

# Individual Differences in Opioid Efficacy for Chronic Noncancer Pain

Joseph L. Riley, III, PhD and Barbara A. Hastie, PhD

**Objective:** Over a decade ago, Jamison noted the lack of studies that identify patient profiles or specific groups that might be best suited for opioid treatment of chronic noncancer pain.

**Methods:** This paper reviews the studies that provide evidence for individual differences in opioid analgesia for chronic noncancer pain.

**Results:** What we have found is that few investigations have addressed these important aspects of pain treatment. The most consistent finding is that depression and anxiety are associated with increased risk for drug abuse and decreased opioid efficacy.

**Discussion:** The question remains whether the psychologic disorders antedated the pain condition or whether the experience of chronic pain exerts psychologic pressures that cause changes in behavior and psychologic processes. Additionally, the overall pattern suggests that younger age is predictive of opioid abuse and greater opioid efficacy. We also present a brief review of biologic mechanisms that support individual differences on opioid analgesia.

**Key Words:** opioids, adverse events, outcome, depression, review, chronic pain, chronic noncancer pain

(*Clin J Pain* 2008;24:509–520)

Chronic noncancer pain (CNCP) is common in a myriad of medical settings as it affects approximately 20% of the population and involves substantial costs to individuals and society, including billions in lost work days and healthcare expenses.<sup>1,2</sup> As such, CNCP has become a critical public health issue.<sup>2–5</sup> CNCP occurs in diverse ethnic/racial groups, affects both sexes and represents heterogeneous pain states with varying degrees of severity, distribution, and functional impact, and it can be of nociceptive or neuropathic origin.<sup>5–9</sup> The mechanisms involved in producing chronic pain are unclear, with central sensitization, increased sensitivity at the level of the spinal cord, and decreased functioning of normal

inhibitory pathways proposed as potential causal factors.<sup>10–12</sup>

In recent years, pain research focusing on these underlying mechanisms has burgeoned with the hope of offering insight for better clinical pain management. Given the magnitude of the problem of CNCP and the concurrent pressure on the medical professional to offer effective treatments, it is imperative to consider what empirical evidence might be available to identify predictive characteristics of the patient to enhance clinical decision-making toward optimal outcomes, especially for the use of opioids for CNCP. The original charges for this invited review were to identify and organize evidence for predictors of opioid efficacy for treatment of CNCP. We hoped we could identify a set of empirically-based decision rules that could guide clinical practice toward more consistent positive outcomes. What we found was surprising. Although there were no shortages of practice guidelines, for whatever reason, we found insufficient evidence to support any specific clinical recommendations. This paper reviews the few studies that provide evidence for individual differences in opioid analgesia for CNCP (Table 1). Following this, we present a brief review of biologic mechanisms that support individual differences on opioid analgesia.

## BIOPSYCHOSOCIAL ETIOLOGY

It has long been proposed that chronic pain be viewed as a multidimensional problem with the currently accepted theory being the biopsychosocial model.<sup>13–15</sup> This model suggests dynamic interactions and reciprocal relationships between biologic, psychologic, and social factors. Consistent with this, there are a number of individual-level psychologic and social predictors of pain becoming chronic.<sup>16–18</sup>

Environmental factors, such as job satisfaction and cultural background, have been reported as risk factors for pain becoming chronic.<sup>3,5,19–21</sup> Premorbid personality and psychologic functioning (eg, psychologic stress, somatization, catastrophizing cognition), as well as traumatic past life events, have also been shown to be risk factors for the development of chronic pain.<sup>22–25</sup> Researchers have recently asserted that unmanaged postoperative pain and increased central sensitization place individuals at higher risk for long-term adverse outcome and CNCP.<sup>26,27</sup> Depending on the type of pain condition, the epidemiology of chronic pain varies, but in general, women report higher incidences of CNCP as do

Received for publication January 27, 2008; Accepted January 28, 2008. From the Department of Community Dentistry and Behavioral Science, College of Dentistry, University of Florida, FL.

Reprints: Joseph L. Riley III, PhD, Department of Community Dentistry and Behavioral Science, University of Florida, PO Box 103628, Gainesville, FL 32610-3628 (e-mail: jriley@dental.ufl.edu). Copyright © 2008 by Lippincott Williams & Wilkins

**TABLE 1.** Empirically-based Risk Factors for Poor Outcome

Abuse and Misuse	Adverse Events	Pain Reduction and Relief
History of abuse	Older age	Depression/anxiety
Depression/anxiety	Female sex	Older age
Younger age	White race	Lower heat pain threshold
Pain at multiple sites		Lower baseline pain

older adults, although the latter tend to report better mental health compared with younger adults, who seem to be more significantly impacted by CNCP.<sup>28,29</sup>

Whether these external factors predispose someone to chronic pain or whether natural demographic factors such as sex, age, and ethnicity impose additional vulnerability in today's healthcare system has yet to be determined. It is likely that transition to CNCP is a combination of factors that are dynamic, interrelated, and with bidirectional influences, which move a person from acute pain to a chronic pain situation. Nevertheless, consistent with this biopsychosocial model, the impact of chronic pain is broad and substantial, and necessitates efficient assessment with the aim for effective treatment and optimal outcome.

### TREATMENT OPTIONS

Healthcare providers have a range of possible options for the treatment of CNCP. Most notable treatment options include physical, surgical, psychological, and pharmacologic factors and will be briefly discussed. With regard to physical treatment, generally positive outcomes have been reported. Options typically include physical therapy and rehabilitation, but other physical options can include acupuncture and electrical stimulation (eg, transcutaneous electrical nerve stimulator). Many of the gains are long-term, although rarely is such treatment independent of other treatment modalities. Next, surgical options can be minimally invasive or may involve significant procedures with longer recovery times. It is becoming increasingly common to conduct presurgical assessments to predict surgical outcomes. Additionally, a majority of the time, surgical procedures are followed by a combination of physical and pharmacologic treatment. Psychological therapy is typically concomitant with other physical, surgical, or pharmacologic options and involves a plethora of modalities including cognitive-behavioral and operant-behavioral therapy.<sup>30-32</sup> Pharmacologic treatment for CNCP seems to be the most common modality and can include nonsteroidal anti-inflammatory medications, tricyclic antidepressants (TCAs), and opioid therapy.<sup>33-35</sup> Evidence suggests that combining these 4 aforementioned modalities, as is typical in multidisciplinary pain programs, generates the most positive outcomes.

Although overwhelmingly accepted as a treatment for chronic cancer pain, opioid therapy for CNCP is controversial<sup>33-36</sup> because of the potential for tolerance and opioid-induced hyperalgesia<sup>37</sup> combined with concerns about misuse/abuse and opioid dependence.<sup>38,39</sup>

Even with these potential drawbacks, opioid treatment is frequently recommended for both chronic neuropathic and nociceptive pain and use of opioids for CNCP has increased significantly in recent years.<sup>40,41</sup> Whereas some physicians suggest that opioids should be considered only when other treatments have failed, the "last resort" approach, others recommend opioid pain medications as a first-line therapy.<sup>42-45</sup>

From a systematic review that included 11 randomized and controlled trials on oral opioids in noncancer pain using the World Health Organization criteria, Kalso et al<sup>46</sup> concluded that opioids provided pain relief for both neuropathic and musculoskeletal pain. A more inclusive review by Furlan et al<sup>47</sup> also found that opioids provided greater pain relief than placebo or other drugs, but did not outperform the nonsteroidal anti-inflammatory drug naproxen or the TCA nortriptyline on functional outcomes. It is well recognized that patient responses to opioids used for the treatment of chronic pain can be highly variable, just as patients with chronic pain are not a homogeneous group.

