Pain Physician 2017; 20: S93-S109• ISSN 1533-3159

Comprehensive Review

Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 11-17-2015
Revised manuscript received: 11-04-2016
Accepted for publication: 01-12-2017

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Chronic pain and prescription opioid abuse are extremely prevalent both in this country and worldwide. Consequences of opioid misuse can be life-threatening with significant morbidity and mortality, exacting a heavy toll on patients, physicians, and society. Individuals with chronic pain and co-occurring substance use disorders and/or mental health disorders, are at a higher risk for misuse of prescribed opioids. Opioid abuse and misuse occurs for a variety of reasons, including self-medication, use for reward, compulsive use because of addiction, and diversion for profit.

There is a significant need for treatment approaches that balance treating chronic pain; while minimizing risks for opioid abuse, misuse, and diversion. The use of chronic opioid therapy for chronic non-cancer pain has increased dramatically in the past 2 decades in conjunction with associated increases in the abuse of prescribed opioids and accidental opioid overdoses. Consequently, a validated screening instrument which provides an effective and rational method of selecting patients for opioid therapy, predicting risk, and identifying problems once they arise could be of enormous benefit in clinical practice. Such an instrument could potentially curb the risk of iatrogenic addiction. Although several screening instruments and strategies have been introduced in recent years, there is no single test or instrument which can reliably and accurately predict those patients not suitable for opioid therapy or identify those who need increased vigilance or monitoring during therapy. At present, screening for opioid abuse includes assessment of premorbid and comorbid substance abuse; assessment of aberrant drug-related behaviors; risk factor stratification; and utilization of opioid assessment screening tools. Multiple opioid assessment screening tools and instruments have been developed by various authors. In addition, urine drug testing, monitoring of prescribing practices, prescription monitoring programs, opioid treatment agreements, and utilization of universal precautions are essential. Presently, a combination of strategies is recommended to stratify risk, to identify and understand aberrant drug related behaviors, and to tailor treatments accordingly.

This manuscript builds on the 2012 opioid guidelines published in Pain Physician and the 2016 guidelines released by the Centers for Disease Control and Prevention. It reviews the current state of knowledge regarding the growing problem of opioid abuse and misuse; known risk factors; and methods of predicting, assessing, monitoring, and addressing opioid abuse and misuse in patients with chronic non-cancer pain.

Key words: Opioids, misuse, abuse, chronic pain, prevalence, risk assessment, risk management, drug monitoring, aberrant drug-related behavior

Pain Physician Opioid Special Issue 2017; 20:S93-S109

Opioids produce effects throughout the body, including the brain and spinal cord, resulting in both analgesia and euphoria. The mood altering action of opioids, in addition to the physical dependence and addictive qualities of this class of drugs, can result in abuse (nonmedical use). Opioid abuse and misuse occurs for a variety of reasons, including self-medication, use for reward, compulsive use because of addiction, and diversion for profit (1-4). Individuals with chronic pain and co-occurring substance use disorders and/or mental health disorders are at higher risk for misuse of prescribed opioids (5-43). In spite of governmental pressures to develop abuse deterrent formulations, the increased usage of opioid analgesics in the treatment of chronic non-cancer pain, as well as the introduction of high-potency, extended-release oral tablet formulations, has increased opportunities for the illicit use of prescription opioids (1-6,8-9,13,17,19-43). Such use is a major societal problem that has now reached epidemic proportions, even exceeding the use of street narcotics in the United States (1,2,4,44-60). In April 2011, the White House unveiled a multi-agency plan aimed at reducing the "epidemic" of prescription drug abuse in the United States (61). The plan is a collaborative effort involving agencies of the Departments of Justice, Health and Human Services (HHS), Veterans Affairs, Defense, the Food and Drug Administration, and others. According to a recent director of the White House Office of National Drug Control Policy (ONDCP) this plan "provides a national framework for reducing prescription drug abuse and the diversion of prescription drugs for recreational use" (61). Advocacy for prescribing opioids despite the lack of long-term effectiveness, unproven standards, and guidelines with conflicting recommendations contributes to the epidemic of opioid abuse (1,4,11,29,35,37,62-76). In March 2016, The Centers for Disease Control and Prevention (CDC) published their own recommendations for primary care clinicians who prescribe opioids as therapy for "chronic pain outside of active cancer treatment, palliative care and end-of-life care" (7). The CDC's guidelines are focused on primary care physicians who represent the largest group of opioid prescribers in this country and address pertinent issues including when to begin or end opioids in the treatment of chronic pain, dosage, selection, duration, and assessing the risks and harms of opioid use. This updated review extends guidelines last presented in 2012 for clinical pain physicians on what is a complicated and challenging topic.

