Sorbi, & Sensing, 1998).

The prevalence of chronic pain in the general population is believed to be quite high, although published reports have varied greatly. Cautious cross-national estimates of chronic pain range from 10% (Verhaak et al., 1998) to close to 20% (Gureje, Simon, & Von Korff, 2001), which would represent 30 to 60 million Americans. A national survey of 35,000 households in the US, conducted in 1998, estimated that the prevalence among adults of moderate to severe non-cancer chronic pain was 9% (American Pain Society, 1999). A large survey (N=18,980) of general populations across several European countries reported that the prevalence for chronic painful physical conditions was 17.1% (Ohayon & Schatzberg, 2003).

Chronic pain is a highly complex phenomenon, which may or may not be primarily driven by tissue injury. Conventionally, the most common forms of chronic pain are divided into those labeled “nociceptive”, or pain caused by ongoing stimulation of pain receptors by tissue damage, and those labeled “neuropathic”, or pain presumed to be related to damage to or dysfunction of the peripheral or central nervous system. These categories of pain simplify a complex reality in which both acute and chronic pain are induced by multiple peripheral and central mechanisms, which continually interact with each other and with numerous pain modulating systems. The perturbations that ultimately results in pain perception are caused by neurophysiological processes and other related systems. For example, recent evidence has begun to highlight the role of neuroimmune activation following a tissue injury as an important mechanism in the development of chronic pain (DeLeo, 2006). The role of cytokines and other inflammatory mediators is obvious in inflammatory nociceptive pains, such as some types of arthritis, but new data suggest an equally salient role in the development of chronic neuropathic pain associated with central sensitization of neural pathways following peripheral injury (Deleo, 2006).

All chronic pain is profoundly influenced by psychological processing and responses (Turk & Melzack, 2001). Pain severity and pain-related functional impairment are often found to be associated with psychological and social factors, and patients with identical diseases associated with pain, such as degenerative disk disease, may vary greatly in their reports of pain severity and pain behaviors (Aronoff, 1999). There is an extensive literature documenting the importance of operant conditioning factors (Fordyce, 1976) and cognitive-behavioral factors (Turk, Meichenbaum, & Genest, 1983) in the maintenance of chronic pain behaviors.

Chronic pain also is influenced by psychosocial and psychiatric disturbances, such as cultural influences, social support, comorbid mood disorder, and drug abuse (Gatchel, Peng, Peters, Fuchs & Turk, 2007). Classic studies of pain behavior indicate that cultural differences in the beliefs and attitudes towards pain (e.g., Zbrowski, 1969) and the social/environmental context of the pain (e.g., Beecher, 1959) have a significant impact on pain behaviors.

The contribution of psychological, social and psychiatric factors should not lead to the conclusion that a pain syndrome is primarily psychogenic. Pain related exclusively or primarily to psychological factors occurs, but is far less prevalent than pain associated with organic processes that are powerfully influenced by psychosocial mediators and psychiatric comorbidities (Portenoy, Payne, & Passik, 2004).

The “pattern of suffering” or the pain-related disability that often occurs in concert with persistent pain commonly touches on all domains of function. Patients with chronic pain may demonstrate pain-related interference with ability to perform usual activities at home, work, or school; maladaptive or dysfunctional behaviors, social isolation, and poor sleep patterns; and frequent health care utilization (Dworkin & Sherman, 2001). The recognition that acute pain can compromise health has led major medical associations and accreditation committees to designate pain severity as a “fifth vital sign”, along with blood pressure, temperature, heart rate, and respiration (Fishman, 2005). Further recognition of the increased interest in the

assessment and management of pain is underscored by the U.S. Federal Law (Pain Relief Promotion Act of 2000) that declared the first decade of the 21st century as the Decade of Pain Control and Research (Gatchel et al., 2007).

Chronic pain is a major public health problem, which is associated with devastating consequences to patients and families, a high rate of health care utilization, and huge society costs related to lost work productivity. The existing treatments for chronic pain are unable to address the problem and better therapies are urgently needed. The need for these therapies is the backdrop for the expanding use of opioid drugs. An extensive clinical experience indicates that long-term opioid therapy is able to help selected patients have a better quality of life, less use of health care, and improved productivity. The medical community is no longer debating the reality of these outcomes, but rather, is now focused on a more fruitful debate about patient selection and the benefits and burdens of these drugs in varied subpopulations. Whether the frame of reference is the individual patient and family, or society-at-large, the issue is about balancing the potential benefits of these drugs in the large and diverse population with chronic pain with its potential risks.

Terminology of Opioid Abuse: Dependence, Tolerance, Addiction

Concerns that addiction is a frequent iatrogenic consequence of the medical use of opioids may partially be attributed to confusion over terminology, as a well as failure to recognize that both addiction and chronic pain have a multifactorial etiology. In an effort to develop universal agreement on terminology related to addiction, the American Academy of Pain Medicine (AAPM), the American Pain Society (APS), and the American Society of Addiction Medicine (ASAM) approved a consensus document that clarified this terminology (ASAM, 2001; Savage, 2003).

According to the consensus document, *tolerance* is defined as a decreased subjective and objective effect of the same amount of opioids used over time, which concomitantly requires an increasing amount of the drug to achieve the same effect. Although tolerance to most of the side effects of opioids (e.g., respiratory depression, sedation, nausea) does appear to occur routinely, there is less evidence for clinically significant tolerance to opioids—analgesic effects (Collett, 1998; Portenoy et al., 2004). For example, there are numerous studies that have demonstrated stable opioid dosing for the treatment of chronic pain (e.g., Breitbart, et al., 1998; Portenoy et al., 2007) and methadone maintenance for the treatment of opioid dependence (addiction) for extended periods (Strain and Stitzer, 2006). However, despite the observation that tolerance to the analgesic effects of opioid drugs may be an uncommon primary cause of declining analgesic effects in the clinical setting, there are reports (based on experimental studies) that some patients will experience worsening of their pain in the face of dose escalation (Ballantyne, 2006). It has been speculated that some of these patients are not experiencing more pain because of changes related to nociception (e.g. progression of a tissue-injuring process), but rather, may be manifesting an increase in pain as a result of the opioid-induced neurophysiological changes associated with central sensitization of neurons that have been demonstrated in preclinical models and designated opioid-induced hyperalgesia (Mao, 2002; Angst & Clark, 2006). Analgesic tolerance and opioid-induced hyperalgesia are related phenomena, and just as the clinical impact of tolerance remains uncertain in most situations, the extent to which opioid-induced hyperalgesia is the cause of refractory or progressive pain remains to be more fully investigated. *Physical dependence* represents a characteristic set of signs and symptoms (opioid withdrawal) that occur with the abrupt cessation of an opioid (or rapid dose reduction and/or administration of an opioid antagonist). Physical dependence symptoms typically abate when an opioid is tapered under medical supervision. Unlike tolerance and physical dependence which appear to be predictable time-limited drug effects,

addiction is a chronic disease that “represents an idiosyncratic adverse reaction in biologically and psychosocially vulnerable individuals” (ASAM, 2001).