Although the mechanisms that underlie this variability are not well understood, a number of authors have proposed preopioid administration screening guidelines.<sup>34,48-52</sup> Likewise, in recent years practice guidelines espoused by the Federation of State Medical Boards and various medical organizations have asserted the importance and the need to adequately assess patients before opioid administration.<sup>53-55</sup> In fact, most practice guidelines discuss the important and inevitable risks of opioid administration, which include unsatisfactory outcomes such as side effects and drop-out/termination issue, misuse and abuse, and tolerance/hyperalgesia.<sup>43,53</sup> Consistent with a biopsychosocial model, other potential predictors for poor outcome include excessively high pain ratings, history of drug or alcohol abuse or misuse, psychiatric history, and poor psychosocial status that could include depression, high emotionality, maladaptive pain beliefs, ineffective coping, unstable social situation, and inconsistent employment history. Unfortunately, few references are provided to support this second group of factors. In fact, although the need for assessments is asserted, it is implied that these will incorporate biologic, psychological, and social factors along with issues of quality of life and functional status. Although these factors are touted as important, most preopioid administration instruments are aimed almost exclusively at assessing the potential for aberrant behavior and addiction.

In a comprehensive review of pretreatment assessment strategies, Jamison<sup>50</sup> noted the lack of studies that identify patient profiles or specific groups that might be best or least suited for opioid treatment of CNCP. He also asserted the need to evaluate a multitude of factors in considering opioid administration including: (1) pain intensity, (2) functional capacity, (3) personality and mood, (4) pain beliefs, (5) medication usage, (6) adverse effects, (7) healthcare utilization, and (8) medical and psychosocial history. That was over 10 years ago, and

despite the magnitude of untreated pain along with mounting concerns about the use of opioids for CNCP, a dearth of research still exists in this arena. This review examines the empirical evidence for characteristics of persons more or less likely to respond favorably to opioids for CNCP and updates Jamison's review.

The wide variability in treatment outcomes makes it important to identify patient characteristics that are associated with outcomes for various interventions, with the eventual goal of tailoring pain treatments to individual patients.

### INDIVIDUAL DIFFERENCES IN OPIOID EFFICACY

To our knowledge, no single tool exists to assess or predict characteristics or profiles for opioid efficacy. Given the current evidence base, it seems as though the consensus construct in most of the instruments is the focus on potential for opioid misuse. It is important to note that although prediction of opioid abuse is vitally important, there may be a scientific and clinical myopia by neglecting to work toward development of a tool for predicting opioid efficacy, or at least in identifying more sound evidence for characteristics that might predict adequate outcome.

At the present time, what is predominant in the literature are assessments that tend to identify negative opioid "outcomes." We address those below and we also offer other realms of possibilities for consideration of contributing factors influencing opioid treatment. It is acknowledged that factors that influence prescribing habits might be demonstrably different than the patient-factors influencing opioid efficacy. We assert the need for consideration of factors from both sides of the argument. The primary benefit should be enhanced assurance for successful treatment, and for patients in their quest for pain relief, functional restoration, and improved quality of life. On the other hand, it could potentially aid clinicians in their prescribing practice related to legal/regulatory protection. To that end, we address current views of opioid outcomes and studies, albeit limited, that have examined such factors.

### Opioid Abuse as an Outcome

Although the incidence and prevalence of opioid abuse and misuse in patients treated for chronic pain differs depending on the definition and the patient-sample studied,<sup>56,57</sup> there is no disagreement that it occurs.<sup>40,58-61</sup> Notably, several reports indicate that opioid abuse is a key behavioral factor for which to be screened in considering use of opioid treatment for CNCP.

As such, most instruments that purport to predict the likelihood of opioid treatment success almost exclusively focus on abuse and addiction as if to assume that lack of opioid addiction indicates success. Few tools assess the host of factors that might be related to opioid success, and even less address the issues of pseudoaddiction or other behavioral issues related to undermanagement of pain.<sup>62</sup> The limited literature available on these data suggest that substance abuse of prescribed opioids in

pain patient populations may occur at comparable or higher rates than in the general population, ranging from 3.2% to 18.9% on average.<sup>40,63</sup> Yet, Fields<sup>64</sup> argues that it is highly unlikely that a pain patient would "slip into addiction through medically justified prescriptions" but the more likely scenario is that a patient's propensity for substance abuse antedated their contact with a pain clinician. This begs the question of what patient characteristics might be predictive of successful opioid treatments, including decreased pain intensity, improved quality of life, and increased functional restoration, but the focus in the field as reflected in assessment tools seems to have been more on the negative outcomes of opioid therapy, namely addiction.

Opioid abuse itself, in its myriad manifestations, is regarded as a poor outcome, and pain specialists as well as primary care providers tend to consider that a sufficient reason for cessation.<sup>65</sup> There is extensive literature in predicting abuse among nonpain patients.<sup>52</sup> Although the subject of another review in this series, we will present several studies that have identified patient-level factors predisposing CNCP patients to opioid misuse.

Reid et al<sup>66</sup> performed a chart review of 98 patients from 2 hospital-based primary clinics who received 6 or more months of opioid prescriptions for CNCP during a 1-year period. Opioid abuse was defined as lost or stolen opioid medications or prescriptions, documented use of other sources to obtain opioid medications, or requests for 2 or more early refills. Twenty-seven of these patients (28%) met one or more of these criteria. The significant predictors were a lifetime history of a substance use disorder and younger age; depression approached statistical significance, but there was no associations between opioid abuse and race, sex, or pain duration. Although retrospective information from charts is useful, predictors were not specifically chosen with that research question in mind and consequently, the results must be interpreted with caution.

A 12-month prospective study of 196 CNCP patients receiving opioid therapy at an academic pain clinic provides stronger evidence.<sup>67</sup> The authors report good enrollment with 196 of 199 consecutive patients starting the study and little attrition (4 patients were lost to follow-up and 3 were transferred to a primary care clinic). Abuse was prospectively monitored by review of medications, review of outside medical records, communication with pharmacies and providers, and urine toxicologic screenings. Opioid misuse occurred in 62 (32%) of the patients. The strongest predictors of misuse were self-reported histories of previous alcohol or cocaine abuse, or previous criminal drug or alcohol-related convictions. Younger age was also predictive, but the effect was not large. Sex, race, literacy, disability, and measures of socioeconomic status were not associated with misuse. There was not a consistent correlation between pain scores and the risk of misuse.

Manchikanti et al<sup>68</sup> reported a prospective study of 500 consecutive pain patients from an outpatient clinic who were prescribed stable doses of opioids for CNCP.

Patients were evaluated for psychopathology (ie, somatoform disorder), depression, anxiety, opioid abuse, and illicit drug use during regular pain management treatment. Abuse was defined as a patient receiving controlled substances from any source other than the prescribing physician. They reported opioid abuse in 9% and illicit drug use in 16% of the chronic pain patients. They also found that substance abuse was significantly higher in depressed compared with nondepressed patients (12% vs. 5%, respectively). Current illicit substance abuse was higher in depressed women versus nondepressed women and compared with depressed and nondepressed in men. Additionally, current substance abuse was higher in men with diagnosed somatization disorder than men without the disorder. This recent study demonstrated that psychologic features of depression and somatization disorder might be predictors for substance abuse among chronic pain patients. Notably, age, pain after accidents, pain in multiple body regions, and history of illicit drug use were also identified as risk factors.

Wasan et al<sup>69</sup> examined the role of psychiatric history and psychologic adjustment on drug abuse among 226 patients, recruited from 3 pain management centers, who were taking opioids for CNCP. Groups were formed based on low or high psychiatric morbidity according to self-reported symptoms of anxiety and depression, history of sexual or physical abuse, and psychologic adjustment. A “drug misuse index” and urine toxicology were used as outcomes. Wasan and colleagues found that patients with high psychiatric morbidity showed more drug misuse behavior and were likely to have positive urine sample. Not all studies are conclusive as Chabal et al<sup>70</sup> failed to show an association between current opiate abuse and a history of abuse, depression, and pain intensity among a sample veterans receiving opioid therapy for chronic pain.