1.0 Definitions

The rates of misuse, abuse, and iatrogenic addiction have historically been difficult to estimate in chronic pain treatment with opioid analgesics, due in part to a dearth of universally accepted definitions and criteria for substance use disorder (1,2,4,8-10,30,34,41-43,61,71,73,77,78). As reported in the ACTTION review, the definitions of misuse, abuse, and related events have often been defined inconsistently, idiosyncratically, or in ways that overlap with other misuse terms (79,80). With the increasing frequency of chronic opioid therapy, a thorough understanding of appropriate terminology is important prior to establishing the prevalence of substance use disorder in this patient population. Until recently, the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV), classified substance "abuse" and substance "dependence" as separate diagnoses. The individual diagnoses were based on abuse as a mild or early phase, and cemented dependence as the more severe manifestation (81). With "dependence" classified as a normal physiologic response to a substance, individuals were often incorrectly linked to the diagnosis of "addiction" (82,83). Accordingly, the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-V), has combined the above 2 diagnoses into the single diagnosis of "substance use disorder" (84). The DSM-V recommends 11 diagnostic criteria for substance use disorder, including tolerance and withdrawal. These criteria remain similar to the DSM-IV with the exception of removing "legal problems" and the addition of "substance craving" (81). The criteria of "tolerance" and "withdrawal" created controversy within chronic opioid therapy, as these symptoms are inevitable consequences of the treatment itself. The DSM-V responded by eliminating these criteria from consideration when diagnosing substance use disorders in patients undergoing appropriate treatment with prescribed medications (e.g., opioids, sedatives, etc.). Therefore, based on these criteria, substance use disorders will be diagnosed on aberrant behaviors displayed by patients. However, unlike the behaviors listed by the DSM-V (e.g., failure to fulfill major role obligations at work, school, or home), aberrancy between pain patients can differ (e.g., doctor shopping, frequent lost prescriptions, repeated request for early prescriptions), leading to diagnostic challenges (82). Furthermore, these aberrant drug-seeking behaviors are not displayed exclusively by illicit drug users, and may in fact manifest as the result of uncon-

trolled pain, anxiety, or fear of withdrawal; such issues continue to complicate the diagnosis and treatment of prescription opioid patients (1-4,9,11-14). Remembering that the current understanding of addiction and drug dependence derives largely from experience with illicit drug users, several hurdles remain if the medical community is to develop adequate concepts, measures, and polices on which we may rely (79).

Healthcare providers continue to struggle over how to best treat chronic pain. Drug tolerance, hyperalgesia, and addiction remain constant concerns. Many medical practitioners, health care systems, regulatory boards, and medical societies are addressing this dilemma (85). Vital to this initiative is the adoption of universally acceptable terminology; streamlined communication among health care providers and regulatory enforcement agencies will undoubtedly improve patient care and reduce health care cost (15-17). Table 1 lists the common definitions of relevant concepts.

2.0 Scope of the Problem

Although nonpharmacologic therapy is preferred, the use of chronic opioid therapy (COT) for chronic non-cancer pain (CNCP) has increased dramatically in the past 2 decades (1-20,62,67). Simultaneously, there has been a marked increase in the abuse of prescribed opioids and in accidental opioid overdoses (1,18,44-76,87-97). What led to this crisis? A cultural shift in the prescribing habits of physicians from being opioid phobic to prescribing opioids liberally, spurred by alleged evidence of under-treatment of pain, availability of newer long-acting opioid formulations with good bioavailability, aggressive marketing techniques by drug manufacturers, disregard for the lack of long-term effectiveness, biased guidelines developed by authorities, physician ignorance with respect to the abuse potential of opioids, and promulgation of reassuring implicit messages by well-meaning "pain experts" that abuse, addiction, and diversion were not key issues in the practice of pain medicine, led to an exponential increase in the number of patients who were treated with opioids (1-4,61-76). The problem compounds further with the lack of physician training on key issues such as recognizing drug diversion, addiction, and signs of abuse; recent estimates suggest that only 20% of US physicians have received such training (98). Regardless,

Table 1. *Common definitions of relevant concepts.*

Concept	Definition
Substance use disorder	A cluster of cognitive, behavioral and physiological symptoms indicating that an individual continues to use the substance despite significant substance-related problems. A diagnosis based on pathological pattern of behaviors related to use of the substance (86).
Tolerance	A state of adaptation in which markedly increased drug doses are required to achieve desired effect or exposure results in diminution of one or more opioid effects over time (14,15).
Physical Dependence	A state of adaptation manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (15).
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving (15). This term is no longer applied as a diagnostic term (86).
Aberrant drug-related behavior	A behavior outside the boundaries of the agreed-on treatment plan, which is established as early as possible in the doctor-patient relationship (16).
Misuse	Use of a medication for nonmedical use, or for reasons other than prescribed (DSM IV TR 2000). Misuse can be willful or unintentional use of a substance in a manner not consistent with legal or medical guidelines, such as altering dosing or sharing medicines, which has harmful or potentially harmful consequences. It does not refer to use for mind altering purposes (17).
Abuse	Misuse with consequences (DSM IV TR 2000). The use of a substance to modify or control mood or state of mind in a manner that is illegal or harmful to oneself or others. Potentially harmful consequences include accidents or injuries, blackouts, legal problems, and sexual behavior that increases the risk of human immunodeficiency virus infection (17).
Diversion	The intentional transfer of a controlled substance from legitimate distribution and dispensing channels into illegal channels or obtaining a controlled substance by an illegal method (17).
Withdrawal	A syndrome occurring when blood or tissue concentrations of a substance decline who had maintained prolonged heavy use resulting in withdrawal symptoms that vary greatly across the classes or substances (86).

as opioid use escalated, so did opioid misuse and its adverse consequences. And today, despite growing acknowledgement of the extent of this issue, widespread geographical variation in opioid prescribing (more so than for other types of medications) reflects continued weak consensus regarding the appropriate use of opioids (99).