The distinction between physical dependence and addiction is not always made clear in the pain literature (Ferrell, McCaffery, Rhiner, 1992). Most patients who are administered opioids for chronic pain behave differently from patients who abuse opioids and do not ever demonstrate behaviors consistent with craving, loss of control or compulsive use (e.g., Cowan et al., 2001). Of course, pain and addiction are not mutually exclusive and some patients who are treated for pain do develop severe behavioral disturbances indicative of a comorbid addictive disorder.

Some patients who are treated with opioids for pain display problematic behaviors that, on careful assessment, do not reflect addiction, but rather, appear to relate to a different process. This may be another psychiatric disorder associated with impulsive drug-taking, an unresolved family issue, a disorder of cognition, or criminal intention. In addition, there appear to be some patients who engage in problematic behaviors related specifically to desperation about unrelieved pain. The term *pseudoaddiction* was coined to describe the latter phenomenon (Weissman & Haddox, 1989).

Behaviors that may represent pseudoaddiction and behaviors that reflect addiction or some other serious psychopathology can occur simultaneously, and presumably, one type of phenomenon may incite the others. The diagnosis of these and other conditions may be challenging and requires a careful assessment of clinical phenomenology, specifically a range of drug-related behaviors during treatment with a potentially abusable drug (Portenoy, 1994, Lue, Passik, & Portenoy, 1998).

The term *aberrant drug-related behaviors* has been used to indicate the broad array of problematic nonadherence behaviors (Passik, Kirsh, Donaghy, & Portenoy, 2006), the nature of which is uncertain until a diagnosis can be developed based on astute clinical assessment. Some aberrant drug-related behavior strongly suggests the existence of addiction. These may include the use of alternative routes of administration of oral formulations (e.g., injection or sniffing), concurrent use of alcohol or illicit drugs, and repeated resistance to changes in therapy despite evidence of adverse effects; examples of aberrant behavior less suggestive of addiction are drug hoarding during periods of reduced symptoms, occasional unsanctioned dose escalation, and aggressive complaining about the need for more drugs (Portenoy, 1994).

Distinction between Withdrawal and Chronic Pain

Because addiction is associated with psychological distress and physical discomfort in the form of opioid withdrawal symptoms, it may be difficult to distinguish primary chronic pain complaints from withdrawal pain. Withdrawal also may have the potential to increase baseline pain related to other processes. For example, based on anecdotal evidence from chronic pain patients, withdrawal from opioids can greatly increase pain in the original pain site. These phenomena suggest the need to carefully assess the potential for withdrawal during long-term opioid therapy (e.g., at the end of a dosing interval or during periods of medically-indicated dose reduction).

These phenomena notwithstanding, there also is evidence that experienced drug abusers are able to distinguish withdrawal pain from chronic pain. For example in studies of methadone maintenance patients, both the phenomenology and correlates of chronic pain were different than for withdrawal pain (Karasz et al., 2004; Rosenblum et al., 2003). Chronic pain is typically localized (e.g., back pain, headache) and persists (although with varying degrees of severity) for long periods of time (Gureje, Von Korff, Simon & Gater, 1998). Although certain subjective experiences of withdrawal (e.g., muscle ache) are similar to some distinct pain syndromes,

other withdrawal experiences such as yawning, sweating and hot and cold flashes are likely to be more commonly associated with subjective drug withdrawal than with primary pain conditions. Moreover, the constellation of words used to describe withdrawal pain is likely to be different than words used to describe other painful disorders. Qualitative studies of addicts going through withdrawal typically refer to the experience as “being sick” (similar to a moderate to severe flu-like illness) and not as representing a distinct pain (Farrell, 1994). The subjective experience of withdrawal can be validly measured with an instrument such as the Subjective Opiate Withdrawal Scale (SOWS; Handelsman, et al., 1987). Withdrawal from short-acting opioids, such as heroin, is typically short-lived; physical symptoms are likely to reach their maximum intensity over a 36–72 hour period and to reduce in intensity after that (Farrell, 1994).

Co-occurring Chronic Pain and Opioid Addiction

The prevalence of addictive disorders among chronic pain patients is difficult to determine (Covington and Kotz 2003). One 1992 literature review found only seven studies that utilized acceptable diagnostic criteria and reported that estimates of substance use disorders among chronic pain patients ranged from 3.2% – 18.9% (Fishbain, Rosomoff, & Rosomoff, 1992). A Swedish study of 414 chronic pain patients reported that 32.8% were diagnosed with a substance use disorder (Hoffmann, Olofsson, Salen, & Wickstrom, 1995). In two US studies, 43 to 45% of chronic pain patients reported aberrant drug-related behavior; the proportion with diagnosable substance use disorder is unknown (Katz et al., 2003; Passik et al., 2004). All these studies evaluated patients referred to pain clinics and may overstate the prevalence of substance abuse in the overall population with chronic pain.

A relatively high prevalence of substance abuse disorders among persons with chronic pain can also be inferred by the high co-occurrence of these two disorders. There have been several reports that the prevalence of chronic pain among persons with opioid and other substance use disorders is substantially higher than the pain prevalence found in the general population (Breitbart, et al., 1996; Brennan, Schutte, & Moos, 2005; Jamison, Kauffman, & Katz, 2000; Rosenblum et al., 2003; Sheu, et al., 2008).

Opioid Treatment for Chronic Pain

Opioid therapy is the mainstay approach for the treatment of moderate to severe pain associated with cancer or other serious medical illnesses (Patt & Burton, 1998; World Health Organization, 1996). Although the use of opioid analgesics for the treatment of CNMP has been increasing in recent years (Joranson, Ryan, Gilson & Dahl, 2000) and has been endorsed by numerous professional societies (AAPM, APS, 1997; American Geriatric Society, 1998; Pain Society, 2004), the use of opioids remains controversial due to concerns about side effects, long-term efficacy, functional outcomes, and the potential for drug abuse and addiction. The latter concerns are especially evident in the treatment of CNMP patients with substance use histories (Savage, 2003).

Other concerns that may contribute to the hesitancy to prescribe opioids may be related to perceived and real risks associated with regulatory and legal scrutiny during the prescribing of controlled substances (Office of Quality Performance, 2003). These concerns have propelled extensive work to develop predictors of problematic behaviors or frank substance abuse or addiction during opioid therapy. Questionnaires to assist in this prediction and monitoring have been developed and used in research and field trials. Examples include the Prescription Drug Use Questionnaire (PDUQ; Compton et al., 1998); the Pain Assessment and Documentation Tool (PADT; Passik et al., 2004) and the Current Opioid Misuse Measure (COMM; Butler et al., 2007). These instruments are not used in practice settings at this time.