As noted above, several papers have recently introduced screening instruments for assessing abuse risk.<sup>70–74</sup> These instruments have been designed generally to screen patients but may not prove to be comprehensive enough to identify the relative salience of specific factors that contribute to the etiology of opioid abuse or more importantly, for opioid efficacy in CNCP patients.<sup>71,72,74–79</sup>

### Adverse Events as an Opioid Outcome

Adverse side-effects associated with opioid therapy for CNCP are common and include respiratory depression, nausea, sedation, euphoria or dysphoria, constipation, and itching.<sup>47,48,80,81</sup> The development of adverse effects from opioids often hinders their use or prevents dose escalation necessary to achieve adequate pain relief. Consequently, because of intolerable effects that prevent appropriate dosage, side effects can be defined as risk factors for poor outcome from opioid therapy for CNCP. A meta-analysis of 34 randomized trials for a range of opioids has documented the prevalence of adverse events as ranging from 25% to 100%, with one in 5 patients discontinuing the trials because of adverse events.<sup>81</sup> Another review of placebo trials that used the World

Health Organization’s “3 step ladder” for opioid administration in CNCP reported that 80% of patients reported one or more adverse events.<sup>46</sup> In that review of patients on open label treatments, only 44% were still on opioids 7 to 24 months after initiation of opioid therapy.

Only one study was found that identified patient level characteristics that increase the risk of development of side effects for CNCP patients. Cepeda et al<sup>82</sup> examined the effects of age, sex, and race on the incidence of nausea/vomiting and respiratory depression. The data come from a retrospective surveillance study where this cohort of 8855 inpatients received parenteral opioids (meperidine, morphine, or fentanyl). The participants were not limited to CNCP patients, but were a mix of patients with acute, chronic, or cancer pain. In the statistical analysis, adjustments were made for other medications with side-effect potential and opioid dosage. The probability of nausea and vomiting decreased with age, were lower in men than in women and were higher in White patients than in Black patients. For respiratory depression, older patients had increased risk but no differences occurred for sex or race.

### Pain Relief as an Opioid Outcome

It is generally understood that the goal of opioid therapy is reduced pain and increased function. Most studies that have examined opioid efficacy have been initiated to validate pharmaceutical efficacy and have not addressed patient-level factors that might contribute to outcome. Likewise, studies that report general “pain reduction” do not necessarily address whether there were clinically significant reductions or, more importantly, whether the patient would report it as “adequate pain reduction.” However, in the past decade, trends for assessing adequate relief have changed. For example, although researchers might report a reduction of pain from 6 out of 10 to 4.5 out of 10 as statistically significant, it may not be clinically relevant. Simple numbers do not tell us what factors contributed to outcomes. Farrar and colleagues<sup>83</sup> have distinguished “cut points” for clinical significance, but it still leaves unanswered the questions raised by Jamison and colleagues about whether, as a discipline, pain researchers and clinicians might identify patient characteristics or profiles that might predict better or worse outcomes from opioid therapy, including prediction of opioid efficacy.

### Individual-level Predictors From Clinical Trials

We are able to identify only 2 studies that directly test for patient characteristics of opioid outcome during randomized trials. The primary purpose of the study by Wasan et al<sup>84</sup> was to test whether various levels of psychopathology influenced the outcome of opioid analgesia. These data came from 60 patients with chronic low back pain that participated in a double blind, placebo-controlled, randomized, crossover trial of intravenous morphine. Inclusion criteria included the requirement that patients were not taking long-acting oral or intrathecal medication at baseline, had no history of

opioid abuse, and reported an average pain intensity rating of 4 on a 0 to 10 scale. The trial was preceded by a 2-week washout period for any short-acting opioids; however, all other pain and psychiatric medications were maintained throughout the study period of 2 to 3 weeks. This was followed by a single injection of morphine (0.075 mg/kg ideal body weight) or saline placebo on separate visits approximately 1 week apart. An active placebo (ie, diazepam) was not used because of a possible greater interaction with the affective components of pain in the high or moderate group than in those with low symptoms.

The patients received a psychiatric evaluation and using a model for classifying the degree of psychopathology from an aggregate measure of psychologic symptoms, patients were classified as Low, Moderate, or High negative affect. The High group had at least 2 of these diagnoses: major depression, dysthymia, an anxiety disorder, or a personality disorder; whereas the Low group was low on most measures. Patients were recruited until there were 20 in each group. The groups were the same on all social and demographic variables with the exception that a higher percentage of the Low group was employed. In terms of other medications, significant differences were found only for use of anticonvulsants. With regard to potential confounding variables, the groups differed on baseline pain ratings, disability, and mobility, but not on McGill Pain Questionnaire (MPQ) scores or neuropathic pain characteristics.

During the 3-hour postinjection observation period, the patients rated pain and pain relief (0 to 10 scales) every 20 minutes. Every 40 minutes patients completed the short-form MPQ and the Neuropathic Pain Questionnaire, a measure designed to quantify neuropathic pain symptoms. The key finding from this study is that the High group reported substantially less analgesia from morphine than the Low group. They also differed on percentage change in pain among the 3 groups. When adjusting for placebo effects, the Moderate group had 40% less analgesia and the High group had 63% less analgesia than the Low group. When work status and education level were considered, persons in the Low group who were highly educated and employed had the best analgesia, whereas those in the High group who were poorly educated and unemployed had the least analgesic effect. Sex of the patient, pain ratings, and expectations for relief were not significant in the model.

Edwards et al<sup>85</sup> demonstrated an association between opioid efficacy and experimental basal heat pain threshold with data collected as part of a randomized, placebo-controlled, crossover trial of opioids and TCAs in patients with chronic postherpetic neuralgia. Patients with a history of substance abuse and pain intensity ratings less than 4 on a 0 to 10 numeric rating scale were excluded. Patients underwent 3 treatment periods in random order: 1 with an opioid, 1 with a TCA, and 1 with a placebo. Each treatment period lasted approximately 8 weeks and had a titration, maintenance, and taper phase. Doses were titrated to maximal relief or

intolerable side effects. Only 64 of 76 patients received heat pain threshold assessment. Of those patients, 60 provided assessment results for 1 treatment period, 51 provided data for 2 treatments, and 40 provided data for all 3 treatments with 55 receiving opioid treatment. The pain outcomes were pain intensity (0 to 10) and pain relief (0% to 100%) collected by twice-weekly telephone interviews at the end of the maintenance period.

At baseline, heat pain threshold was assessed contralateral to the affected site whereby 64% were classified as having a thoracic or lumbosacral distribution and 36% had a primarily trigeminal distribution. To account for differences in sensitivity across body regions, threshold scores were standardized within the 2 anatomic regions to allow for across-site comparisons. Using regression models that adjusted for differences in age, sex, and baseline clinical pain, higher baseline heat pain threshold was associated with larger pain reduction and higher ratings of pain relief. Heat threshold was not correlated with change in pain intensity for TCA or placebo. Younger age and higher baseline pain intensity were associated with greater reduction in pain intensity and more pain relief after treatment with opioids. Sex approached statistical significance as a predictor of pain relief with women reporting marginally more pain relief than men during the opioid phase. The authors acknowledge several methodologic problems that included the small sample size, issues associated with testing different anatomic sites, and study attrition.