2.1 Prevalence

Opioid abuse and dependence among patients on prescription opioids in the United States may be higher than expected (1,2). A review of major epidemiologic databases shows that the prevalence of opioid abuse climbed sharply through the 1990s and the early part of the previous decade. In 2009, there were 7.0 million, 2.8% of persons aged 12 or older, who used prescription-type psychotherapeutic drugs nonmedically in the past month. In 2010, 12.2 million people used a pain reliever nonmedically for the first time, and from 2002-2011 an estimated 25 million people initiated nonmedical use of pain relievers (100,101). These estimates were higher than in 2008 (6.2 million or 2.5%), but similar to estimates in 2007 (6.9 million or 2.8%) (1-4,89,102,103). The number of prescriptions for CNCP also increased markedly in this decade and will continue to increase as the baby boom generation ages further; the intersection of these 2 public health problems is a serious concern (19,98). The true incidence of addiction in opioid-treated chronic pain patients in the United States is unknown and may be higher than expected. A large US health care system reported the rate of opioid abuse to be as high as 26% among outpatients on long-term opioid therapy (90). Another study estimated possible misuse at 24% of COT recipients in the commercially insured sample and 20% in the Medicaid sample (20,21). Another study describes dependence and addiction developing in up to one-third of patients on COT (104). A proactive surveillance program to monitor and characterize abuse, called the Research Abuse, Diversion and Addiction Related Surveillance (RADARS) System, discovered that prescription drug abuse is heavily localized in rural, suburban, and small urban areas and that hydrocodone and extended and immediate release oxycodone are by far the most widely abused drugs in the country (105). Spiller et al (22) studied trends among social, geographic, and demographic factors and abuse of select scheduled drugs and found strong positive trends among the poverty rate, the unemployment rate, and prescription opioid drug abuse rate. Rates of prescription opioid drug abuse increased as the poverty rate and the unemployment rate increased consistently over the 4 years of the study and was strongly influenced by hydrocodone and methadone abuse rates. The high school graduation rate trend over 4 years was also strongly influenced by the hydrocodone and methadone abuse rate (22). There were no temporal trends in the abuse and misuse of prescription drugs associated with weekends versus weekdays over the 5 year period 2003 through 2007 (23).

2.2 Age and Gender Differences

Results from the 2007 National Survey on Drug Use and Health (NSDUH) reported increases in the numbers using prescription opioids between 2002 and 2007 from 4.1% to 4.6% in young adults aged 18-25, and from 1.3% to 1.6% for adults aged 26 years and older (25). There are important sex differences in prescription opioid abuse. Significantly more men than women had lifetime (15.9% vs. 11.2%) and past-year (5.9% vs. 4.2%; $P < 0.0001$) use in the NSDUH study. Men are more likely than women to obtain prescription opioids for free from family or friends, and are more likely to purchase them from a dealer. Polysubstance use and treatment underutilization are common among both men and women; however, significantly fewer women than men receive alcohol or drug abuse treatment ($P = 0.001$) (26). The section on opioids from a 2013 study on the misuse of all prescription drugs largely mirrors the above characteristics of opioid abuse (106).

2.3 Drugs of Abuse

Abuse of all prescription opioids has grown since the inception of RADARS (105); nevertheless, hydrocodone and oxycodone (both extended and immediate release) are the drugs of choice in 75% of patients, whereas potent μ-opioid agonists (fentanyl, hydromorphone, and morphine) with the greatest predicted abuse potential are very rarely chosen (< 5% each) (92). Among street drug users, methadone is used (71.9%) and sold (64.7%) at a higher level than OxyContin, Vicodin, and Percocet (91). Oral administration is heavily preferred versus nonoral administration (e.g., snorting, injecting), with 72-97% of opioid abusers preferring oral administration (107). It is estimated that Americans consume 80% of the global opioid supply, 99% of the global hydrocodone supply, and two-thirds of the world's illegal drugs (1,2,61). Approximately 20% of Americans report using prescription opioids for nonmedical use. Retail sales of commonly used opioid medications in 2007 showed an overall increase of 149% with increases ranging from

222% for morphine to 1,293% for methadone (1,2,61). Sales of oxycodone alone increased from $48 million in 1996 to $1.1 billion in 2000, and by 2010 sales of all prescription opioids had increased to more than 4 times their 1999 levels (99,108).