Narrative reports on the use of opioids for CNMP have underscored the effectiveness of opioid therapy for selected populations of patients and there continues to be a consensus among pain specialists that some patients with CNMP can benefit greatly from long-term therapy (Ballantyne & Mao, 2003; Trescot et al., 2006). This consensus, however, has received little support in the literature. Systematic reviews on the use of opioids for diverse CNMP disorders report only modest evidence for the efficacy of this treatment (Trescot et al., 2006; 2008). For example, a review of 15 double-blind, randomized placebo-controlled trials reported a mean decrease in pain intensity of approximately 30% and a drop-out rate of 56% only three of eight studies that assessed functional disturbance found improvement (Kalso, Edwards, Moore, & McQuay, 2004). A meta-analysis of 41 randomized trials involving 6,019 patients found reductions in pain severity and improvement in functional outcomes when opioids were compared with placebo (Furlan, Sandoval, Mailis-Gagnon, & Tunks, 2006). Among the 8 studies that compared opioids with non-opioid pain medication, the six studies that included so-called “weak” opioids (e.g., codeine, tramadol) did not demonstrate efficacy, while the two that included the so-called “strong” opioids (morphine, oxycodone) were associated with significant decreases in pain severity. The standardized mean difference (SMD) between opioid and comparison groups, although statistically significant, tended to be stronger when opioids were compared with placebo (SMD = 0.60) than when strong opioids were compared with non-opioid pain medications (SMD = 0.31). Other reviews have also found favorable evidence that opioid treatment for CNMP leads to reductions in pain severity, although evidence for increase in function is absent or less robust (Chou, Clark, & Helfand, 2003; Eisenberg, McNicol, & Carr, 2005). Little or no support for the efficacy of opioid treatment was reported in two systematic reviews of chronic back pain (Deshpande, Furlan, Mailis-Gagnon, Atlas, & Turk, 2007; Martell, et al., 2007). Because patients with a history of substance abuse typically are excluded from these studies, they provide no guidance whatsoever about the effectiveness of opioids in these populations.

Adding further to the controversy over the utility of opioid analgesics for CNMP is the absence of epidemiological evidence that an increase in the medical use of opioids has resulted in a lower prevalence of chronic pain. Noteworthy is a Danish study of a national random sample of 10,066 respondents (Eriksen, Sjøgren, Bruera, Ekholm, & Rasmussen, 2006). Denmark is known for having an extremely high national usage of opioids for CNMP and this use has increased by more than 600% during the past two decades (Eriksen, 2004). Among respondents reporting pain (1,906), 90% of opioid users reported moderate to very severe pain, compared with 46% of non-opioid users; opioid use was also associated with poor quality of life and functional disturbance (e.g., unemployment).

Although this epidemiological study may be interpreted as demonstrating that opioid treatment for CNMP has little benefit, the authors acknowledge that these disquieting findings do not indicate causality and could be influenced by the possibility of widespread undertreatment, leading to poorly managed pain. This latter interpretation is supported by a commentary on the Eriksen et al. study (Keane, 2007). Keane notes that among the 228 pain patients receiving opioids only 57 (25%) were using strong opioids, while the remainder was using weak opioids. European (as well as United States) clinical guidelines generally recommend long-acting formulations of strong opioids for the treatment of chronic moderate to severe pain, which may be supplemented with short-acting opioids for breakthrough pain (Pain Society, 2004; OQP, 2003; Gourlay, 1998; Vallerand, 2003; Fine & Portenoy, 2007).

The possibility of inappropriate opioid treatment is further supported by another Danish study that assigned pain patients who were on opioid therapy to either a multidisciplinary pain center (MPC) or to general practitioners (GP) who had received initial supervision from the MPC staff (Eriksen, Becker, & Sjøgren, 2002). At intake, a substantial number of patients in both groups were apparently receiving inappropriate opioid therapy for chronic pain (60% were

being treated with short-acting opioids and 49% were taking opioids on demand). At the 12 month follow-up, 86% of MPC patients were receiving long-acting opioids and 11% took opioids on demand. There was no change in the administration pattern in the GP group. These findings suggest that a significant proportion of opioid-treated CNMP patients may be receiving inappropriate opioid treatment and that educating general practitioners in pain medicine may require more than initial supervision.

It is generally acknowledged that there is a wide degree of variance in the prescribing patterns of opioids for chronic pain (Lin, Alfandre, & Moore, 2007; Trescot et al., 2006). Some opioid treatment practices persist despite evidence that they might be harmful or have little benefit, such as the over-prescribing of propoxyphene among the elderly (Barkin, Barkin, & Barkin, 2006; Singh, Sleeper, & Seifert, 2007). Nursing home patients being treated with opioids have been found to be inadequately assessed for pain and to be more likely treated with short-acting rather than long acting opioids (Fujimoto & Coluzzi, 2000). A substantial number of physicians are reluctant or unwilling to prescribe long-acting opioids to treat CNMP, even when it may be medically appropriate (Nwokeji, et al., 2007).

Controversy about the long-term effectiveness of opioid treatment also has focused on the potential clinical implications of opioid-induced hyperalgesia. As noted earlier, exposure to opioids can result in an increased sensitivity to noxious stimuli in animals, and an increased perception of some types of experimental pain in humans (c.f., Koppert & Schmeltz, 2007; Angst & Clark, 2006). Anecdotal reports of hyperalgesia occurring with very high or escalating doses of opioids (Angst & Clark, 2006) has been viewed as a clinical correlate of these experimental findings. The extent to which this phenomenon is relevant to the long-term opioid therapy administered to most patients with chronic pain is unknown. Although experimental evidence suggests that opioid-induced hyperalgesia might limit the clinical utility of opioids in controlling chronic pain (Chu, Clark, & Angst., 2006), there have been no reports of observations in the clinical literature to suggest that it should be a prominent problem. More research is needed to determine whether the physiology underlying opioid-induced hyperalgesia may be involved in a subgroup of patients who develop problems during therapy, such as loss of efficacy (tolerance) or progressive pain in the absence of a well defined lesion.

Outcome studies of long term use of opioids are compromised by methodological limitations which make it difficult to acquire evidence of efficacy (Noble, Tregear, Treadwell, & Schoelles, 2007). Methodological limitations may be unavoidable because of the ethical and practical challenges associated rigorous studies such as randomized controlled trials. Guidelines for opioid therapy must now be based on limited evidence; future evidence may be acquired by utilizing other study designs (Noble et al., 2007) such as practical clinical trials (Tunis, Stryer, & Clancy, 2003). These studies should include at least three criteria to reflect a positive treatment response: i.e., reduction of pain severity (derived from subjective reports or scores on pain scales), recovery of function (improved scores on instruments that measure some aspect of function), and quality of life.