### Individual-level Predictors in Nonclinical Trials

Although less methodologically rigorous, we present data from 2 nonclinical trials that failed to find patient-level predictors. Haythornthwaite et al<sup>86</sup> examined predictors of pain relief among 19 patients receiving long-acting oral opioids. Twelve patients that improved by one or more points on a 0 to 6 pain rating scale were defined as responders whereas the 7 patients that scored within 1 unit were classified as nonresponders. No differences were found for pain severity, duration, or depression, although there would be little statistical power for such a comparison. No group mean values were reported. Limitations include that the data came from a convenience sample from the clinic.

Portenoy et al<sup>35</sup> examined the prevalence of breakthrough pain for 228 patients with a mix of chronic noncancer pain (52% reported low back pain). To be eligible, patients were required to have had good pain control for the previous 7 days. The patients participated in a telephone interview survey using a breakthrough pain assessment algorithm approximately 1 week after a clinic visit. At that time, 168 (74%) reported having experienced severe breakthrough pain episodes at least once since the clinical visit. The 2 groups did not differ on age, sex, baseline pain, or duration of pain.

### Physician Prescriptive Practices

On the basis of a few studies that support patient-level predictors of opioid outcome for CNCP patients, it

seems as though most published guidelines for patient selection are not based entirely on empirical data. Nonetheless, below several studies are reviewed that described characteristics of patients who were using opioids and, therefore, these reports provide insight into physician prescription practices retrospectively.

The first study to report on patient level predictors of physicians' decision to prescribe opioid prescriptions for chronic pain consisted of a retrospective chart review of 191 referrals to a tertiary pain clinic.<sup>87</sup> Using a regression model, Turk and Okifuji<sup>87</sup> found that a measure of observed pain behaviors predicted patients who had been prescribed opioids. Additionally, univariate analysis indicated opioid users were also more depressed and reported greater physical disability but did not differ on pain severity, pain duration, employment status, or physical findings compared with nonopioid users.

In a retrospective comparison of 243 chronic pain patients referred to a tertiary pain clinic, Ciccone et al<sup>88</sup> found that opioid users were more likely to be female, reported greater than usual pain, had more pain locations, and were more depressed and physically disabled than nonopioid users. No differences were found for age, race/ethnicity, or pain duration.

Fanciullo et al<sup>89</sup> compared 867 patients who were using opioids with 24,612 patients with pain of mixed origin (ie, chronic and acute back pain) that were not all using opioids, all of whom had been evaluated at specialty spine centers across the United States. Those who received opioids reported greater pain and physical disability, and were more likely to be unemployed, use tobacco, be obese, and have objective findings (eg, radiation of pain, neurologic signs). No differences were found for sex, age, education level, or compensation status.

Other researchers revealed that patients with back pain had similar pain scores whether or not they used opioids, but they had more affective distress and self-reported disability than patients who did not use opioids.<sup>90</sup> No differences were found for age, sex, or pain duration. Breckenridge and Clark<sup>91</sup> contrasted 100 US veterans using opioids with 100 veterans using only nonsteroidal anti-inflammatory drugs for chronic back pain. Using data from a chart review, the groups did not differ in pain intensity, sex, or body mass index, but age, depression, personality disorder, and substance abuse disorders were associated with opioid use.

Another study specifically tested whether opioid use for chronic pain was associated with common psychiatric disorders in the US general population.<sup>92</sup> They found diagnoses of depression, anxiety, or substance abuse significantly increased the probability of having regularly taken an opioid pain medication in the past year. A non-US epidemiologic study of 1906 persons in Denmark with CNCP determined that the 228 individuals who were on opioid medication reported more severe pain, were less likely to be employed, had reduced physical functioning, and diminished quality of life.<sup>93</sup> It can be seen that there

were few consistent patterns with the exception of opioid users reporting greater disability, prior substance abuse, and depression compared with nonopioid users. From the available literature, there have been no consistent differences reported for sex or pain duration. Some, but not all, studies have found increased opioid use and higher reported pain and only 1 of 4 studies showed an age effect.

From the above literature, the overall pattern reported would suggest that younger age is predictive of opioid abuse and greater opioid efficacy. Females may receive less relief than men (suggested by their self-reported increased use); not one study has found males using more opioids. Whether this is a reporting bias or a true representation has yet to be fully determined. For the most part, the literature reports that CNCP patients with higher levels of depression and anxiety seem to be more likely to use opioids, more likely to have issues of opioid abuse, and decreased opioid efficacy. The question remains whether the psychologic disorders antedated the pain condition or whether the experience of chronic, unrelenting or unmanaged pain exerts psychologic pressures on individuals that is far above the norm and subsequently causes changes in behavior and psychologic processes. Although it is tempting to assume that the aforementioned retrospective reports on opioid use and abuse are consistent across all groups and pain conditions, new areas of research may lend understanding to potential physiologic, genetic, and pharmacogenetic mechanisms that might influence opioid efficacy, side effects, and propensity for opioid abuse. Moreover, new research is unveiling novel understandings about psychologic distress (ie, anxiety and depression), pleasure (eg, leading to addiction), physiologic experience of pain, and the mechanisms of actions and processing of opioids as interrelated entities that potentially share common pathways with the particular influence of genetics and ultimately effect pharmacologic processes.

### MECHANISMS THAT SUPPORT INDIVIDUAL DIFFERENCES IN OPIOID EFFICACY

The pain literature is replete with reporting associations between pain and mood, coping, and the psychologic impact of chronic pain. In fact, the literature has related psychologic components, the most notable being depression and anxiety, as significant contributing factors to an individual's experience with pain.<sup>30-32,94</sup> Studies have related genetic factors to psychologic health.<sup>95</sup> Moreover, recent evidence points to the critical role of psychologic state in the development of chronic pain. For example, Young Casey et al<sup>25</sup> reported that traumatic life events and depressed mood were the most predictive of chronic pain and disability. These paths seem to suggest strong associations with one's psychologic status and physiologic effects of pain. What is less clear are the genetic associations, neuromechanisms, and shared substrates of cognitive-affective responses to pain and their potentially interactive relationship with opioid efficacy.

## Genetic Factors

Recent translational research has shown genetic predispositions to be associated with increased pain sensitivity, development of pain conditions and the link with psychologic factors, genetics, and variations in susceptibility to pain.<sup>96-98</sup> How such genetic variations might be related to opioid efficacy and related patient characteristics have yet to be fully explicated. Nonetheless, a recent example involves of catechol-O-methyltransferase (COMT), an enzyme that metabolizes catecholamines and a key regulator of pain perception, cognitive function, and affective mood. Diatchenko et al<sup>99</sup> identified 3 genetic variants (haplotypes) of the COMT gene that designated individuals as possessing low pain sensitivity, average pain sensitivity, and high pain sensitivity. Such haplotypes encompass 96% of the human population, and 5 combinations of these haplotypes were strongly associated with variations in the sensitivity to experimental pain. How that relates to clinical pain is that the presence of a single low pain sensitivity haplotype diminished, by as much as 2.3 times, the risk of developing the chronic pain condition of temporomandibular joint disorder. Other investigators<sup>95</sup> reported an interaction between pain catastrophizing and COMT diplotype and how those factors collectively influence preoperative pain ratings in individuals seeking surgery for shoulder pain. Although the authors do not address opioid efficacy or long-term treatment outcome, this study suggests the potential value of assessing genetic and psychologic factors in presurgical consideration and how collectively, psychosocial and genetic contributions might influence the pain experience.

