Management of Opioid Medications in Patients With Chronic Pain and Risk of Substance Misuse

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When prescribed appropriately and used as prescribed, opioid medications can safely and effectively treat pain. Best practices with respect to their use in chronic non–cancer-related pain (CNCP) are evolving. Opioids may be subject to misuse for a variety of purposes, including self-medication, use for reward, compulsive use because of addiction, and diversion for profit. Individuals with chronic pain and co-occurring substance use, mental health disorders, and other conditions may be at increased risk for misuse of prescribed opioids. Interdisciplinary pain management, the use of universal precautions in all patients, and special attention to the structure of care in those at higher risk for opioid misuse may improve outcomes in opioid treatment of CNCP. This article discusses evolving research and clinical literature related to the care of individuals with CNCP at a higher risk for opioid misuse.

Introduction

Historical context

Therapeutic use of opioids

Opioids are the most effective clinically available class of analgesic medications. It has long been recognized, however, that therapeutic opioid use is sometimes associated with misuse or addiction and tolerance to their therapeutic effects. Periods of widespread medical use often have been followed by periods of relative disfavor in response to observation of negative consequences.

In the mid–20th century, the use of opioid medications was discouraged in mainstream medicine largely because of concern about their addiction potential: a 1941 paper in the *Journal of the American Medical Association* stated, "The use of narcotics in the terminal cancer patient is to be condemned … due to undesirable side effects … dominant in the list of these … is addiction" [1]. As understanding of opioid pharmacology and the neurobiology and clinical phenomenology of addiction and pain evolved over ensuing decades, more aggressive use of opioids in the treatment of cancer-related and acute pain was encouraged [2]. Positive outcomes of such treatment, including reduced suffering, shorter hospital stays, and improved quality of life, are well documented.

The observation that cancer patients and others who used opioids on a prolonged basis for pain did not routinely develop addiction or unmanageable tolerance led to consideration of a broader role for opioids in the treatment of chronic non–cancer-related pain (CNCP) [3]. It is now widely accepted that opioids may play a valuable role in the treatment of all types of pain, including some CNCP, although their specific indications and optimum management continue to be debated [4].

Misuse of prescription opioids

Expanding use of opioids has been paralleled with expanding nonmedical use [5]. The 2006 National Survey on Drug Use and Health (NSDUH) found that 13.6% of Americans report lifetime nonmedical use of opioids, and 5.1% and 2.1% reported nonmedical use in the past year or past month, respectively. Misuse of opioids is reflected in increasing emergency department visits related to prescription opioid misuse [6], increased admissions for treatment of prescription opioid addiction (rising between 1992 and 2007 from 0.9% to 5% of addiction treatment requests nationally at federally funded treatment centers and from 1.1% to 20% in West Virginia, a region rife with prescription opioid abuse) [7], and increased involvement of opioid medications in overdose drug deaths [8].

The first decade of the 21st century has been rich with research and clinical consensus activities aimed at better understanding the phenomenology of prescription opioid misuse and developing strategies to reduce it. The following review addresses key questions and their emerging answers.

What Is the Risk of Prescription Opioid Misuse?

Motivators of misuse

To properly assess risk and address opioid misuse, it is important to consider motivations for misuse. Little epidemiologic information exists on the relative distribution of reasons for misuse [9]; however, they may include self-medication of symptoms, elective use to produce reward or euphoria, compulsive use because of addiction, and diversion for profit.

Self-medication of symptoms

In addition to their indicated clinical uses in the treatment of pain, addiction, cough, and diarrhea, opioids sometimes have other effects that individuals may experience as therapeutic: sedation may help to induce sleep or blunt anxiety, euphoria may elevate depressive symptoms [10], and the impact of traumatic memories may be modulated [11]. Therefore, people with access to opioids—clinically or through street sources—may use them to self-medicate diverse symptoms. More specific, effective, and longitudinally appropriate treatments are usually preferred; however, when such effects accompany legitimate treatment and are resonant with the goals of therapy, they may be perceived as salutary side effects. Risks of self-medication include unsafe dosing; omission of more effective treatment options; and, theoretically, that the reinforcing effects of opioids may drive increased symptoms, increased medication use, alternating periods of relief and withdrawal, and enhanced vulnerability to addiction [12,13].