Guidelines for the use of opioids for the treatment of chronic pain have been published (AAFP et al., 1996–2002; OQP, 2003), and recent guidelines have emphasized the need to initiate, structure and monitor therapy in a manner that both optimizes the positive outcomes of opioid therapy (analgesia and functional restoration) and minimize the risks associated with abuse, addiction and diversion (Portenoy et al., 2004). These guidelines discuss patient selection (highlighting the likelihood of increased risk among patients with prior histories of substance use disorders), the structuring of therapy to provide an appropriate level of monitoring and a presumably lessened risk of aberrant drug-related behavior, the ongoing assessment of drug-related behaviors and the need to reassess and diagnose should these occur, and strategies that might be employed in restructuring therapy should aberrant behaviors occur and the clinician

decide to continue treatment. They also note that therapy should be undertaken initially as a trial, which could lead to the decision to forego more therapy, and that an “exit strategy” must be understood to exist should the benefits in the individual be outweighed by the burdens of treatment.

The relatively recent recognition that guidelines for the opioid treatment of chronic pain must incorporate both the principles of prescribing as well as approaches to risk assessment and management may represent an important turning point for this approach to pain management. Acknowledging that prescription drug abuse has increased during the past decade, a period during which the use of opioid therapy by primary care physicians and pain specialists has accelerated, pain specialists and addiction medicine specialists now must collaborate to refine guidelines, help physicians identify the subpopulations that can be managed by primary care providers, and discover safer strategies that may yield treatment opportunities to larger numbers of patients.

Treating Patients with Addictive Disorders

Safe and effective pain treatment is especially important for persons with a drug use history because inadequate treatment or lack of treatment for pain may have problematic consequences, such as illicit drug use (e.g., heroin), misuse of prescription opioids and other pain medications (e.g., benzodiazepines), psychiatric distress, functional impairment and a tendency for health providers to attribute pain complaints and requests for pain medication to an addictive disorder rather than to a pain disorder (Gureje, et al., 2001; Scimeca, Savage, Portenoy, & Lowinson, 2000). Undertreatment of pain among addicted persons may lead to the adverse medical, social and personal consequences associated with continued drug-seeking behavior (Savage, 1996). Pain complaints may be most problematic among persons with opioid addiction, as this group may have lower tolerance for pain than other addicted populations (Compton, 1994; Compton, Charuvastra, & Ling, 2001). Pain and opioid addiction may be further intertwined among persons who have a history of abusing controlled opioid pain medications, such as oxycodone or hydrocodone.

A Possible Role on the use of Buprenorphine for the Treatment of Chronic Pain

Increasing interest in developing clinical protocols for opioid treatment of chronic pain in the population with substance abuse histories has highlighted the role of opioid medications that may have lower abuse potential. One medication that is beginning to be examined is buprenorphine, a partial opioid mu agonist that is well recognized as an analgesic (Johnson, Fudala, & Payne, 2005). In 2002, a sublingual tablet (both in mono form – Subutex® - and combined with naloxone - Suboxone®) was approved by the U.S Food and Drug Administration as a Schedule III medication for the treatment of opioid dependence. In numerous controlled clinical trials, it has been demonstrated to be highly efficacious in reducing illicit opioid use and promoting treatment retention among opioid abusers (e.g., Johnson, Strain, & Amass, 2003; Kakko, Svanborg, Kreek, Heilig, 2003; O'Connor et al., 1998; Fudala et al., 2003). In opioid addicts, it suppresses the craving and withdrawal symptoms associated with opioid use and also blocks the euphoric effects of subsequent opioid use (See Bickel & Amass, 1995 for a review).

As a partial mu-agonist, buprenorphine has a ceiling effect on its agonist activity (Lewis, 1985; Walsh, Preston, Bigelow & Stitzer, 1995). It is less likely than a full agonist to cause respiratory depression in opioid-naïve patients (Cowan, Lewis & Macfarlane, 1977). This property of buprenorphine increases its safety profile by reducing the risk of accidental overdose (Walsh, Preston, Stitzer, Cone & Bigelow, 1994). The partial agonism of

buprenorphine would presumably yield a ceiling effect for analgesia as well, which would limit the clinical use of the drug in pain management, but there is some question about the extent of this ceiling effect in practice (Dahan, et al., 2006).

Although the combination buprenorphine/naloxone tablet (Suboxone) may precipitate withdrawal in opioid-tolerant persons if it is injected, making it relatively unattractive for diversion (CSAT, 2004), there is nevertheless evidence of diversion, as would be expected with any psychoactive drug that has hedonic properties (Cicero & Inciardi, 2005; Smith, Bailey, Woody, & Kleber, 2007). Rates of abuse are relatively low compared to full mu agonists and buprenorphine rarely is endorsed as a primary drug of abuse (Cicero, Suratt, & Inciardi, 2007; Rosenblum et al., 2007; SAMHSA, 2006).

In Europe, a transdermal formulation of buprenorphine has been approved for the treatment of chronic pain (e.g., Griessinger, Sittl, & Likar, 2005; Sittl, 2005). In post-marketing surveillance studies and in a multicenter randomized controlled clinical trial, the transdermal patches were reported to be effective and well-tolerated in the treatment of cancer and non-cancer chronic pain (Griessinger et al., 2005; Sittl, 2005; Sorge and Stittl, 2004; Sittl, Nuijten, & Nautru, 2006). A transdermal formulation of buprenorphine is not presently available in the United States.

The off-label use of sublingual buprenorphine tablets to treat chronic pain has been described in two clinical reports, one describing its use in a series of chronic pain patients who were responding poorly to other opioid analgesics (Malinoff et al., 2005) and the other describing the response of patients with both pain and addiction (Heit & Gourlay, 2008). In both of these reports, the authors reported that their patients were successfully treated with buprenorphine, e.g., pain relief and improved mood and functioning.

In a similar manner, two earlier publications describe the open-label use of the parenteral formulation of buprenorphine administered sublingually to treat patients with chronic pain (Adriaensen, Mattelaer, & Vanmeenen, 1985; Nasar, McLeavy, & Knox, 1986). Although most patients were followed up for less than one month, both studies reported good analgesia and low incidence or time-limited unwanted side effects. There is also evidence from several preclinical studies and one study with human subjects that, in contrast to pure mu-agonists, buprenorphine exerts a lasting anti-hyperalgesic effect (Hans, 2007; Koppert, et al., 2005). The transdermal trials conducted in Europe, the anecdotal reports of sublingual administration in North America, and buprenorphine's comparatively high safety profile suggest that it would be valuable to systematically study buprenorphine as a treatment of pain in patients with substance use disorders.