Relating genetics with psychologic pathways as potential mediators for medication efficacy and chronic pain, Diatchenko et al<sup>100</sup> demonstrated the first direct evidence that low COMT activity leads to increased pain sensitivity via a  $\beta(2/3)$ -adrenergic mechanism. Notably, adrenergic receptor  $\beta(2)$  is a primary target for epinephrine, and it has a vital role in mediating physiologic and psychologic responses to environmental stressors. Functional genetic variants of adrenergic receptor  $\beta(2)$  contribute to the development of a common chronic pain condition and is associated with increased levels of psychologic distress and low blood pressure, factors that are strongly influenced by the adrenergic system.<sup>98,100</sup> These new discoveries are of considerable clinical importance as they establish the link between pain, psychologic distress, and potential targets and mediators for medication efficacy.

Additional reports assert that idiopathic pain disorders, such as temporomandibular joint disorder, fibromyalgia syndrome, irritable bowel syndrome, chronic headaches, interstitial cystitis, and chronic pelvic pain among others, share common pathways of vulnerability including the associations with pain amplification and psychologic distress.<sup>101-104</sup> It is speculated that such conditions are mediated by an individual's genetic variability and exposure to certain environmental stimuli and events, thereby influencing the experience and the

perpetuation of CNCP.<sup>97,100</sup> Studies have been conducted to uncover evidence of the associations of genes and patient-level psychologic characteristics with postoperative outcome and chronic pain. Max et al<sup>105</sup> examined psychotropic efficacy among chronic pain patients, including the disparate reasons why some patients experience less efficacy to certain medications and what genetic factors might explain this variation. Resistance to medication efficacy might be because of the unique neurochemical contribution to mood by afferent pain projections through the spino-parabrachial-hypothalamic-amygdalar systems and respective projections. In seeking to identify molecular mediators and genetic contributors to medication efficacy among 280 patients with sciatica owing to lumbar disc herniation, they found no associations of postoperative mood with polymorphisms of COMT, serotonin transporter, and brain-derived neurotrophic factor. However, exploratory examination of 25 other genes showed pain-gene interactions on postoperative mood with  $\mu$ -opioid receptors (MORs) for short-term effects of acute pain on mood and the galanin-2 receptor for effects of pain on mood 1 year after surgery.

These new areas of discovery are of particular relevance if simple genetic screening could be conducted to offer prediction for which class of opioid to use that would be most effective for a specific group or sex. Given the nascent nature of this field, little is known about the contributions of sex, race, ethnicity, and age. To date, Diatchenko et al<sup>96,97,99</sup> has demonstrated how genetics can predict the likelihood of development of certain pain conditions and the shared common pathways of vulnerability that include neuronal response to psychologic distress. Max et al<sup>105</sup> has shown the role of pain with mood and psychotropic efficacy. Correspondingly, it is likely that future research will uncover key genetic contributors (such as haplotypes) that could identify patient profiles for likelihood of success for specific classes of drugs that could then guide treatment decision-making for opioid therapy for CNCP.

## Neural Links Between Pain, Mood, and Opioid Efficacy

Wasan et al<sup>106</sup> asserted the necessity of assessing psychopathology in the context of opioid treatment. Indeed, the literature seems to suggest that psychologic factors may antedate CNCP. In the context of emerging literature, what is important to consider are new findings from neuroimaging studies that demonstrate the common neural pathways of pain, mood, and reward/avoidant "centers" in the brain and the limited literature on how those relate to opioid response.<sup>107,108</sup> For example, it has been shown that certain brain regions such as the anterior cingulate cortex (ACC), insula, and dorso-lateral prefrontal cortex process both pain and affect.<sup>109</sup> Other researchers have shown that the ACC and insula are laden with opioid receptors<sup>110</sup> and these regions have consistently shown abnormalities in patients with

psychopathology such as depression,<sup>111,112</sup> along with changes in attention and cognition.<sup>113</sup>

One can postulate that patients with chronic pain and psychopathology have altered opioid or other analgesia mechanisms in the ACC, insula, and dorsolateral prefrontal cortex compared with those with few psychologic symptoms. Indeed, Brown et al<sup>114</sup> reported a model wherein psychologic measures and pain severity are more predictive of decrements in cognitive function than specific opioid preparations or daily opioid dose. This further underscores the importance of assessing psychologic health, an important predictor of cognitive dysfunction, and a component in opioid management. However, limited literature is available to explicate the mechanisms accounting for the complex interplay of pain, psychologic factors, and opioid efficacy.

Though speculative, it could be that efficacy and response to opioids might change if the actual structure and receptors to which opioids are targeted have been altered owing to chronic pain or psychologic distress. What is not speculative, but has been shown in the literature, is the relationship between psychologic components (ie, depression) and pain. In fact, investigators have shown loss of gray matter and other neurobiologic effects of chronic pain, including effects on emotional processing and learning.<sup>115</sup> These effects might be important determinants of psychosocial factors related to opioid efficacy but heretofore have not been substantiated in the literature.

Positron emission tomography studies have shown modulation of neuronal activation associated with various types and doses of opioids and findings have revealed significant changes in cerebral blood flow, especially for the ACC and orbitofrontal cortex. Those changes have been associated with pain, modulation of pain by hypnosis, and placebo analgesia.<sup>116–119</sup>

Recent studies in neuroimaging and basic science have provided evidence as to possible underlying mechanisms of opioid efficacy and the complex interrelationships with mood and pain. For example, Zhuo<sup>10</sup> provides a compelling model for understanding the role of genetics and molecular basis for central plasticity of pain, long-term potentiation, and also the role of the hippocampus, amygdala, and ACC as they relate to central sensitization, chronic pain, and pain-related emotional disorders. Novel approaches to understanding and investigating such signaling pathways related to ACC long-term potentiation may help to identify novel drug targets for pain and related psychologic disorders. Such work would also lend insight into potential avenues for prospective studies to identify patient profiles for opioid efficacy.

Leppa et al<sup>120</sup> and others have used functional magnetic resonance imaging to examine acute opioid effects on brain and central nervous system functions. Not too surprisingly, areas rich in receptors (such as MOR) show strong activations, especially when individuals are administered a  $\mu$ -opioid agonist, whereas the primary somatosensory cortex that has the lowest density of MORs demonstrated negligible activation. Notably,

the cingulate (which is rich in opioidergic neurons), orbitofrontal, posterior parietal, and insular cortices along with the amygdala revealed activation which were temporally related to most subjective ratings of sensation that were strongest after drug administration. Importantly, such studies demonstrate the relationship between pain and opioids since such areas belong to the neural circuitry that modulates the affective experience of sensory stimuli such as pain. Thus, the field of pharmacologic magnetic resonance imaging has emerged as a way to investigate the combined effects of drug administration, cognitive tasks, and sensory stimulation.<sup>121</sup> However, this nascent technique has been conducted primarily among substance abusers and in addiction medicine<sup>122,123</sup> and it has yet to be fully adopted in the pain field.

Nonetheless, findings from the pain community coupled with literature from addiction medication lend some speculation to the possibility of neurophysiologic and genetic influences on opioid efficacy and psychologic factors related to pain. Ballantyne and LaForge<sup>59</sup> and others<sup>107</sup> have provided reviews on the complex interactions between the facets of opioid actions (analgesia, hyperalgesia, tolerance, dependence, addiction, etc) and their role in chronic pain management. They report that opioid addiction and tolerance arise from complex adaptations within defined neurocircuitry. Such adaptations do not occur simply owing to continued drug use but as the interaction of the drug with genetic, environmental, psychosocial, and behavioral factors among others. These factors result in long-term adaptations in various groups of neurons in the brain, which lends explanation to the enduring nature of addiction and repeated stimulation of reward circuitry.<sup>59</sup> It is conceivable that the same cascade influences opioid efficacy among chronic pain patients and that psychologic determinants that function along similar neural pathways might simultaneously influence opioid response, pain, and mood.