2.4 Costs of Opioid Abuse

The mean annual direct health care costs for patients who abuse opioids is 8.7 times higher than nonabusers (93). Patients on Medicaid who have opioid abuse/dependence had more comorbidities and higher medical costs in 2002-2003 than Medicaid control patients (94). Compared to nonabusers, opioid abusers are more likely to utilize medical services such as the emergency department (ED) (4 times more likely), physician or mental health outpatient facilities (11 times more likely), and inpatient hospital stays (12 times more likely) (100). The proportion of patients with one or more ED visit in a 12-month period ranged from 17.4-80.8% (100). The mean per capita annual direct health care costs for commercially insured beneficiaries in the United States from 1998 to 2012 was nearly $21,000 for abusers of prescription and nonprescription opioids compared with approximately $1,800 for nonabusers with at least one prescription insurance claim; the total cost of prescription opioid abuse in 2007 was estimated at $55.7 billion, including workplace, health care, and criminal justice expenditures (89,100). Opioid misuse and dependence affects attendance and productivity at work. The NSDUH found that patients who abuse opioids miss more than 2.2 days of work monthly, compared with the 0.83 days per month reported for the average person (93). Opioid overdose results in 830,652 years of potential life lost before the age of 65, which is comparable to the years of potential life lost from motor vehicle accidents (100). Taking into account the medical, economic, social, and criminal effects of this abuse, the annual cost is nearly half a trillion dollars (95).

2.5 Fatality

The rates of fatal overdose increased concomitant with an increase in the number of patients on longterm opioid therapy. Patients who receive higher doses of prescribed opioids are at increased risk for overdose. Dowell et al (7) suggests physicians remember when prescribing opioids to patients for acute or chronic pain, they should be cautious, and prescribe the lowest effective dosage in the form of immediate release tablets as long as benefits outweigh risks. In this regard, the CDC guidelines have recommended prescribing three days of acute care opioids, based on unknown data. Acute and chronic pain states have varied definitions. Acute pain is expected to be of limited duration, whereas chronic pain manifests as a complicated interaction of variables inclusive of genetic disposition, diagnostic, and physiologic components. It is incumbent of the physician to understand the difference, and apply judgement based on expectations of treatment. As an example, an acute fractured femur is unlikely to be satisfactorily treated with three days of opioids. Treatment of acute pain may lead to to long-term opioid therapy.

This can be avoided by again, prescribing the lowest effective dosage in the form of immediate release tablets, but also by prescribing 3 to 7 (rare) days' worth of medication (7). In a study of 9,940 adults receiving long-term opioid therapy for CNCP, those who received 100 mg/d or more of morphine equivalent had an 8.9 fold increase in overdose risk (95% confidence interval [CI] 4.0-19.7) (18). Moreover, prescription opioid misuse is associated with high and increasing mortality; 107 deaths were associated with licit or illicit fentanyl use in Massachusetts from September 2005 to November 2006. Deaths due to illicit fentanyl use were more common in younger people, with higher fentanyl blood concentrations, and more frequent cocaine co-intoxication (65%) (102). The incidence of opioid-associated fatalities in New York City (NYC) has been especially scrutinized. From 1990 through 2006, the mortality rate from opioid overdose increased seven-fold, while the rate of overdose from all drugs increased only 27% (109). Furthermore, of the 1,286 chemical intoxication fatalities in NYC from 2011-2013, 42.5% were associated with prescription opioids (110). Only 36.7% of the 547 decedents possessed a valid opioid prescription. Similar trends in opioid overdose-related deaths are seen nationwide, with 5,528 of the total 15,125 drug overdose deaths in 2002 (37%) to 14,800 of the 36,450 drug overdose deaths in 2008 (41%) (100,111). A report from the CDC reported a rise in prescription opioid-related deaths of 68% from 1999 throught 2004 (48), and similar increases have been reported by others (47-59,96,97,102,103).

2.6 Malpractice Claims

Malpractice claims that arise from chronic pain management have increased in number and in severity over recent years, along with an increasing prevalence of drug use and interventional techniques (1,2,9,37,44,45,47,61,66-68,105,112-131). Malpractice claims for pain medicine increased from 3% of 2,966

total malpractice claims in the Anesthesia Closed Claims Project database in 1980-1989 to 18% of 2,743 anesthesia claims in 2000-2012, and more often included severe outcomes such as death and permanent injury (132). The American Society of Anesthesiologists (ASA) Closed Claims Database (2005 through 2008), review revealed that 17% of 295 CNCP claims were related to medication management problems, and the majority of these claims involved patients with a history of risk behaviors associated with medication misuse (121). Most claims (82%) involved patients who did not cooperate in their care (69%) or who had inappropriate medication management by physicians (59%). Death was the most common outcome in medication management claims; factors associated with death included long-acting opioids, additional psychoactive medications, and 3 or more factors commonly associated with medication misuse; addiction from prescribed opioids was suspected in 24% of the deaths (67).