Self-medication of pain

Much of the nonmedical use of opioids in the general population may in fact reflect self-medication of pain. A recent Internet survey of more than 3500 college students found that 13.9% reported lifetime and 7.2% past year use of opioid medications that were not prescribed for them. Among lifetime users, 42.4% reported use only to relieve pain, 23.9% reported use to get high, and 33.9% reported mixed self-treatment and recreational use [14].

Patients prescribed opioids for pain may use them in higher doses than prescribed to self-medicate pain. Patients are usually advised to titrate opioids only with supervision of their prescribing clinician. Repeated episodes of self-initiated titration may indicate an emerging opioid use disorder. However, there are several reasons that patients may require higher-than-anticipated doses of opioids to achieve analgesia, and some may autotitrate doses if clinicians do not recognize and accommodate these.

Higher dose requirements

First, analgesic dose requirements for the same pain generator may vary widely between individuals based on biogenetic and other influences [15]. Second, neuropathic pain may shift the opioid dose–response curve such that higher doses of opioids are required to achieve the same level of analgesia than in nonneuropathic pain [16]. Third, tolerance may occur over time, with some individuals developing tolerance more rapidly than others [15]. Finally, some patients appear to develop increasing generalized pain or painful hypersensitivity (allodynia) that may be caused by opioids. Opioid-induced hyperalgesia is suggested by observation of increasing nonfocal or more diffuse pain and hypersensitivity with diminishing duration and intensity of analgesic responses in the absence of apparent progression of pathology [17]. Patients may feel driven to increase their medication doses with the hope of attenuating the increasing pain.

Emerging evidence suggests that hyperalgesia, progressive tolerance, medication use problems, and/or generally diminishing returns are more common with higher-dose opioids, which some experts define as greater than the analgesic equivalent of 200 mg/d of morphine [18•]. Therefore, when opioid dose requirements appear to be climbing beyond this level in individuals with CNCP and stable pathology, some clinicians recommend rotating to a new opioid at somewhat lower equianalgesic doses to avoid or address tolerance or hyperalgesia [19]. As incomplete cross-tolerance is usually present to a new opioid, better analgesia at lower doses of the new drug may occur. Using this technique, some patients can be managed by rotating as needed between moderate doses of different opioids [20]. Alternatively, some patients with escalating pain in the context of stable pathology appear to experience improved analgesia by simply tapering opioid doses, possibly due to the reversal of hyperalgesic mechanisms [21].

Despite these concerns, some patients clearly benefit from opioid doses well above 200 mg/d of morphine equivalents, so clinical judgment must be used to determine whether to rotate, taper, maintain, or increase the dose. Stability of pain relief in response to dose increase, focal versus generalized nature of pain, and overall well-being and function of the patient must be considered in decision making. Special care is indicated in monitoring patients who require higher-than-usual doses of opioids.

Use for reward

Opioids induce reward (or euphoria) in some, but not all, individuals, and some who experience reward may elect to use opioids for euphoria. Biogenetics shape individual responses to opioids, including analgesic responses, reward, and side effects [22]. It is clear that different μ-opioids (eg, morphine, oxycodone, methadone, fentanyl, and hydrocodone) variably affect different μ-subreceptors and that different individuals variably express μ-opioid subreceptors and thus may respond differently to different medications [23]. It is conceivable that someday, through biogenetic profiling, clinicians will be able to match opioids to individual patients based on prospective identification of relative analgesia and reward effects [24].

Compulsive misuse caused by addiction

Some individuals who use opioids therapeutically or recreationally are vulnerable to the development of opioid

addiction, particularly if opioids are used in a manner that creates reward. Addiction in the context of therapeutic use of opioids may be reflected in a maladaptive pattern of use that includes impaired control over use, compulsive use caused by craving, and continued use despite harm. Five of the seven *DSM-IV* criteria for substance dependence cannot be reliably used to diagnose addiction in the context of prescribed use, as they may reflect expected physiologic consequence of use (tolerance and physical dependence), responses to underlying pain (use of more drug or use longer than intended, unsuccessful attempts to cut down), or difficulty finding pain treatment (much time spent seeking opioids). Because of confusion between the terms *substance dependence* and *physical dependence*, many experts recommend using the term *addiction*, especially in the context of opioid treatment of pain, in place of substance dependence [25].