As such, underlying mechanisms further account for response to opioids including change in gene transcription as well as RNA and in protein processing and synaptic structure.<sup>124–127</sup> Gene expression or protein translation in turn confers long-term alterations on behavior by causing physical remodeling of the synapses and circuits.<sup>128,129</sup> This complex network of interactions involves a multitude of endogenous and exogenous factors including the dynamic interaction of psychosocial, genetic, and drug components. The role of the drug initiation (eg, stimulating the mesocorticolimbic reward circuitry, mode of administration, maintenance) produces neuroadaptations associated with lifelong cravings, and with anhedonic state and reinforcement. Other genetic factors include drug disposition of “pharmacokinetic genes” affecting drug metabolism and transport as well as gene variation affecting pharmacodynamics that influence pain and analgesic responses, dependence, and addiction. All of these factors collectively play a role to varying degrees in their influence of the impact of opioids and factors related to their effectiveness for pain relief.

Such work could lend insight into potential avenues for prospective studies to identify patient profiles for opioid efficacy. Therefore, if these new areas of investigations are further validated through genetics and imaging, these anatomic neuromechanisms could link opiate efficacy to mood, especially depression, potentially through depression's common pathway with pain. Moreover, evidence from the pharmacology literature suggests large variability in response to classes and doses of medications, including opioids, and some of these differences can be explained by genetic variations by sex and ethnicity/race.<sup>130–133</sup> As the field of pain genetics and neuroimaging of pain and analgesia is burgeoning, it is likely that pharmacogenetics will shed more light on the mechanisms influencing differences in response to and efficacy of opioids.

### SUMMARY

This review was intended to examine the empirical evidence for individual-level factors predicting positive response and opioid efficacy among CNCP patients. Apart from a few select empirical studies,<sup>50,84,85</sup> limited literature has been devoted to this important topic. What is evident is a predominant focus in the literature on retrospective accounts of psychologic factors related to opioid abuse or dependence. Some articles see appropriate outcome measures as functional restoration, decreased depression, and improved quality of life as proxy measures for efficacy of opioid trials, with side effects and opiophobia as the driving forces for attrition. Yet, few studies actually address these dimensions in the context of prediction of successful opioid therapy.

Over a decade ago, Jamison asserted the points to evaluate when considering opioid therapy and maintenance (pain intensity, functional capacity, personality and mood, pain beliefs, medication usage, adverse effects, and healthcare utilization along with medical and psychosocial history), but few investigations have taken up the challenge to examine these biopsychosocial factors prospectively. It would certainly behoove clinical decision-making to have predictive measures for opioid prescribing, and it might offer more sound judgment for opioid choice rather than relying primarily on clinical lore. However, to date, addiction literature has dominated the pain field. Moreover, given the advances in the area of pain genetics and pharmacogenetics, the field of pain management would be remiss if we fail to take into consideration these growing areas of discovery. Surprisingly, with regard to prediction of success for opioid treatment or for evaluating patient profiles for opioid efficacy, the field of pain management is woefully behind. The few investigations that have addressed these important aspects of pain treatment have shed light on the bidirectional multimodal, complex labyrinth of pain care and the complexity of finding effective treatments within a true biopsychosocial model. In this regard, there is a clarion call for the scientific and clinical communities to work collectively to advance its knowledge to be able to

adequately assess the value (or lack thereof) of opioids for CNCP. The potential is enormous for improving prediction of treatment outcomes for opioid efficacy for CNCP, for the sake of patients but also as advancing science demands it.

### REFERENCES

- Edlund MJ, Steffick D, Hudson T, et al. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007;129:355–362.
- Green CR, Anderson KO, Baker TA, et al. The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain Med*. 2003;4:277–294.
- Andersson HI, Ejlertsson G, Leden I, et al. Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. *Clin J Pain*. 1993;9:174–182.
- Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. *Neurology*. 2002;58:885–894.
- Torrance N, Smith BH, Bennett MI, et al. The epidemiology of chronic pain of predominantly neuropathic origin: results from a general population survey. *J Pain*. 2006;7:281–289.
- Macfarlane GJ. Generalized pain, fibromyalgia and regional pain: an epidemiological view. *Baillieres Best Pract Res Clin Rheumatol*. 1999;13:403–414.
- Smith BH, Elliott AM, Chambers WA, et al. The impact of chronic pain in the community. *Fam Pract*. 2001;18:292–299.
- Smith BH, Elliott AM, Hannaford PC, et al. Factors related to the onset and persistence of chronic back pain in the community: results from a general population follow-up study. *Spine*. 2004;29:1032–1040.
- Smith BH, Elliott AM, Hannaford PC. Is chronic pain a distinct diagnosis in primary care? Evidence arising from the Royal College of General Practitioners' Oral Contraception Study. *Fam Pract*. 2004;21:66–74.
- Zhuo M. A synaptic model for pain: long-term potentiation in the anterior cingulate cortex. *Mol Cells*. 2007;23:259–271.
- Nielsen LA, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition. *Best Pract Res Clin Rheumatol*. 2007;21:465–480.
- Ge HY, Madeleine P, Arendt-Nielsen L. Sex differences in temporal characteristics of descending inhibitory control: an evaluation using repeated bilateral experimental induction of muscle pain. *Pain*. 2004;110:72–78.
- Merskey H. Variable meanings for the definition of disease. *J Med Philos*. 1986;11:215–232.
- Turk DC, Flor H. Primary fibromyalgia is greater than tender points: toward a multiaxial taxonomy. *J Rheumatol*. 1989;19:80–86.
- Dworkin RH, Breitbart WS, eds. *Psychosocial Aspects of Pain: A Handbook for Health Care Providers*. Seattle, WA: IASP Press; 2004.
- Pincus T, Burton AK, Vogel S, et al. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine*. 2002;27:E109–E120.
- Blyth FM, Macfarlane GJ, Nicholas MK. The contribution of psychosocial factors to the development of chronic pain: the key to better outcomes for patients? *Pain*. 2007;129:8–11.
- Nicholas MK, Molloy AR, Brooker C. Using opioids with persisting noncancer pain: a biopsychosocial perspective. *Clin J Pain*. 2006;22:137–146.
- Verhaak PF, Kerssens JJ, Dekker J, et al. Prevalence of chronic benign pain disorder among adults: a review of the literature. *Pain*. 1998;77:231–239.
- Elliott AM, Smith BH, Hannaford PC, et al. The course of chronic pain in the community: results of a 4-year follow-up study. *Pain*. 2002;99:299–307.