2.7 Drug Diversion

Data from national surveys suggest that the increase in the prevalence of prescription opioid abuse is not simply due to opioid abuse by the patients prescribed opioids for pain, but is indicative of a much broader problem of lack of control over what are now large quantities of prescription opioids in the community (19). A 2007 national survey showed that casual or careless diversion is a major problem; 56.5% of the nonmedical use of prescription opioids came from a friend or relative, (25) and diversion was a factor in over 50% of overdose fatalities (47). The primary sources of prescription drugs on the street are the elderly, patients with pain, and doctor shoppers, as well as pill brokers and dealers who work with all of the former. The popularity of prescription drugs in the street market is rooted in the abusers' perceptions of these drugs as less stigmatizing, less dangerous, and less subject to legal consequences than illicit drugs. For many, the abuse of prescription opioids also appears to serve as a gateway to heroin use (46). Some areas of the country have experienced encouraging results in the effort to curb prescription opioid diversion (101). Florida experienced a substantial decrease in the diversion of prescription analgesics, in particular oxycodone, after the implementation of regulatory measures in 2010 and 2011.

2.8 Disability Escalation

Opioid therapy has not been illustrated to reduce functional disability or improve functional ability (1-8,36,37,70). In contrast, opioid therapy has been described to increase disability and cost of care. More importantly, opioid use has been associated with subsequent surgery and continued or late opioid use (1,4,69,122-128). Vogt et al (124) reported an association between opioid prescribing and an increase in overall health care costs for low back pain, implying higher levels of utilization. Similarly, Mahmud et al (125) found an association between opioid use for more than a week for acute low back pain and disability duration in a workers' compensation cohort. A 2014 study of 9,291 patients reported that prescription opioid users, on average, missed 13.3 more days of work because of disability or medical absenteeism annually versus non-users (133). Webster et al (122) showed that patients receiving more than a 450 mg equivalent of morphine over a period of several months were, on average, disabled 69 days longer than those who received no early opioids, had a 3-times increased risk for surgery, and had a 6-times greater risk of receiving late opioids. Fillingim et al (126) indicated that opioid use was associated with greater self-reported disability and poorer function. Sites et al (134) echoed these findings in a 2014 report that described no appreciable changes among opioid users in self-reported physical health status; physical limitations; home, work, or school limitations; social limitations; physical activity, or any limitations.

Franklin et al (127) studied early opioid prescription and subsequent disability among 18,443 workers with lost work time work-claims. Nearly 14% of the sample received work disability compensation at one year, more than one-third of the workers received an opioid prescription within 6 weeks and 50.7% of these received a prescription at the first medical visit. Rhee et al (128) showed in a sample of 13,760 patients with low back pain due to mechanical causes that 45% of them used opioids. Patients with low back pain taking opioids had significantly higher rates of comorbid conditions than patients with low back pain who did not use opioids; the comorbid conditions included hypertension, arthritis, depression, anxiety, and cancer.

Emergency department visits were also higher for patients taking opioids along with health care costs, which were approximately 3-times higher in patients taking opioids compared to those not taking them. An epidemiological study from Denmark (69), where opioids are prescribed liberally for chronic pain, demonstrated worse pain, higher health care utilization, and lower activity levels in patients treated with opioids

compared to a matched cohort of patients with chronic pain who did not use opioids, suggesting that when opioids are prescribed liberally, even if some patients benefit, the overall population does not.

3.0 Risk Factors for Opioid Abuse and Misuse

The burgeoning rate of prescription opioid misuse, abuse, addiction, and opioid-related overdose deaths has gained substantial professional and national media attention. However, an accurate assessment of the prevalence of misuse, abuse, and addiction in the pain population has been challenging due to inconsistent definitions among studies (135). In order to address the problem, the most important step is to identify patients who are most "at-risk" for developing prescription drug abuse. Several risk factors have been described, and include sociodemographic factors, pain and drug-related factors, genetics and environment, psychosocial and family history, psychopathology, and alcohol and substance use disorders (129). However, none of these factors alone will increase the risk of drug abuse in a given individual. It is suggested that the risk of prescription drug abuse is greatest when risk factors in 3 categories, (i.e., psychosocial factors, drug related factors, and genetic factors) occur in the same individual. In the absence of psychosocial comorbidities and genetic predisposition, patients with pain on stable doses of opioids in a controlled setting are unlikely to abuse opioids or develop addiction. On the other hand, patients with a personal or family history of substance abuse, and psychosocial comorbidity, are at increased risk, especially if treatment with opioids is not carefully structured and monitored (13). In a study of primary care patients with high levels of pain disability, unemployment, and psychosocial stressors, prescription drug use disorder was concentrated among those with a family history of substance use disorder, those who have spent time in jail, are current cigarette smokers, are white male, and those with pain-related functional limitations and posttraumatic stress disorder (PTSD). The vast majority had co-occurring substance use disorder (129).

3.1 Demographic Factors

Studies have reported a significant association of young, white men with prescription drug abuse (90,129-131). A strong inverse relationship between age and a diagnosis of opioid abuse/dependence is reported; those with prescription drug use disorder are more likely to be young. In fact, abuse and misuse behaviors are negatively associated with older age (136). McCabe et al (137) examined the motives for medical misuse of prescription opioids among adolescents and assessed differences in motives by demographic characteristics, substance abuse, and diversion behaviors. A survey was conducted from 2011 to 2012 on 2,964 adolescents (51% female). Thirteen-percent reported past-year medical use of prescription opioids and the most prevalent motives for medical misuse were "to relieve pain" (84.2%) and "to get high" (35.1%). The results indicated that the majority of medical misuse is associated with pain relief and that novel strategies could be developed to reduce opioid medication misuse among adolescents (137).