Conclusion

Opioids are among the most effective medications for moderate to severe pain. Although there is a consensus on their utility as a treatment for chronic cancer pain, their long-term use for chronic non-malignant pain remains controversial. Several medical professional organizations acknowledge the utility of opioid therapy and many case series and large surveys report satisfactory reductions in pain, improvement in function and minimal risk of addiction. However, the clinical trials that have been conducted do not provide adequate evidence of long-term effectiveness. Despite the consensus of pain specialists, and the eminently ethical and medically justified commentaries to consider opioid therapy in the armamentarium of treatments for moderate to severe pain (Brennan, Carr, & Cousins, 2007), there is concern that the pendulum has swung from undertreatment to overtreatment (White & Kehlen, 2007). This controversy is enhanced by the increased prevalence of prescription opioid abuse, which has developed concomitantly with an increase in opioid administration in the clinic. The resolution

of this controversy will require much more research and the acceptance of treatment guidelines that recognize the dual obligations of the prescriber: to optimize the balance between analgesia and side effects, and promote other favorable outcomes, while concurrently assessing and managing the risks associated with abuse, addiction and diversion. At this juncture, it is important that the opioid treatment debate evolve from a discussion focused on “too little” or “too much” to one focused on identification and training of best treatment practices. Improvement in opioid therapy can occur through research and training to aid practitioners to determine the appropriate patient subpopulations and treatment protocols to achieve satisfactory outcomes.

Finally, it is imperative to advance a research agenda that leads to the identification of methods that would enhance pain relief while reducing the likelihood of addiction and other adverse events when opioids are selected for therapy. This should include the testing of novel medications that may be safer or more differentially effective for select treatment populations (as the proposal to test buprenorphine with high risk patients, discussed above) and the evaluation of treatment protocols incorporating risk management techniques.

References

- AAPM, APS. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clinical Journal of Pain* 1997;13:6–8. [PubMed: 9084947]
- Adriaensen H, Mattelaer B, Vanmeenen H. A long-term open, clinical and pharmacokinetic assessment of sublingual buprenorphine in patients suffering from chronic pain. *Acta Anaesthesiologica Belgica* 1985;36:33–40. [PubMed: 4013631]
- American Academy of Family Physicians (AAFP). Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act. A Joint Statement From 21 Health Organizations and the Drug Enforcement Administration. 1996–2002. Retrieved on February 25 from <http://www.ampainsoc.org/advocacy/promoting.htm>
- American Geriatric Society. The management of chronic pain in older persons. American Geriatric Society Panel on Chronic Pain in Older Persons. *Geriatrics* 1998;53:s8–s24. [PubMed: 9826952]
- American Pain Society (APS). Chronic pain in America: roadblocks to relief. 1999. Retrieved February 12, 2008, from <http://www.ampainsoc.org/links/roadblocks/>
- American Society of Addiction Medicine (ASAM). Definitions Related to the Use of Opioids for the Treatment of Pain. 2001. Retrieved February., 25, 2008 from <http://www.ampainsoc.org/advocacy/opioids2.htm>
- Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006;104:570–587. [PubMed: 16508405]
- Aronoff, GM., editor. Evaluation and Treatment of Chronic Pain. New York: Lippincott, Williams & Wilkins; 1999.
- Askitopoulou H, Ramoutsaki IA, Konsolaki E. Archaeological evidence on the use of opium in the Minoan world. *International Congress Series* 2002;1292:23–97.
- Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain* 2007;129:235–255. [PubMed: 17482363]
- Ballantyne JC, Mao J. Opioid therapy for chronic pain. *New England Journal of Medicine* 2003;349:1943–1953. [PubMed: 14614170]
- Ballantyne JC. Opioids for chronic nonterminal pain. *Southern Medical Journal* 2006;99:1245–1255. [PubMed: 17195420]
- Barkin RL, Barkin SJ, Barkin DS. Propoxyphene (dextropropoxyphene): A critical review of a weak opioid analgesic that should remain in antiquity. *American Journal of Therapeutics* 2006;13:534–542. [PubMed: 17122535]
- Beecher HK. Relationship of significance of wound to pain experienced. *Journal of the American Medical Association* 1959;161:609–613.

- Bickel WK, Amass LA. Buprenorphine treatment of opioid dependence. A review. *Experimental and Clinical Psychopharmacology* 1995;3:477–489.
- Bidlack JM. Detection and Function of Opioid Receptors on Cells from the Immune System. *Clinical and Diagnostic Laboratory Immunology* 2000;7:719–723. [PubMed: 10973443]
- Booth, M. *Opium: A history*. New York: St. Martin's Press; 1986.
- Breitbart W, Passik S, McDonald MV, Rosenfeld B, Smith M, Kaim M, Funesti-Esch J. Patient-related barriers to pain management in ambulatory AIDS patients. *Pain* 1998;76:9–16. [PubMed: 9696454]
- Breitbart W, Rosenfeld BD, Passik SD, McDonald MV, Thaler H, Portenoy RK. The Undertreatment of pain in ambulatory AIDS patients. *Pain* 1996;65:239–245.
- Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesthesia and Analgesia* 2007;105:205–221. [PubMed: 17578977]
- Brennan PL, Schutte KK, Moos RH. Pain and use of alcohol to manage pain: prevalence and 3-year outcomes among older problem and non-problem drinkers. *Addiction* 2005;100:777–786. [PubMed: 15918808]
- Butler SF, Budman SH, Fernandez KC, Houle B, Benoit C, Katz N, Jamison RN. Development and validation of the current opioid misuse measure. *Pain* 2007;130:144–156. [PubMed: 17493754]
- Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: A systematic review. *Journal of Pain and Symptom Management* 2003;26:1026–1048. [PubMed: 14585554]
- Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002–2004. *The Journal of Pain: Official Journal of the American Pain Society* 2005;6:662–672. [PubMed: 16202959]
- Cicero TJ, Inciardi JA. Potential for Abuse of Buprenorphine in Office-Based Treatment of Opioid Dependence. *New England Journal of Medicine* 2005;353:1863–1865. [PubMed: 16251550]
- Cicero TJ, Surratt HL, Inciardi J. Use and misuse of buprenorphine in the management of opioid addiction. *Journal of Opioid Management* 2007;3:302–308. [PubMed: 18290581]
- Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. *Journal of Pain* 2006;7:43–48. [PubMed: 16414554]
- Collett BJ. Opioid tolerance: The clinical perspective. *British Journal of Anaesthesia* 1998;81:58–68.
- Compton MA. Cold-pressor pain tolerance in opiate and cocaine abusers-correlates of drug type and use status. *Journal of Pain and Symptom Management* 1994;9:462–473. [PubMed: 7822886]
- Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: Effect of long-acting maintenance agent. *Drug and Alcohol Dependence* 2001;63:139–146. [PubMed: 11376918]
- Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: Concerns and strategies. *Drug and Alcohol Dependence* 2006;81:103–107. [PubMed: 16023304]
- Compton PJ, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and problematic substance use: evaluation of a pilot assessment tool. *Journal of Pain and Symptom Management* 1998;16:355–363. [PubMed: 9879160]
- Corbett AD, Henderson G, McKnight AT, Paterson SJ. 75 years of opioid research: The exciting but vain quest for the Holy Grail. *British Journal Pharmacology* 2006;147:S153–S162.
- Courtwright, DT.; Joseph, H.; DesJarlais, D. *Addicts who survived*. Knoxville, TN: University of Tennessee Press; 1989.
- Covington, EC.; Kotz, MM. Psychological approaches to the management of pain. In: Graham, AW.; Schulz, TK.; Mayo-Smith, MF.; Ries, RK.; Wilford, BB., editors. *Principles of Addiction Medicine Third Addition*. Chevy Chase, MD: American Society of Addiction Medicine, Inc.; 2003. p. 1421-1438.
- Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *British Journal of Pharmacology* 1977;60:537–545. [PubMed: 409448]
- Cowan DT, Allan LG, Libretto SE, Griffiths P. Opioid drugs: A comparative survey of therapeutic and “Street” use. *Pain Medicine* 2001;2:193–203. [PubMed: 15102251]