21. Bergman S, Herrstrom P, Hogstrom K, et al. Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study. *J Rheumatol*. 2001;28:1369–1377.
22. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. 2000;85:317–332.
23. McBeth J, Macfarlane GJ, Hunt IM, et al. Risk factors for persistent chronic widespread pain: a community-based study. *Rheumatology*. 2001;40:95–101.
24. Pincus T, Vlaeyen JW, Kendall NA, et al. Cognitive-behavioral therapy and psychosocial factors in low back pain: directions for the future. *Spine*. 2002;27:E133–E138.
25. Young Casey C, Greenberg MA, Nicassio PM, et al. Transition from acute to chronic pain and disability: a model including cognitive, affective, and trauma factors. *Pain*. 2008;134:69–79.
26. Peters ML, Sommer M, de Rijke JM, et al. Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. *Ann Surg*. 2007;245:487–494.
27. Juhl GI, Jensen TS, Norholt SE, et al. Central sensitization phenomena after third molar surgery: a quantitative sensory testing study. *Eur J Pain*. 2008;12:116–127.
28. Combie IK, Croft PR, Linton SJ, et al, eds. *Epidemiology of Pain*. Seattle: IASP Press; 1999.
29. Wittink HM, Rogers WH, Lipman AG, et al. Older and younger adults in pain management programs in the United States: differences and similarities. *Pain Med*. 2006;7:151–163.
30. Chou R, Huffman LH, American Pain Society, American College of Physicians. Nonpharmacological treatments for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med*. 2007;147:492–504.
31. Gatchel RJ, Peng YB, Peters ML, et al. The biopsychosocial approach to chronic pain: advances and future directions. *Psychol Bull*. 2007;133:581–624.
32. Molton IR, Graham C, Stoelb BL, et al. Current psychological approaches to the management of chronic pain. *Curr Opin Anaesthesiol*. 2007;20:485–489.
33. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. *J Pain Symptom Manage*. 1996;11:203–217.
34. Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25:171–186.
35. Portenoy RK, Bennett DS, Rauck R, et al. Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *J Pain*. 2006;7:583–591.
36. Large RG, Schug SA. Opioids for chronic pain of non-malignant origin-caring or crippling. *Health Care Anal*. 1995;3:5–11.
37. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*. 2006;104:570–587.
38. Katz NP, Adams EH, Benneyan JC, et al. Foundations of opioid risk management. *Clin J Pain*. 2007;23:103–118.
39. Portenoy R. Opioid therapy for chronic nonmalignant pain: clinicians' perspective. *J Law Med Ethics*. 1996;24:296–309.
40. Gilson AM, Ryan KM, Joranson DE, et al. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. *J Pain Symptom Manage*. 2004;28:176–188.
41. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain*. 2004;109:514–519.
42. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol*. 2003;60:1524–1534.
43. Jovey RD, Ennis J, Gardner-Nix J, et al. Use of opioid analgesics for the treatment of chronic noncancer pain: a consensus statement and guidelines from the Canadian Pain Society, 2002. *Pain Res Manag*. 2003;8:3A–28A.
44. Gilson AM, Joranson DE. Controlled substances and pain management: changes in knowledge and attitudes of state medical regulators. *J Pain Symptom Manage*. 2001;21:227–237.
45. Joranson DE, Gilson AM. Wanted: a public health approach to prescription opioid abuse and diversion. Comment on: *Pharmacoepidemiol Drug Safety*. 2006;15:618–627. *Pharmacoepidemiol Drug Safety*. 2006;15:632–634.
46. Kalso E, Edwards JE, Moore RA, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372–380.
47. Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ*. 2006;174:1589–1594.
48. Kalso E, Allan L, Dellemijn PL, et al. Recommendations for using opioids in chronic non-cancer pain. *Eur J Pain*. 2003;7:381–386.
49. Graziotti PJ, Goucke CR. The use of oral opioids in patients with chronic non-cancer pain: management strategies. *Med J Aust*. 1997;167:30–34.
50. Jamison RN. Comprehensive pretreatment and outcome assessment for chronic opioid therapy in nonmalignant pain. *J Pain Symptom Manage*. 1996;11:231–241.
51. Breivik H. Opioids in chronic non-cancer pain, indications and controversies. *Eur J Pain*. 2005;9:127–130.
52. Nedeljkovic SS, Wasan A, Jamison RN. Assessment of efficacy of long-term opioid therapy in pain patients with substance abuse potential. *Clin J Pain*. 2002;18:S39–S51.
53. Joranson DE, Gilson AM, Dahl JL, et al. Pain management, controlled substances, and state medical board policy: a decade of change. *J Pain Symptom Manage*. 2002;23:138–147.
54. Joranson DE, Gilson AM. A much needed window on opioid diversion. *Pain Med*. 2007;8:128–129.
55. Joranson DE, Gilson AM. Pharmacists' knowledge of and attitudes toward opioid pain medications in relation to federal and state policies. *J Am Pharm Assoc*. 2001;41:213–220.
56. Martell BA, O'Connor PG, Kerns RD, et al. Opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146:116–127.
57. Turk DC, Monarch ES, Williams AD. Cancer patients in pain: considerations for assessing the whole person. *Hematol Oncol Clin North Am*. 2002;16:511–525.
58. Ballantyne JC. Opioid analgesia: perspectives on right use and utility. *Pain Physician*. 2007;10:479–491.
59. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129:235–255.
60. Ballantyne JC. Opioids for chronic nonterminal pain. *South Med J*. 2006;99:1245–1255.
61. Manchikanti L. National drug control policy and prescription drug abuse: facts and fallacies. *Pain Physician*. 2007;10:399–424.
62. Zacny J, Bigelow G, Compton P, et al. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alcohol Depend*. 2003;69:215–252.
63. Fleming MF, Balousek SL, Klessig CL, et al. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain*. 2007;8:573–582.
64. Fields HL. Should we be reluctant to prescribe opioids for chronic non-malignant pain? *Pain*. 2007;129:233–234.
65. Nishimori M, Kulich RJ, Carwood CM, et al. Successful and unsuccessful outcomes with long-term opioid therapy: a survey of physicians' opinions. *J Palliat Med*. 2006;9:50–56.
66. Reid MC, Engles-Horton LL, Weber MB, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med*. 2002;17:173–179.
67. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res*. 2006;6:46.
68. Manchikanti L, Giordano J, Boswell MV, et al. Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients. *J Opioid Manag*. 2007;3:89–100.
69. Wasan AD, Butler SF, Budman SH, et al. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related

