

Narrative Review

Prescription Opioid Abuse in Chronic Pain: A Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse

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Both chronic pain and prescription opioid abuse are prevalent and continue to exact 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.

Treatment approaches that balance treating chronic pain while minimizing risks for opioid abuse, misuse, and diversion are much needed. The use of chronic opioid therapy for chronic noncancer pain has increased dramatically in the past 2 decades in conjunction with a marked increase in the abuse of prescribed opioids and accidental opioid overdoses. Consequently, a validated screening instrument that 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. Such an instrument could potentially curb the risk of iatrogenic addiction. Although several screening instruments and strategies have been introduced in the past decade, there is no single test or instrument that can reliably and accurately predict patients who are 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 pre-morbid 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, identify and understand aberrant drug related behaviors, and tailor treatments accordingly.

This manuscript will review 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 noncancer pain.

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

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Opioids produce both analgesia and euphoria. The mood altering action of opioids in addition to the physical dependence and addictive qualities of this class of drugs encourages 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). The increasing use of opioid analgesics for treating chronic noncancer pain, and the introduction of high-dose, extended-release oral tablet formulations of opioids with good bioavailability, has increased opportunities for the illicit use of prescription opioids (1-9,13,17,19-43). Such use has become a major societal problem, reaching epidemic proportions; it now exceeds 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, and others. According to the 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).

1.0 DEFINITIONS

The lack of a universally accepted definition or criterion for addiction that arises in the context of chronic pain treatment with opioid analgesics has hindered attempts at determining the rates of misuse, abuse, and iatrogenic addiction in this population (1,2,4,7-

10,30,34,39,41-43,61,71-73,77,78). According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), diagnostic criteria for substance abuse include tolerance, physical dependence, and 5 additional behaviors associated with illicit drug use (9,11,13,79). A problem with this definition is that tolerance and physical dependence are inevitable consequences of chronic opioid use and therefore irrelevant in the context of therapeutic opioid use. Hence these 2 criteria cannot be included to define abuse or addiction during opioid therapy (13). In addition, when patients receiving prescription opioids display aberrant drug seeking behaviors, distinguishing between individuals who use drugs illicitly from those who manifest these behaviors due to uncontrolled pain, anxiety, or fear of withdrawal is especially challenging (1-4,9,11-14). A consensus document by the American Pain and Addiction Societies identifies 4 criteria for addiction: impaired control over drug use, compulsive use, continued use despite harm, and craving (15). These criteria have not been validated or tested in large studies according to the principles of evidence-based medicine (EBM) (80-84). In the era of multiplying regulations, EBM, comparative effectiveness research (CER), and ever changing concepts, it is essential to follow proper guidelines and regulations (85-96). A universally acceptable terminology is vital in improving communication between health care providers and regulatory and enforcement agencies, which should lead to improved treatments of pain and addictive disorders, and reduce health care costs (Table 1) (15-17).

Table 1. Illustration of multiple definitions utilized in clinical practice.

Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time (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).
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).

2.0 SCOPE OF THE PROBLEM

The use of chronic opioid therapy (COT) for chronic noncancer 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 (1,18,44-76,83,84,97-105). 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 undertreatment 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). As opioid use escalated, so did opioid misuse and its adverse consequences.

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. 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%) (1-4,97,106,107). The number of prescriptions for CNCP also increased markedly in this decade; the intersection of these 2 public health problems is a serious concern (19). 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 U.S. health care system reported the rate of opioid abuse to be as high as 26% among outpatients on long-term opioid therapy (98). Another study estimated possible misuse at 24% of COT recipients in the commercially insured sample and 20% in the Medicaid sample (20,21). 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 (108). 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 opiate 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 under-utilization are common among both men and women; however, significantly fewer women than men receive alcohol or drug abuse treatment ($P = 0.001$) (26).

2.3 Drugs of Abuse

Abuse of all prescription opioids has grown since the inception of RADARS (108); nevertheless, hydrocodone and oxycodone (both extended and immediate release) are the drugs of choice in 75% of patients, whereas potent μ -opioid agonists (fentanyl, hydro-morphone, and morphine) with the greatest predicted abuse potential are very rarely chosen ($< 5\%$ each) (100). Among street drug users, methadone is used (71.9%) and sold (64.7%) at a higher level than Oxy-Contin, Vicodin, and Percocet (99). 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).