Diversion

Diversion of opioids from their intended therapeutic track may occur in a variety of ways. Preclinical diversion may occur through theft at manufacturing plants, in transit situations, or from pharmacies [26]. Pharmacists, physicians, or other health care professionals may sell, trade, or misuse medications. Postclinical diversion occurs when patients share, sell, or misuse medications they have been prescribed or when medications are stolen from them. Some diversion may seem relatively innocent (eg, a patient sharing medication left over from surgery with a spouse for an acute pain problem) or clearly criminal (eg, a doctor shopper feigning pain to obtain opioids to sell for profit); however, all diversion risks harmful consequences.

The 2006 NSDUH study found that among individuals who reported nonmedical use of opioids, 70.5% obtained opioids from friends or relatives, 19.1% had prescriptions from one doctor, 1.6% had prescriptions from more than one doctor, 3.9% obtained them from a dealer or stranger, and 0.1% acquired them via the Internet. Of those who obtained opioids from friends or relatives, 80.7% believed their sources obtained opioids from one doctor, and 3.3% from more than one doctor [27]. This suggests that about 20% of those who use opioids nonmedically receive them as patients but that patients (with or without their knowledge) are a major source of diverted opioids.

Clinical presentation of opioid misuse

Opioid misuse may present in diverse, aberrant drug-related behaviors (ADRBs) such as requests for early renewals, reports of lost or stolen prescriptions, observable intoxication or withdrawal, demanding behaviors, or a failure to respond to treatment. Identified ADRBs merit careful assessment to identify and appropriately address the cause of the behaviors. With the exception of diversion for profit, misuse most often reflects co-occurring clinical problems that demand further clinical attention.

Prevalence of misuse, abuse, and addiction among patients treated for pain

The prevalence of prescription opioid misuse and new-onset addiction in the context of pain treatment has long been a subject of debate. Early studies of street addicts suggested many became addicted during medical treatment, which led to perceptions of a high risk of addiction in individuals treated with opioids [28]. Conversely, retrospective reviews, widely quoted in the late 20th century, of medical patients without addiction histories who received short-term opioid treatment suggested negligible risk of addiction [29,30]. More recent studies suggest an intermediate reality.

A structured, evidence-based review of available quality studies assessing clinically identified opioid "abuse" or "addiction" or observed ADRBs found that the rate of abuse/addiction identified by clinicians in patients using opioids for chronic pain across all studies was 3.27%, and the rate of ADRBs was 11.5%. In studies that excluded individuals with current or prior history of a substance use disorder (SUD), the identified abuse/addiction rate fell to an average of 0.19%, and that of ADRBs to 0.59%. A subset of five studies using urine toxicologies—a more objective measure of adherence—found no prescribed opioid in on average 20.4% of patients and an illicit drug in 14.5% (range, 4.3% to 57%); these studies did not exclude patients with SUDs [31•].

The higher rates of ADRBs than clinically identified abuse or addiction may reflect clinical abuse/addiction that is undiagnosed by clinicians or co-occurring problems with self-medication or other forms of misuse. Higher rates of unexpected urine drug screen findings suggest that this more objective measure, used together with behavioral observation, has a greater power to identify opioid misuse, abuse, and/or addiction than observation alone and that actual rates of abuse/addiction may be higher than that reflected in studies that did not use this measure. Although there are clearly inherent limitations in such a review, it provides the best currently available range of estimates for abuse and addiction risks associated with opioid treatment of CNCP.

Who Is at Risk for Prescription Opioid Misuse, Abuse, and Addiction?

Comorbidity of chronic pain, substance use disorders, and mental health conditions

Chronic pain frequently co-occurs with psychological conditions, including anxiety, depression, and post-traumatic stress disorder. In turn, these conditions have a high co-occurrence with SUDs. The convergence of psychological comorbidities with chronic pain and SUDs suggests a potentially high risk among chronic pain patients for misuse of prescribed opioids directed at self-medication or use for reward or caused by addiction. Individuals presenting for substance abuse treatment have a relatively high prevalence of chronic pain. As noted previously, however,

the actual prevalence of opioid misuse, abuse, and addiction in individuals prescribed opioids for CNCP seems relatively low. It may be that clinicians less frequently prescribe opioids to people with substance use or mental health conditions. Some evidence suggests that opioid reward is reduced in the presence of pain [32,33], which may reduce risks of misuse to some degree. Nonetheless, a subset of chronic pain patients prescribed opioids do misuse opioids, and several recent studies aimed to characterize who is at risk.