Although substance abuse is rarely associated with individuals nearing or at retirement age (138,139), there is an increasing need to understand the nature and extent of drug use among older adult populations. Raebel et al (140) studied chronic opioid use the year after bariatric surgery among patients who did not use opioids chronically before surgery and concluded that older age (odds ratio [OR], 0.84 [95%CI, 0.73-0.97] each decade) was associated with decreased likelihood of chronic opioid use after surgery. Levi-Minzi et al (141) evaluated the motivations for use and diversion of opioids among elderly prescription opioid misusers. Their findings suggest that this group of elderly patients often misuse their own prescriptions for pain management, highlighting the need to educate prescribing professionals on appropriate pain management for older adults while still being sensitive to issues of substance abuse and dependence.

Women are at greater risk of misusing opioids because of emotional issues and affective distress, whereas men tend to misuse opioids because of legal and problematic behavioral issues (142). For both women and men, illicit drug use is associated with the nonmedical use of prescription opioids. Certain factors are, however, gender-specific. For instance, nonmedical use of prescription opioids among men but not women, was associated with past-year inhalant use in one survey; in the case of women who first used illicit drugs at 24 years or older, serious mental illness, and cigarette smoking were associated with the nonmedical use of prescription opioids (131).

The association of white men with prescription opioid abuse has been documented in clinical and population studies (129,143,144). Whites are prescribed more opioid analgesics in emergency departments and primary care practices, perhaps reflecting a cultural bias

by patients and physicians toward use of prescription opioids (145,146).

3.2 Pain Severity and Interference

Patients classified at high-risk for opioid misuse report more subjective pain, multiple pain complaints, and a greater degree of pain-related limitations (129,147,148). Low pain tolerance in patients with active and past addictions has been reported previously (149,150). It is not known if the low pain threshold increases risk for addiction or addiction itself lowers pain thresholds. Irrespective of the reason, treating pain is challenging in these patients.

Martel et al (151) recently studied self-reports of medication side effects and pain-related activity interference in patients with chronic pain. A total of 111 patients with chronic musculoskeletal pain were asked to provide, once a month for a period of 6 months, self-reports of medication use and the presence of any perceived side effects (e.g., nausea, dizziness, headaches) associated with their medications. At each of these time points, patients were also asked to provide self-reports of pain intensity, negative affect, and pain-related activity interference. Importantly, multilevel models revealed that perceived medication side effects were associated with heightened pain-related activity interference. As a result, this study provides preliminary evidence that reports of medication side effects are associated with heightened pain-related activity interference in patients with chronic pain.

A high rate of disabling chronic pain has previously been reported among prescription opioid decedents (10). Lanier et al (111) conducted a case-control study to better understand the risk factors of prescription opioid death in Utah from 2000 through 2009. Having chronic pain was reported by 81.3% of the decedents overall. Among decedents who reportedly had used their own prescription pain medication during the previous year, the prevalence of chronic pain (93.6%) was 3-times that of the comparison group (31.6%) (exposure prevalence ratio: 3.0; 95% CI, 2.7–3.3) suggesting that misuse, abuse, and dependence opioid prevention efforts might best be focused on those patients suffering from chronic pain.

3.3 Psychosocial Factors

Prior studies indicate that individuals who are younger; unmarried; unemployed; have a lower education level; have poor/fair health; and use tobacco, alcohol, and illicit drugs are more likely to engage in nonmedical use of prescription drugs (NMUPD) and abuse or depend on prescription drugs (ADPD). However, gender, race, and ethnicity show a mixed association with NMUPD and ADPD (152-159). Nonmodifiable factors such as young age, back pain, multiple pain complaints, and substance abuse disorders identify patients at high risk for misuse. Toblin et al (10) determined that a combination of 4 variables (i.e., age, depression, psychotropic medications, and pain impairment) predicted an increased risk for current opioid dependence, compared to individuals without these factors (OR = 8.01, $P < 0.001$).

Multiple studies have indicated that health insurance has been found to be negatively associated with NMUPD (131,152,153,155). A recent study by Bali et al (106) demonstrated that Hispanics with private health insurance were more likely to engage in NMUPD when compared with uninsured Hispanic individuals, demonstrating that there is a higher likelihood of NMUPD among Hispanics despite private health insurance due to acculturation challenges and to lower education. Similarly, individuals with lower family incomes (< $20,000) are more likely to have lower education and consequently poor knowledge about the harms of NMUPD (160). This indicates that efforts aimed at reducing NMUPD and ADPD should involve both public health efforts such as increasing awareness and policy changes such as providing health coverage.