- behavior among patients with chronic pain. *Clin J Pain*. 2007;23:307–315.
70. Chabal C, Erjavec MK, Jacobson L, et al. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. *Clin J Pain*. 1997;13:150–155.
  71. Butler SF, Budman SH, Fernandez K, et al. Validation of a screener and opioid assessment measure for patients with chronic pain. *Pain*. 2004;112:65–75.
  72. Adams LL, Gatchel RJ, Robinson RC, et al. Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. *J Pain Symptom Manage*. 2004;27:440–459.
  73. Akbik H, Butler SF, Budman SH, et al. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). *J Pain Symptom Manage*. 2006;32:287–293.
  74. Holmes CP, Gatchel RJ, Adams LL, et al. An opioid screening instrument: long-term evaluation of the utility of the Pain Medication Questionnaire. *Pain Pract*. 2006;6:74–88.
  75. Passik SD, Kirsh KL. Assessing aberrant drug-taking behaviors in the patient with chronic pain. *Curr Pain Headache Rep*. 2004;8:289–294.
  76. Passik SD, Kirsh KL. Managing pain in patients with aberrant drug-taking behaviors. *J Support Oncol*. 2005;3:83–86.
  77. Passik SD, Kirsh KL, Whitcomb L, et al. Monitoring outcomes during long-term opioid therapy for noncancer pain: results with the Pain Assessment and Documentation Tool. *J Opioid Manag*. 2005;1:257–266.
  78. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005;6:432–442.
  79. Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and “problematic” substance use: evaluation of a pilot assessment tool. *J Pain Symptom Manage*. 1998;16:355–363.
  80. 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. *JAMA*. 2005;293:3043–3052.
  81. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther*. 2005;7:1046–1051.
  82. Cepeda MS, Farrar JT, Baumgarten M, et al. Side effects of opioids during short-term administration: effect of age, gender, and race. *Clin Pharmacol Ther*. 2003;74:102–112.
  83. Farrar JT, Portenoy RK, Berlin JA, et al. Defining the clinically important difference in pain outcome measures. *Pain*. 2000;88:287–294.
  84. Wasan AD, Davar G, Jamison R. The association between negative affect and opioid analgesia in patients with discogenic low back pain. *Pain*. 2005;117:450–461.
  85. Edwards RR, Haythornthwaite JA, Tella P, et al. Basal heat pain thresholds predict opioid analgesia in patients with postherpetic neuralgia. *Anesthesiology*. 2006;104:1243–1248.
  86. Haythornthwaite JA, Menefee LA, Quatrano-Piacentini AL, et al. Outcome of chronic opioid therapy for non-cancer pain. *J Pain Symptom Manage*. 1998;15:185–194.
  87. Turk DC, Okifuji A. What factors affect physicians’ decisions to prescribe opioids for chronic noncancer pain patients? *Clin J Pain*. 1997;13:330–336.
  88. Ciccone DS, Just N, Bandilla EB, et al. Psychological correlates of opioid use in patients with chronic nonmalignant pain: a preliminary test of the downhill spiral hypothesis. *J Pain Symptom Manage*. 2000;20:180–192.
  89. Fanciullo GJ, Ball PA, Girault G, et al. An observational study on the prevalence and pattern of opioid use in 25,479 patients with spine and radicular pain. *Spine*. 2002;27:201–205.
  90. Fillingim RB, Doleys DM, Edwards RR, et al. Clinical characteristics of chronic back pain as a function of gender and oral opioid use. *Spine*. 2003;28:143–150.
  91. Breckenridge J, Clark JD. Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. *J Pain*. 2003;4:344–350.
  92. Sullivan MD, Edlund MJ, Steffick D, et al. Regular use of prescribed opioids: association with common psychiatric disorders. *Pain*. 2005;119:95–103.
  93. Eriksen J, Sjogren P, Bruera E, et al. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006;125:172–179.
  94. Lynch ME, Campbell F, Clark AJ, et al. A systematic review of the effect of waiting for treatment for chronic pain. *Pain*. 2007; doi:10.1016/j.pain.2007.06.018.
  95. George SZ, Wallace MR, Wright TW, et al. Evidence for a biopsychosocial influence on shoulder pain: pain catastrophizing and catechol-O-methyltransferase (COMT) diplotype predict clinical pain ratings. *Pain*. 2007. In press. doi: 10.1016/j.pain.2007.06.019.
  96. Diatchenko L, Anderson AD, Slade GD, et al. Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2006;141:449–462.
  97. Diatchenko L, Nackley AG, Slade GD, et al. Idiopathic pain disorders: pathways of vulnerability. *Pain*. 2006;123:226–230.
  98. Nackley AG, Tan KS, Fecho K, et al. Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors. *Pain*. 2007;128:199–208.
  99. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet*. 2005;14:135–143.
  100. Diatchenko L, Nackley AG, Slade GD, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain*. 2006;125:216–224.
  101. McBeth J, Macfarlane GJ, Benjamin S, et al. Features of somatization predict the onset of chronic widespread pain: results of a large population-based study. *Arthritis Rheum*. 2001;44:940–946.
  102. Bradley LA, McKendree-Smith NL. Central nervous system mechanisms of pain in fibromyalgia and other musculoskeletal disorders: behavioral and psychologic treatment approaches. *Curr Opin Rheumatol*. 2002;14:45–51.
  103. Verne GN, Price DD. Irritable bowel syndrome as a common precipitant of central sensitization. *Curr Rheumatol Rep*. 2002;4:322–328.
  104. Gracely RH, Geisser ME, Giesecke T, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain*. 2004;127:835–843.
  105. Max MB, Wu T, Atlas SJ, et al. A clinical genetic method to identify mechanisms by which pain causes depression and anxiety. *Mol Pain*. 2006;192:14.
  106. Wasan AD, Correll DJ, Kissin I, et al. Iatrogenic addiction in patients treated for acute or subacute pain: a systematic review. *J Opioid Manag*. 2006;2:16–22.
  107. Bond C, LaForge KS, Tian M, et al. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. *Proc Natl Acad Sci*. 1998;95:9608–9613.
  108. Rainville P, Doucet JC, Fortin MC, et al. Rapid deterioration of pain sensory-discriminative information in short-term memory. *Pain*. 2004;110:605–615.
  109. Rainville P. Brain mechanisms of pain affect and pain modulation. *Curr Opin Neurobiol*. 2002;12:195–204.
  110. Vogt BA, Wiley RG, Jensen EL. Localization of mu and delta opioid receptors to anterior cingulate afferents and projection neurons and input/output model of mu regulation. *Exp Neurol*. 1995;135:83–92.
  111. Rogers MA, Bellgrove MA, Chiu E, et al. Response selection deficits in melancholic but not nonmelancholic unipolar major depression. *J Clin Exp Neuropsychol*. 2004;26:169–179.
  112. Rogers MA, Kasai K, Koji M, et al. Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neurosci Res*. 2004;50:1–11.
  113. Swick D, Jovanovic J. Anterior cingulate cortex and the Stroop task: neuropsychological evidence for topographic specificity. *Neuropsychologia*. 2002;40:1240–1253.

114. Brown RT, Zuendorf M, Fleming M. Adverse effects and cognitive function among primary care patients taking opioids for chronic nonmalignant pain. *J Opioid Manag.* 2006;2:137–146.
115. Baliki MN, Apkarian AV. Neurological effects of chronic pain. *J Pain Palliat Care Pharmacother.* 2007;21:59–61.
116. Adler LJ, Gyulai FE, Diehl DJ, et al. Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. *Anesth Analg.* 1997;84:120–126.
117. Rainville P, Duncan GH, Price DD, et al. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science.* 1997;277:968–971.
118. Iadarola MJ, Berman KF, Zeffiro TA, et al. Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain.* 1998;121:931–947.
119. Petrovic P, Kalso E, Petersson KM, et al. Placebo and opioid analgesia: imaging a shared neuronal network. *Science.* 2002;295:1737–1740.
120. Leppä M, Korvenoja A, Carlson S, et al. Acute opioid effects on human brain as revealed by functional magnetic resonance imaging. *Neuroimage.* 2006;31:661–669.
121. Wise RG, Williams P, Tracey I. Using fMRI to quantify the time dependence of remifentanyl analgesia in the human brain. *Neuropsychopharmacology.* 2004;29:626–635.
122. Breiter HC, Gollub RL, Weisskoff RM, et al. Acute effects of cocaine on human brain activity and emotion. *Neuron.* 1997;19:591–611.
123. Stein EA, Pankiewicz J, Harsch HH, et al. Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. *Am J Psychiatry.* 1998;155:1009–1015.
124. Nestler EJ. Molecular basis of long-term plasticity underlying addiction. *Nat Rev Neurosci.* 2001;2:119–128. Erratum in: *Nat Rev Neurosci.* 2001;2:215.
125. Nestler EJ. Under siege: the brain on opiates. *Neuron.* 1996;16:897–900.
126. Nestler EJ. Historical review: molecular and cellular mechanisms of opiate and cocaine addiction. *Trends Pharmacol Sci.* 2004;25:210–218.
127. Nestler EJ. Molecular mechanisms of drug addiction. *Neuropharmacology.* 2004;47(suppl 1):24–32.
128. Hope BT, Nye HE, Kelz MB, et al. Induction of a long-lasting AP-1 complex composed of altered Fos-like proteins in brain by chronic cocaine and other chronic treatments. *Neuron.* 1994;13:1235–1244.
129. Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat Rev Neurosci.* 2001;2:695–703.
130. Kim K, Johnson JA, Derendorf H. Differences in drug pharmacokinetics between East Asians and Caucasians and the role of genetic polymorphisms. *J Clin Pharmacol.* 2004;44:1083–1105.
131. Schwartz JB. The influence of sex on pharmacokinetics. *Clin Pharmacokinet.* 2003;42:107–121. Erratum in: *Clin Pharmacokinet.* 2004;43:732.
132. Meibohm B, Beierle I, Derendorf H. How important are gender differences in pharmacokinetics? *Clin Pharmacokinet.* 2002;41:329–342.
133. Gaedigk A, Ndjountche L, Divakaran K, et al. Cytochrome P4502D6 (CYP2D6) gene locus heterogeneity: characterization of gene duplication events. *Clin Pharmacol Ther.* 2007;81:242–251.