Prescription opioid misuse and mental health conditions

A 2009 analysis of the 2002 National Epidemiologic Study of Alcohol and Related Condition, a survey of more than 40,000 people, found that mood disorders (including a spectrum of depressive and anxiety disorders) were associated with an elevated risk for prescription opioid misuse and supported a self-medication model of misuse [34]. The same study also found that individuals who misused opioids had an increased risk of developing mood disorders in the absence of preexisting comorbidity.

An analysis of the 2003 NSDUH found that individuals with any co-occurring mental health conditions had twice the risk for initiation of nonmedical use of opioids, and those with depressed feelings for 2 or more weeks had 2.5 times the risk of those with no co-occurring condition [35]. The NSDUH study also found that any lifetime use of marijuana, cocaine, or heroin was associated with increased likelihood of nonmedical use of prescription opioids and that whites had twice the likelihood of misusing compared with African Americans.

A recent study of patients presenting to an emergency department for a renewal of opioids found that trait anxiety and panic disorder, as assessed using five validated self-report instruments and a structured clinical interview, correlated with a positive screen for risk of opioid misuse using a validated screen for risk of opioid misuse [36].

Prescription opioid misuse and co-occurring substance use disorders

Mounting evidence supports history of an SUD as a major risk factor for misuse of prescription opioids. A study of longitudinal administrative data on 15,160 veterans found a history of SUD to be a strong predictor of opioid misuse, and co-occurring mental health disorder to be a moderately strong predictor of recognized prescription opioid abuse or dependence. Because mental health disorders were more prevalent (45.3% vs 7.6%), they accounted for greater attributable risk in the population than history of an SUD [37]. A more controlled study of 127 veterans prescribed opioids in a primary care setting found that patients with a history of an SUD were three to six times more likely to misuse opioid medications than patients without a history of an SUD [38].

Another study found younger age, history of alcohol abuse or current marijuana or cocaine use, and history of legal problems with alcohol or drugs increased the risk of prescribed opioid misuse [39], and another found that individuals with evidence of cocaine use were much less likely to resolve opioid misuse in a structured prescribing program than other patients [40].

A recent study found that individuals seeking treatment for prescription opioid addiction were more likely to recall reward effects on their first exposure to opioids than a control group of chronic pain patients on long-term opioid treatment who did not develop addiction [41]. Another identified presence of medication craving as a predictor of prescribed opioid misuse [42]. These suggest that underlying vulnerability in the limbic reward system may drive prescribed opioid misuse.

Taken in aggregate, these studies support expectations that individuals with some mental health disorders, preexisting SUDs, and/or substance-related legal problems may be at higher risk for prescription opioid misuse. Two recent reviews of evidence related to opioid misuse risk prediction generally supported these conclusions; however, both noted that available evidence is limited, that studies could not always determine whether SUDs or mental health conditions preceded or were a consequence of chronic pain and opioid treatment, and that more research is needed to confirm the suggested associations [43,44]. In addition, they emphasized that risk prediction does not equate with actual misuse, so recognition of variables associated with increased risk must be integrated with other clinical information.

Can Risk for or Actual Misuse, Abuse, or Addiction Be Detected in Clinical Settings?

Clinical evaluation

Clinical history, physical examination, and pertinent laboratory review can provide important clinical information for patients being considered for opioid treatment of chronic pain. In addition to comprehensive pain evaluation, history taking should include personal and family substance use histories, current substance use patterns, history of legal problems associated with alcohol or drugs, and assessment for co-occurring psychiatric conditions. Physical examination for findings associated with potentially harmful drug or alcohol use (eg, intravenous tracks or stigmata of alcoholism) or signs of intoxication or withdrawal may be revealing. Laboratory findings such as increased liver function studies; mean corpuscular volume; or positivity for HIV, hepatitis B, or hepatitis C antibodies may suggest a need to further evaluate for alcohol or injection drug use. Urine drug screen may provide objective evidence of recent use of illicit drugs or nonprescribed controlled substances.