- CSAT (Center for Substance Abuse Treatment). Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement (Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939.
- Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, Danhof M. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *British Journal of Anesthesia* 2006;96:627-632.
- DeLeo JA. Basic Science of Pain. *The Journal of Bone and Joint Surgery* 2006;88A:58-62.
- DeLeo JA, Tanga FY, Tawfik VL. Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. *Neuroscientist* 2004;10:40-52. [PubMed: 14987447]
- Deshpande A, Furlan A, Mailis-Gagnon A, Atlas S, Turk D. Opioids for chronic low-back pain. *Cochrane Database System Review*. 2007(2007 Jul 18;(3):CD004959)
- Di Chiara G. Nucleus accumbens shell and core dopamine: Differential role in behavior and addiction. *Behavior and Brain Research* 2002;137:75-114.
- Dikotter, F.; Laaman, L.; Xun, Z. *Narcotic Culture: A history of drugs in China*. Chicago: University of Chicago Press; 2004.
- Dworkin, SF.; Sherman, JJ. Relying on objective and subjective measures of chronic pain: Guidelines for use and interpretation. In: Turk, DC.; Melzack, R., editors. *Handbook of Pain Assessment*. New York: The Guilford Press; 2001. p. 619-638.
- Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: Systematic review and meta-analysis of randomized controlled trials. *Journal of the American Medical Association* 2005;293:3043-3052. [PubMed: 15972567]
- Eriksen, J. Unpublished master's thesis. Copenhagen: University of Copenhagen; 2004. Long-term/chronic non-cancer pain. Epidemiology, healthcare utilization, socioeconomy and aspects of treatment.
- Eriksen, J.; Becker, N.; Sjogren, P. San Diego, CA: 10th World Congress on Pain; 2002 Aug. Use of Opioids in Chronic Non-Malignant Pain Patients Treated at a Multidisciplinary Pain Center Or in General Practice.
- Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: An epidemiological study. *Pain* 2006;2006:172-179. [PubMed: 16842922]
- Farrell M. Opiate withdrawal. *Addiction* 1994;89:1471-1475. [PubMed: 7841858]
- Ferrell BR, McCaffery M, Rhiner M. Pain and addiction: An urgent need for change in nursing education. *Journal of Pain Symptom Management* 1992;7:117-124.
- Field, MJ.; Cassel, CK., editors. *Approaching death: Improving care at the end of life*. Washington, DC: National Academy Press; 1997.
- Fine, PG.; Portenoy, RK. *A Clinical Guide to Opioid Analgesia*. New York: Vendome Group Health Care Division; 2007.
- Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence and addiction in chronic patients. *Clinical Journal of Pain* 1992;8:77-85. [PubMed: 1633386]
- Fishman SM. Pain as the fifth vital sign: How can I tell when back pain is serious. *Journal of Pain & Palliative Care Pharmacotherapy* 2005;19:77-79. [PubMed: 16431837]
- Fordyce, WE. *Behavior Methods for Chronic Pain and Illness*. St. Louis, MO: CV Mosby; 1976.
- Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine* 2003;349:949-958. [PubMed: 12954743]
- Fujimoto D, Coluzzi PH. Survey of analgesic use for nonmalignant pain in long-term care facilities in southern California. *Journal of the American Medical Association* 2000;1:109-113.
- Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. *Canadian Medical Association Journal* 2006;174:1589-1594. [PubMed: 16717269]
- Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychological Bulletin* 2007;133:581-624. [PubMed: 17592957]

- Gourlay GK. Sustained relief of chronic pain: Pharmacokinetics of sustained release morphine. *Clinical Pharmacokinetics* 1998;35:173–190. [PubMed: 9784932]
- Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice—a post-marketing surveillance study in 13,179 patients. *Current Medical Research and Opinion* 2005;21:1147–1156. [PubMed: 16083522]
- Gureje O, Simon GE, Von Korff M. A Cross-National Study of the Course of Persistent Pain in Primary Care. *Pain* 2001;92:195–200. [PubMed: 11323140]
- Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: A World Health Organization study in primary care. *Journal of the American Medical Association* 1998;280:147–151. [PubMed: 9669787]
- Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *American Journal of Drug and Alcohol Abuse* 1987;13:293–308. [PubMed: 3687892]
- Hans G. Buprenorphine: A review of its role in neuropathic pain. *Journal of Opioid Management* 2007;3:195–206. [PubMed: 17957979]
- Heit HA, Gourlay DL. Buprenorphine: New tricks with an old molecule for pain management. *Clinical Journal of Pain* 2008;24:93–97. [PubMed: 18209513]
- Hoffmann NG, Olofsson O, Salen B, Wickstrom L. Prevalence of abuse and dependency in chronic pain patients. *The International Journal of the Addictions* 1995;30:919–927. [PubMed: 7558484]
- Hosztafi S. The history of heroin. *Acta Pharmaceutica Hungarica* 2001;71:233–242. [PubMed: 11862675]
- Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 1975;18:577–580. [PubMed: 1207728]
- Jaffe, JH.; Jaffe, AB. Neurobiology of opioids. In: Galanter, M.; Kleber, HD., editors. *Textbook of Substance Abuse Treatment*. Washington, DC: American Psychiatric Publishing; 2004. p. 17-30.
- Jaffe, JH.; Martin, WR. Narcotic analgesics and antagonists. In: Goodman, LS.; Gilman, A., editors. *The Pharmacological Basis of Therapeutics*. New York: Macmillan; 1990. p. 485-521.
- Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. *Journal of Pain and Symptom Management* 2000;19:53–62. [PubMed: 10687327]
- Johnson RE, Fudala PJ, Payne R. Buprenorphine: Considerations for pain management. *Journal of Pain Symptom Management* 2005;29:297–326.
- Johnson RE, Strain EC, Amass L. Buprenorphine: how to use it right. *Drug and Alcohol Dependence* 2003;70:S59–S77. [PubMed: 12738351]
- Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *Journal of the American Medical Association* 2000;5:1710–1714. [PubMed: 10755497]
- Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: A randomized, placebo-controlled trial. *Lancet* 2003;361:662–668. [PubMed: 12606177]
- Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain* 2004;112:372–380. [PubMed: 15561393]
- Karasz A, Zallman L, Berg K, Gourevitch M, Selwyn P, Arnstein JH. The experience of chronic severe pain in patients undergoing methadone maintenance treatment. *Journal of Pain Symptom Management* 2004;28:517–525.
- Katz NP, Adams EH, Chilcoat H, Colucci RD, Comer SD, Goliber P, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clinical Journal of Pain* 2007;23:648–660. [PubMed: 17885342]
- Katz NP, Sherburne S, Beach M, Rose RJ, Vielguth J, Bradley J, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesthesia and Analgesia* 2003;97:1097–1102. [PubMed: 14500164]
- Keane M. Caution with epidemiological data in relation to chronic opioid use. *Pain* 2007;129:226–227. [PubMed: 17292546]

- Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. *Science* 1988;242:715–723. [PubMed: 2903550]
- Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. *Best Practice & Research. Clinical Anaesthesiology* 2007;21:65–83. [PubMed: 17489220]
- Koppert W, Ihmsen H, Körber N, Wehrfritz A, Sittl R, Schmelz M, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain* 2005;118:15–22. [PubMed: 16154698]
- Lewis JW. Buprenorphine. *Drug and Alcohol Dependence* 1985;14:363–372. [PubMed: 2986930]
- Lin JJ, Alfandre D, Moore C. Physician attitudes toward opioid prescribing for patients with persistent noncancer pain. *Clinical Journal of Pain* 2007;23:799–803. [PubMed: 18075408]
- Lue, HU.; Passik, SD.; Portenoy, RK. Management of chronic pain in the patient with substance abuse. In: Aronoff, GM., editor. *Evaluation and Treatment of Chronic Pain*. New York: Lippincott, Williams & Wilkins; 1999. p. 421–429.
- Malinoff HL, Barkin RL, Wilson G. Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. *American Journal of Therapeutics* 2005;12:379–384. [PubMed: 16148422]
- Manchikanti L. Health care reform in the United States: Radical surgery needed now more than ever. *Pain Physician* 2008;11:13–42. [PubMed: 18196168]
- Mao J. Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. *Pain* 2002;100:213–217. [PubMed: 12467992]
- Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, et al. Systematic review: Opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Annals of Internal Medicine* 2007;146:116–127. [PubMed: 17227935]
- McQuay H. Opioids in pain management. *Lancet* 1999;353:2229–2232. [PubMed: 10393001]
- Meldrum ML. A capsule history of pain management. *Journal of the American Medical Association* 2003;290:2470–2475. [PubMed: 14612484]
- Melzack R. The tragedy of needless pain. *Scientific American* 1990;262:27–33. [PubMed: 2296714]
- Musto, DF. *The American Disease: Origins of Narcotic Control*. Vol. 3rd ed. New York: Oxford University Press; 1999.
- Nasar MA, McLeavy MA, Knox J. An open study of sub-lingual buprenorphine in the treatment of chronic pain in the elderly. *Current Medical Research and Opinion* 1986;10:251–255. [PubMed: 3780289]
- Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *Journal of Pain and Symptom Management* 2008;35:214–228. [PubMed: 18178367]
- Nwokeji ED, Rascati KL, Brown CM, Eisenberg A. Influences of attitudes on family physicians' willingness to prescribe long-acting opioid analgesics for patients with chronic nonmalignant pain. *Clinical Therapeutics* 2007;29:2589–2602. [PubMed: 18164924]
- Nyswander, ME.; Dole, VP. On the use of methadone to limit physical dependence in the treatment of chronic pain. In: Foley, KM.; Inturrisi, CE., editors. *Advances in Pain Research and Therapy*. Vol. Vol. 8. New York: Raven Press; 1986. p. 187–190.
- O'Connor PG, Oliveto AH, Shi JM, Triffleman EG, Carroll KM, Kosten TR, et al. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *The American Journal of Medicine* 1998;105:100–105. [PubMed: 9727815]
- Office of Quality Performance (OQP). Management of Opioid Therapy for Chronic Pain. 2003. Retrieved February 12, 2008, from http://www.oqp.med.va.gov/cpg/cot/ot_base.htm
- Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Archives of General Psychiatry* 2003;60:39–47. [PubMed: 12511171]
- Pain Society. Recommendations for the appropriate use of opioids for persistent non-cancer pain. 2004. Retrieved February 12, 2008, from http://www.britishpainsociety.org/pub_professional.htm#opioids
- Passik SD, Kirsh KL, Whitcomb L, Portenoy RK, Katz NP, Kleinman L, Dodd SL, Schein JR. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clinical Therapy* 2004;26:552–561.

- Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clinical Journal of Pain* 2006;22:173–181. [PubMed: 16428952]
- Patt, RB.; Burton, AW. Pain associated with advanced malignancy, including adjuvant analgesic drugs in cancer pain management. In: Aronoff, GM., editor. *Evaluation and Treatment of Chronic Pain*. New York: Lippincott, Williams & Wilkins; 1998. p. 337-376.
- Portenoy, RK. Opioid therapy for chronic non-malignant pain: Current status. In: Fields, HL.; Liebeskind, JC., editors. *Progress in Pain Research and Management*. Vol. Vol 1. Seattle: IASP; 1994.
- Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: Report of 38 cases. *Pain* 1986;25:171–186. [PubMed: 2873550]
- Portenoy RK, Lesage P. Management of cancer pain. *Lancet* 1999;353:1695–7000. [PubMed: 10335806]
- Portenoy, RK.; Payne, R.; Passik, SK. Lowinson, JH.; Ruz, P.; Millman, RB.; Langrod, JG. Substance Abuse: A Comprehensive Textbook. Vol. 4th ed.. Philadelphia: Lippincott, Williams & Wilkins; 2004. Acute and Chronic Pain; p. 863-904.
- Portenoy RK, Farrar JT, Backonja MM, Cleland CS, Yang K, Friedman M, Colucci SV, Richards P. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clinical Journal of Pain* 2007;23:287–299. [PubMed: 17449988]
- Raghavendra V, Rutkowski MD, DeLeo JA. The role of spinal neuroimmune activation in morphine tolerance/hyperalgesia in neuropathic and sham-operated rats. *Journal of Neuroscience* 2002;22:9980–9989. [PubMed: 12427855]
- Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *Journal of the American Medical Association* 2003;289:2370–2378. [PubMed: 12746360]
- Rosenblum A, Parrino M, Schnoll SH, Fong C, Maxwell C, Cleland CM, et al. Prescription opioid abuse among enrollees into methadone maintenance treatment. *Drug and Alcohol Dependence* 2007;90:64–71. [PubMed: 17386981]
- SAMHSA. ED Trends from DAWN-Final estimates 1995–2002. Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies; 2004a.
- SAMHSA. DASIS Report. Treatment admissions involving narcotic pain killers: 2002 update. 2004b. Retrieved February 12, 2008, from <http://www.oas.samhsa.gov/2k4/painTX/painTX.htm>
- SAMHSA. Diversion and Abuse of Buprenorphine: A Brief Assessment of Emerging Indicators. 2006. Retrieved February 25, 2008, from http://buprenorphine.samhsa.gov/Buprenorphine_FinalReport_12.6.06.pdf
- Savage SR. Long-term opioid therapy: Assessment of consequences and risks. *Journal of Pain and Symptom Management* 1996;11:274–286. [PubMed: 8636626]
- Savage, SR. Opioid medications in the management of pain. In: Graham, AW.; Shultz, TK.; Mayo-Smith, MF., editors. *Principles of Addiction Medicine*. Vol. 3rd ed. Chevy Chase, MD: American Society of Addiction Medicine; 2003. p. 1451-1463.
- Schiff PL. Opium and its alkaloids. *American Journal of Pharmaceutical Education* 2002;66:186–194.
- Schnoll SH, Weaver MF. Addiction and pain. *American Journal of Addiction* 2003;12:27–35.
- Scimeca MM, Savage SR, Portenoy R, Lowinson J. Treatment of pain in methadone-maintained patients. *Mount Sinai Journal of Medicine* 2000;67:412–422. [PubMed: 11064492]
- Sheu R, Lussier D, Rosenblum A, Fong C, Portenoy J, Joseph H, Portenoy RK. Prevalence and Characteristics of Chronic Pain in Patients Admitted to an Outpatient Drug and Alcohol Treatment Program. *Pain Medicine*. 2008In press
- Singh S, Sleeper RB, Seifert CF. Propoxyphene prescribing among populations older and younger than age 65 in a tertiary care hospital. *The Consultant Pharmacist: The Journal of the American Society of Consultant Pharmacists* 2007;22:141–148. [PubMed: 17367247]
- Sittl R. Transdermal buprenorphine in the treatment of chronic pain. *Expert Review of Neurotherapeutics* 2005;5:315–323. [PubMed: 15938664]
- Sittl R, Nuijten M, Nautrup BP. Patterns of dosage changes with transdermal buprenorphine and transdermal fentanyl for the treatment of noncancer and cancer pain: a retrospective data analysis in Germany. *Clinical Therapeutics* 2006;28:1144–1154. [PubMed: 16982291]

- Smith MY, Bailey JE, Woody GE, Kleber HD. Abuse of buprenorphine in the United States: 2003–2005. *Journal of Addictive Diseases* 2007;26:107–111. [PubMed: 18018814]
- Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, et al. Daily assessment of pain in adults with sickle cell disease. *Annals of Internal Medicine* 2008;148:94–101. [PubMed: 18195334]
- Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: Results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clinical Therapy* 2004;26:1808–1820.
- Strain, EC.; Stitzer, ML., editors. *Methadone and Other Treatments for Opioid Dependence*. Baltimore: Johns Hopkins University Press; 2006.
- Streltzer J, Johansen L. Prescription drug dependence and evolving beliefs about chronic pain management. *American Journal of Psychiatry* 2006;163:594–598. [PubMed: 16585432]
- Streltzer J, Kosten TR. Methadone maintenance therapy and chronic pain. *Journal of the American Medical Association* 2003;290:2403. [PubMed: 14612466]
- Trescot AM, Boswell MV, Atluri SL, Hansen HC, Deer TR, Abdi S, et al. Opioid guidelines in the management of chronic non-cancer pain. *Pain Physician* 2006;9:1–39. [PubMed: 16700278]
- Trescot AM, Glaser SE, Hansen H, Benyamin R, Patel S, Manchikanti L. Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician* 2008:S1–S39. [PubMed: 18443634]
- Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *Journal of the American Medical Association* 2003;290:1624–1632. [PubMed: 14506122]
- Turk, DC.; Meichenbaum, D.; Genest, M. *Pain and Behavioral Medicine: A Cognitive Behavioral Prospective*. New York: Guilford Press; 1983.
- Turk, DC.; Melzack, R. The measurement of pain and assessment of people experiencing pain. In: Turk, DC.; Melzack, R., editors. *Handbook of Pain Assessment*. Vol. 2nd ed. New York: Guilford Press; 2001. p. 3-14.
- Vallerand AH. The use of long-acting opioids in chronic pain management. *The Nursing Clinics of North America* 2003;38:435–445. [PubMed: 14567201]
- Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Sensing JM. Prevalence of Chronic Benign Pain Disorder Among Adults: A review of the Literature. *Pain* 1998;77:231–239. [PubMed: 9808348]
- Walsh SL, Preston KL, Bigelow GE, Stitzer ML. Acute administration of buprenorphine in humans: Partial agonist and blockade effects. *The Journal of Pharmacological and Experimental Therapeutics* 1995;274:361–372.
- Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology buprenorphine: Ceiling affects at high dose. *Clinical Pharmacology and Therapeutics* 1994;55:569–580. [PubMed: 8181201]
- Weissman DE, Haddox JD. Opioid pseudoaddiction-an iatrogenic syndrome. *Pain* 1989;36:363–366. [PubMed: 2710565]
- White PF, Kehlet H. Improving pain management: are we jumping from the frying pan into the fire? *Anesthesia and Analgesia* 2007;105:10–12. [PubMed: 17578944]
- World Health Organization (WHO). *Cancer pain relief, with a guide to opioid availability*. 2nd ed Geneva: 1996.
- Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug and Alcohol Dependence* 2003;69:215–232. [PubMed: 12633908]
- Zbrowski, M. *People in Pain*. San Francisco: Jossey-Bass; 1969.

Acknowledgments

The authors wish to thank two anonymous reviewers who provided extremely thoughtful and helpful comments on an earlier version of this paper. Acknowledgement: Development of this paper was partially supported by a National Institute on Drug Abuse grant R21 DA022675.