Katz et al (161) demonstrated in a population-based national sample that several chronic physical conditions (i.e., arteriosclerosis or hypertension, cardiovascular disease, arthritis, and any assessed medical condition) were associated with the onset of opioid abuse/dependence even after controlling for sociodemographic factors and Axis I and II mental disorders, emphasizing the need for careful screening practices when prescribing opioids. Similarly, tobacco use was associated with a higher risk of NMUPD or ADPD as demonstrated by multiple studies (144,153,159). Thus, physicians and treatment providers need to be careful while prescribing prescription drugs with high abuse potential to individuals with a past history of substance abuse and also need to monitor the individuals' drug use closely (144,153,159)

3.4 Comorbid Psychopathology

The association between nonmedical use of prescription drugs or abuse/dependence and mental disorders has been well documented in the literature. Past research has demonstrated that having either an Axis I

or Axis II mental disorder is associated with an increased likelihood of NMUPD and abuse/dependence disorder (143,152,162-166).

A history of mood disorder, psychological problems, and psychosocial stressors increase the risk for prescription opioid misuse. A consistent association between psychiatric morbidity and prescription opioid misuse in chronic pain patients has been reported in multiple studies (21,167,168). Chronic pain patients with high psychiatric morbidity tend to be significantly younger, have been taking opioids longer, have significantly higher Screener and Opioid Assessment for Patients with Pain (SOAPP) and Current Opioid Misuse Measure (COMM) scores ($P < 0.001$), a greater frequency of abnormal urine toxicology screens, and significantly higher scores on the drug misuse index (DMI) ($P < 0.001$) (167).

Panic, social phobia and agoraphobia, low self-rated health status, and other substance misuse should alert clinicians to screen for abuse and dependence (152). Depression and anxiety disorders partially account for higher rates of abuse reported in patients taking opioid analgesics compared with those not taking prescribed opioids. It is suggested that mental disorders lead to substance abuse among prescription opioid users more often than the prescription opioids themselves, prompting substance abuse iatrogenically (169).

Mackesy-Amiti et al (170) conducted a recent study on 570 young intravenous drug users who primarily used heroin in order to evaluate the associations of psychiatric disorders with opioid prescription misuse, abuse, and dependence. Their results suggested that past-year prescribed opioids misuse was significantly associated with antisocial personality disorder, past year substance-induced major depression, and prior PTSD. In addition, among male opioid users, PTSD was a significant predictor of opioid abuse and dependence.

Substance abuse among those with schizophrenia is common and is associated with poor clinical outcomes. A significant number of patients with schizophrenia abuse drugs and alcohol and have higher rates of drug dependence than in the general population (171,172). Drug dependence and schizophrenia share common characteristics, including changes in cognition, emotion, motivation and stress reactivity. Thus, common neural pathways between drug dependence and schizophrenia were suggested due to the high comorbidity that exists between these 2 disorders (173). However, despite compelling evidence of the growth in opioid misuse and the potential relationship with mental illness, patients with mental disorders and/or substance abuse are routinely excluded from randomized trials, making it impossible to better understand these phenomena (174).

3.5 Substance Use Disorders

The most consistent variable that has been associated with prescription opioid misuse is a history of substance use disorders (SUD) (175). Patients with chronic pain have high rates of comorbid SUDs. Up to one-third of patients with chronic pain seen in primary care, and 8–35% in specialty pain clinics, have a current SUD (73). These rates of comorbid SUD are consistently higher than the rate of SUDs observed in the general population (163). Patients receiving treatment for SUDs also concomitantly report high rates of chronic pain (176,177). Given the high rates of comorbidity between chronic pain and SUD, and frequent use of prescription opioids to treat chronic pain in this population, Morasco et al (178) recently evaluated the risk factors for prescription opioid misuse among the subgroup of patients with SUD histories. Interestingly, those patients with higher risk for prescription opioid misuse reported more pain and impairment, symptoms of depression, and were more likely to have current SUD, relative to patients with lower risk for prescription opioid misuse.

A detailed substance abuse history and in-depth evaluations are needed to identify the patient with pain who is at risk for abuse and/or diversion of prescribed opioids. A personal history of illicit drug and alcohol abuse (175) and cannabis use (179) strongly predict risk of opioid abuse. The prevalence of cannabis use in patients prescribed COT ranged from 6.2% to 39%, compared with 5.8% in the general population (179). The use of prescription opioids to get high most likely represents the end stage on a continuum of substance abuse, beginning at a very early age. In a survey by Cicero et al (180), the first exposure to an opioid in 79% of males and 85% of females was a legitimate prescription for pain, which subsequently led 60-70% to misuse to get high. The age of first alcohol use, getting drunk, smoking, use of marijuana, stimulants and other nonopioid prescription or illicit drugs occurred very early (13-19 years old) in prescription opioid misusers/abusers, whose first use of opioids did not occur, on average, until age 22. In addition to substance abuse, hepatitis A, B, or C, and poisonings are highly associated with a diagnosis for opioid abuse or dependence (21,94).

Mateu-Gelabert et al (181) conducted a qualitative study to explore the drug use and sexual experiences of

young nonmedical prescribed opioid users and the associated risk for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) transmission. Interestingly, despite initial perceptions of being less addictive and safer than illegal drugs, opioid misuse often led to long-term dependence, a transition to heroin use, and an increase in the risk of sexual violence, intravenous drug use, and unprotected sexual intercourse, thus increasing the risk of HIV and hepatitis C virus (HCV) transmission (181). Moreover, among veterans infected with HCV, pain and substance use disorder diagnoses are common and opioids are frequently prescribed. In one study, 67% of patients with HCV+ had a documented pain diagnosis and 56% had a substance use disorder diagnosis (182). Demographic variables and psychiatric/medical histories are not consistent and may fail to discriminate between patients with pain and those who are substance abusers. Substance abusers and those in the criminal justice system were significantly more likely to have a current diagnosis of psychoactive abuse/dependence and were more likely to be younger and unmarried (183).