Tools to predict risk of misuse

Standard screens for SUDs such as the Alcohol Use Disorders Identification Test, CAGE-AID (CAGE-Adapted to Include Drugs), Short-Michigan Alcohol Screening

Test-Adapted to Include Drugs, Drug Abuse Screening Test, and others may help to identify active substance use problems associated with elevated risk of opioid misuse. However, they are not designed to identify individuals without current use problems who may be at risk for misuse of prescribed opioids. Two promising tools in development for this purpose are the Opioid Risk Tool (ORT) and the Revised Screener and Opioid Assessment for Patients With Pain.

The ORT is a 10-item screen with questions related to age, personal and family substance histories, specific mental health diagnoses, and history of child sexual trauma that can be self- or clinician-administered. Scored results stratify respondents into low-, moderate-, and higher-risk groups. Clinical management recommendations were recently suggested for different ORT risk groups, although no outcomes data on the recommendations are currently available [45].

The Screener and Opioid Assessment for Patients With Pain is a 24-item screen that uses a five-point scale for each item. A score above 18 is reported to have a sensitivity of 80% in predicting actual risk behaviors (20% of those at risk will not be identified) and a specificity of 68% (false positives of 32%) [46].

Tools to identify current misuse

Many tools in development aim to detect misuse of opioids while opioids are prescribed for pain. Among these are the Prescription Drug Use Questionnaire [47], the Current Opioid Misuse Measure (a 17-item self-administered questionnaire) [48], the Pain Medication Questionnaire (a 24-item self-administered questionnaire) [49], and the Addiction Behaviors Checklist (a 20-item clinician-observed checklist) [50]. The Drug Misuse Index, a combination of several measures, including the Screener and Opioid Assessment for Patients With Pain, Current Opioid Misuse Measure, urine toxicology, and other measures, has been used to predict and identify risk behaviors [51].

A recent evidence-based review of these evolving opioid risk prediction and aberrant use identification tools and others noted promise, but also significant limitations, in evidence supporting their validity and generalizability for clinical use in different settings [44].

Identification of substance use disorders

A recent study of 904 chronic pain patients receiving opioid therapy in a primary care setting for an average of 6.4 years attempted to determine which aberrant drug use behaviors might best indicate an active SUD. The study found that a patient's reporting of four or more aberrant behaviors on a self-reported survey of 12 questions was highly predictive of detection of an SUD with a structured clinical interview. Four specific behaviors were most strongly associated with an SUD: oversedation on purpose, feeling of intoxication, early refills, and increased dose on own. Those who screened positive for cocaine use were 14 times more likely to have an SUD [52].

How Can the Potential for Harm Be Minimized in the Presence of Risk?

Interdisciplinary pain care

Persistent pain is a multidimensional experience that often includes biopsychosocial and functional dimensions. Pain that has a discrete, underlying, reversible cause may respond to simple treatment. However, more entrenched chronic pain syndromes often respond best to interdisciplinary care that encourages an active patient role with well-coordinated guidance from a team of diverse professionals, including members of the patient's primary care medical home, physical therapist, mental health provider, pain specialist, and others as indicated. When opioid therapy is indicated for a higher-risk individual, an addiction professional may be an important participant in care. Interdisciplinary care has been demonstrated to reduce misuse of opioids in many patients over time [49]. Thoughtful combinations of pain medications with different mechanisms of action, such as NSAIDs, anticonvulsants, some antidepressants, topical agents, and others as indicated, may improve analgesia and reduce dose requirements for individual medications, including opioids.

Universal precautions

Because prediction of opioid misuse risk is imprecise and can have significant consequences for the prescriber and the patient, the use of universal precautions with all patients using opioids for chronic pain has been recommended to include the following [53]:

- Comprehensive evaluation with attention to pain, psychosocial, and substance-related issues
- Diagnostic formulation of contributing components to pain
- Routine use of opioid informed consent and treatment agreements
- Regular supervision and monitoring
- Routine toxicology screening to document opioid use and detect nonprescribed drug use
- Careful documentation

Routine implementation of such precautions may reduce stigma associated with use of opioid agreements and drug screens and permit early intervention in issues that challenge clinical care.