2.4 Costs of Opioid Abuse

The mean annual direct health care costs for patients who abuse opioids are 8.7 times higher than non-abusers (101). Medicaid patients with opioid abuse/dependence had more comorbidities and higher medical costs in 2002-2003 than Medicaid control patients (102). The mean per capita annual direct health care costs for commercially insured beneficiaries in the United States from 1998 to 2002 was nearly \$16,000 for abusers of prescription and nonprescription opioids compared with approximately \$1,800 for non-abusers with at least one prescription insurance claim; the total cost of prescription opioid abuse in 2001 was estimated at \$8.6 billion, including workplace, health care, and criminal justice expenditures (97). Opioid misuse and dependence affects attendance and productivity at work. The NS-DUH found that patients with opioid abuse miss more than 2.2 days of work monthly, compared with the 0.83 days per month reported for the average person (101). Taking into account the medical, economic, social, and criminal effects of this abuse, the annual cost is nearly half a trillion dollars (103).

2.5 Fatality

The rates of fatal overdose increased concomitant with an increase in the number of patients on long-term opioid therapy. Patients who receive higher doses of prescribed opioids are at increased risk for overdose. 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 between September 2005 and 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%) (105). A report from the Centers for Disease Control and Prevention (CDC) reported a rise in prescription opioid-related deaths of 68% between 1999 and 2004 (48), and similar increases have been reported by others (47-59,65,104-107).

2.6 Malpractice Claims

Malpractice claims that arise from chronic pain management have increased in recent years, along with an increasing prevalence of drug use and interventional techniques (1,2,9,37,44,45,47,61,66-68,108-128). 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 (118). 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 non-medical 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).

2.8 Disability Escalation

Opioid therapy has not been illustrated to reduce functional disability or improve functional ability (1-4,5-8,36,37,70). 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 (1,4,69,119-125). Vogt et al (121) 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 (122) found an association between opioid use for more than a week for acute low back pain and disability duration in a workers' compensation cohort. Webster et al (119) 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 (123) indicated that opioid use was associated with greater self-reported disability and poorer function.

Franklin et al (124) studied early opioid prescription and subsequent disability among 18,443 workers with lost work time work-claims with nearly 14% of the sample receiving 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 (125) showed in a sample of 13,760 patients with low back pain due to mechanical causes that 45% of them used narcotic drugs. 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 room 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 opioid-treated patients compared to a matched cohort of chronic pain patients not using 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

A critical issue in pain management is the ability of the clinician 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, psy-

chopathology, and alcohol and substance use disorders (126). However none of these factors by themselves 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, pain patients 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 male, white, and those with pain-related functional limitations and posttraumatic stress disorder. The vast majority had co-occurring substance use disorder (126).

3.1 Demographic Factors

Studies have reported a significant association of young, white men with prescription drug abuse (98,126-128). 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. Abuse and misuse behaviors are negatively associated with older age (129). 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 (130). For both women and men, illicit drug use is associated with the nonmedical use of prescription opioids. Certain factors are however sex-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 first using illicit drugs at 24 years or older, serious mental illness, and cigarette smoking were associated with nonmedical use of prescription opioids (128). The association of white men with prescription opioid abuse has been documented in clinical and population studies (126,131,132). Whites are prescribed more opioid analgesics in emergency rooms and primary care practices, perhaps reflecting a cultural bias by patients and physicians toward use of prescription opioids (133,134).

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 (126,135,136). Low pain tolerance in patients with active and past addictions has been reported previously (137,138). 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.

3.3 Psychosocial Factors

Non-modifiable factors such as young age, back pain, multiple pain complaints, and substance abuse disorders, identify patients at high risk for misuse. A combination of 4 variables (i.e., age, depression, psychotropic medications, and pain impairment) predicted increased risk for current opioid dependence, compared to those without these factors in one study (odds ratio [OR] = 8.01, $P < 0.001$) (98).

3.4 Comorbid Psychopathology

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 (21,139,140). 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) ($P < 0.001$) (139). Panic, social phobia and agoraphobia, low self-rated health status, and other substance misuse should alert clinicians to screen for abuse and dependence (141). 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 (142).