3.6 Drug-Related Factors

Self-reported craving is a potential marker for individuals "at-risk" for opioid medication misuse. In a recent study, those reporting a craving for opioids had higher scores on the Prescription Drug Use Questionnaire (PDUQ) ($P < 0.001$), a higher incidence of physician-rated aberrant drug behavior, a higher frequency of abnormal urine toxicology screens ($P < 0.001$), and a positive Aberrant Drug Behavior Index (ADBI) ($P < 0.001$) (184). Treatment with high daily dose opioids (especially > 120 mg morphine equivalent per day) and short-acting Schedule II opioids appears to increase the risk of misuse (20). Sullivan et al (148) observed medium to high scores on the Prescribed Opioids Difficulties Scale (PODS) in patients concerned about their ability to control their use of opioid medications, but prior substance abuse diagnoses and receiving excess days' supply of opioids were much less common in these patients than depression and pain-related interference. Further, Manchikanti et al (185) found that patients requesting higher opioids showed no significant difference whether short-acting or long-acting opioids were used, in contrast to the traditional belief that using short-acting opioids increases abuse tendencies.

3.7 Genetic Factors

The μ-opioid receptor is the primary target of opioids and targeted deletions of μ-opioid receptor gene (OPRM1) in mice established its role in the rewarding effects of morphine (186). In the past decade, many functional variations were identified in the OPRM1; the most common variants associated with greater risk for opioid addiction are the 118A>G (187) and the 17C>T SNP (188) in the coding region of OPRM1. The 118G allele is reported to be associated with a greater risk for opioid addiction in a Swedish population, and also in a population of Chinese males (187,189), however these findings have not been replicated, and the role of this variant in susceptibility to opioid addiction remains to be clarified. Variants of the -opioid receptor gene (OPRK1) (190) and δ-opioid receptor (OPRD1) (191) associated with increased risk for opioid addiction have also been reported and include the 36G>T SNP of OPRK1 (156) and 80G>T and 921C>T SNPs of OPRD1 (190,192,193). Furthermore, variants in the noncoding region of all 3 opioid receptor subtypes and their association with a greater risk for heroin dependency have been found (194), emphasizing the importance of further study into variations in these genes and their effects on opioid dependency. In addition to variants in the opioid receptor genes, a variety of other related and unrelated genes that contribute to opioid dependency have been identified.

The preproenkephalin (PENK) gene encodes for peptides that modulate pain perception and play roles in reward and addiction (195). A polymorphism of the PENK gene is associated with an increased likelihood of opiate dependency in multiple studies (196,197).

Stress is a critical risk factor affecting both the development of and the relapse to drug addictions (198). Recently, Levran et al (199) conducted a study to determine if genetic variants in stress-related genes were associated with heroin addiction. The study demonstrated that variations in the FKBP5 gene contribute to the development of opioid addiction by modulating the stress response. These findings may enhance the understanding of the interaction between stress and heroin addiction (199). Consistently, another gene involved in stress responses is the melanocortin receptor type 2 (MC2R); variations in this gene have been associated with both a protective effect and susceptibility to heroin addiction (200).

During the last decade, there was an increasing interest to evaluate the association between polymorphisms in stress-related genes and specific drug addictions in different populations. There are several reports of such associations in cohorts of European ancestry, including the AVPR1A SNP and nonspecific drug use dis-

orders (201), CRHBP in alcohol use disorder (202,203), MC2R SNP in heroin addiction in Hispanics (200), and GAL SNPs and opioid addiction (194,204,205). Recently, a study was conducted in African Americans to establish if specific SNPs in genes were related to stress response in heroin and/or cocaine addiction. Fourteen SNPs showed nominally significant association with heroin addiction ($P < 0.05$), including the African-specific, missense SNP rs5376 (Asn334Ser) in the galanin receptor type 1 gene (GALR1) and the functional FKBP5 intronic SNP rs1360780. Thirteen SNPs showed association with cocaine addiction, including the synonymous SNPs rs237902, in the oxytocin receptor gene (OXTR), and rs5374 in GALR1 and 4 additional SNPs (GALR1 rs2717162, AVP rs2282018, CRHBP rs1875999, and NR3C2 rs1040288) were associated with both addictions and may indicate common liability (206).

Evidence for the involvement of specific genetic variants has been replicated in some cases, whereas others remain uncertain. Future studies are required to replicate association data and to characterize how genetic variations result in functional changes in the proteins encoded by the genes. Understanding the role of these genes in drug dependency and treatment can result in the discovery of novel drug targets (207).

Acknowledgments:

The authors would like to thank Ngoc Vo, MEd and Uyen Ha, BS for their editorial assistance.

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