Opioid agreements support shared understanding of the plan of care and affirm a basis for continuation or cessation of treatment; clear goals of care help to measure the success or failure of therapy. Such goals usually include reduction in pain and improvement in valued functions. Debate continues regarding the routine use of urine drug screens in all patients, but it is clear that random use helps to identify unexpected substance issues and may shape care [54].

Structuring care to support higher-risk patients

In patients identified at higher risk or who demonstrate misuse of opioids, it is possible and prudent to adapt the structure of care to support safe and effective treatment [55]. Some broad elements of structure to consider include the following:

- Setting of care (specialty vs primary care, highly coordinated vs routine)
- Selection of treatments (eg, weighing relative risk–benefit of opioids vs other interventions, selection of quick-onset, intermittent opioids vs steady-state, longer-acting opioids)
- Supply of opioid medications (prescribed vs dispensed at intervals by trusted other, frequency, and quantity released to patient)
- Supportive care (recovery groups, psychotherapy, counseling as indicated)
- Supervision (frequency of clinician visits, urine toxicology screens, and pill counts)

More specific strategies that have been suggested for higher-risk patients include weekly or more frequent medication releases, 24-hour-notice pill counts, substance abuse education worksheets, referral to pain and substance abuse websites, individual compliance counseling, completion of an opioid compliance checklist before receiving opioid prescriptions, and urine drug screens at each visit [51]. Early identification of opioid misuse permits the introduction of strategies to reduce risk of addiction or harmful consequences.

Tightened structure of care appears effective in reducing risk behaviors in many patients and in identifying those for whom opioid therapy may not be appropriate. A Veterans Administration opioid renewal clinic that introduced structured care of patients with active ADRBs found that at 1 year, 45.6% resolved ADRBs, 44.1% self-discharged or were discontinued from opioid therapy for nonadherence to the treatment plan, and 10.2% accepted referral for addiction treatment [40]. The structure of care may change over time in response to the patient's needs or behaviors.

Continuation or cessation of opioid treatment

As with other medical care, if the goals of treatment are being met and untenable side effects or risky behaviors do not occur, continued opioid treatment is appropriate. If pain does not improve with opioid titration, if unmanageable side effects persist and do not respond to medication adjustment, if nonadherence to an agreed-upon treatment plan recurs, and/or if risky drug-related behaviors do not resolve with tightened structure of care, it may be appropriate to discontinue opioid treatment. Treatment of co-occurring problems, such as addiction, should be implemented and alternative pain management approaches offered. If the patient is physically dependent on opioids, opioids should be tapered to prevent withdrawal.

Opioid treatment of addiction versus pain

Opioid agonist treatment of addiction may be helpful for patients with co-occurring opioid addiction and pain who cannot adhere to a safe treatment plan using a pain treatment paradigm for opioid treatment. Methadone maintenance treatment may provide some pain control, but because methadone has an analgesic half-life of 6 to 8 hours, daily dosing as usually provided in methadone maintenance treatment clinics often will not provide adequate analgesia. Split dosing or additional interval methadone provided for pain may be more helpful [56]. Buprenorphine, currently approved for office-based treatment of opioid addiction, is a potent analgesic that shows promise for treatment of addiction and co-occurring pain in some patients with dual diagnosis [57]. Coordination between pain treatment and addiction treatment providers is critical in managing patients with active addiction and pain who require opioid treatment.

Conclusions

Evidence with respect to best practices in opioid treatment of CNCP is evolving. Several professional and regulatory organizations have released clinical guidelines related to the use of opioids in the treatment of chronic pain [18•,45,58,59•]. However, extensive gaps exist in the knowledge base related to opioid prescribing for CNCP, particularly with respect to individuals at higher risk for opioid misuse [60]. In the absence of clear evidence, it has been noted that some guidelines, based on narrow consensus, can have unintended negative consequences on clinical care [61]. At this time, the art of medicine, grounded in respectful care of the whole person and drawing on clinical experience and limited available scientific evidence, must direct care of complex patients with CNCP.

Disclosure

Dr. Savage has served on advisory boards for Ameritox, Meda Pharmaceuticals, and REGISTRAT.

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