3.5 Substance Use Disorders

The risk of opioid abuse/dependence is increased with substance use disorders. A detailed substance abuse history and in-depth evaluations are needed to

identify the pain patient at risk for abuse and/or diversion of prescribed opioids. A personal history of illicit drug and alcohol abuse (143) and cannabis use (144) 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 (144). 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 (145), 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 (21,102). Among veterans infected with the hepatitis C virus (HCV), pain and substance use disorder diagnoses are common and opioids are frequently prescribed. In one study, 67% of HCV+ patients had documented pain diagnoses and 56% had substance use disorder diagnoses (146). Demographic variables and psychiatric/medical histories are not consistent and may fail to discriminate between pain patients and those who are substance abusers. Substance abusers and those in the criminal justice system were significantly more likely to have a current DSM-IV diagnosis of psychoactive abuse/dependence and more likely to be younger and unmarried (147).

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) ($P < 0.001$) (148). 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 (136) 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 (149) 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 opiates and targeted deletions of μ -opioid receptor gene (OPRM1) in mice established its role in the rewarding effects of morphine (150). In the past decade, many functional variations were identified in the OPRM1; the most common variants associated with greater risk for opiate addiction are the 118A>G (152) and the 17C>T SNP (151) in the coding region of OPRM1. The 118G allele is reported to be associated with a greater risk for opiate addiction in a Swedish population, and also in a population of Hans Chinese males (152,153), however these findings have not been replicated, and the role of this variant in susceptibility to opiate addiction remains to be clarified. Variants of the δ -opioid receptor gene (OPRK1) (154) and δ -opioid receptor (OPRD1) (155) associated with increased risk for opiate addiction have also been reported and include the 36G>T SNP of OPRK1 (156) and 80G>T and 921C>T SNPs of OPRD1 (154,156,157). 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 (158), emphasizing the importance of further study into variations in these genes and their effects on opiate dependency. In addition to variants in the opioid receptor genes, a variety of other related and unrelated genes that contribute to opiate dependency have been identified. The proenkephalin (PENK) gene encodes for peptides that modulate pain perception and play roles in reward and addiction (159). A polymorphism of the PENK gene is associated with an increased likelihood of opiate dependency in multiple studies (160,161). 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 (162). Evidence for the involvement of specific genetic variants has been replicated in some cases, whereas others remain uncertain. Future studies are required to replicate associa-

tion 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 (163).

4.0 SCREENING FOR OPIOID ABUSE POTENTIAL

Screening patients to determine their risk of drug abuse prior to beginning opioid therapy is considered good practice. Most tools used to assess individuals for the potential for opioid abuse are based on risk factors discussed in previous sections and the presence of aberrant behaviors. Several opioid-specific screening tools are available for risk assessment, but none has been fully validated in a variety of settings and populations. There is no one procedure or set of predictor variables that can identify chronic pain patients who are "at-risk" for opioid misuse or abuse. Use of external sources of information, such as testing of biologic material (e.g., urine), interviews with spouses, review of medical records, payer opioid prescription data, or input from prescription monitoring programs, should be used to supplement information and improve patient assessment and management. Prior to initiating therapy with opioid analgesics, clinicians must take certain basic steps to prevent opioid abuse: recognize individual risk factors for opioid abuse; screen new patients during their initial visit for abuse potential or addiction; stratify risk and set the level of monitoring appropriate to the risk category; do not make any judgments prior to an appropriate assessment.

4.1 Assess Pre- and Comorbid Substance Abuse

A small number of "at risk" opioid-naive pain patients who might abuse their therapeutically appropriate opioid analgesics can be identified by evaluating for substance use and psychopathology (145). Patients with a history of alcohol or cocaine abuse and alcohol or drug-related convictions require more intense assessment and follow-up for signs of misuse if opioids are prescribed. In addition, "at-risk" patients can be managed with prescriptions of small quantities of opioids, lasting for a few days e.g., weekly prescriptions. Factors that predicted abuse in one prospective study were age, past cocaine abuse (OR, 4.3), drug or driving under the influence (DUI) conviction (OR, 2.6), and past alcohol abuse (OR, 2.6) (164).

4.2 Aberrant Drug-Related Behaviors

Because not all aberrant behaviors have the same origins or implications, it is suggested that physicians must consider a differential diagnosis and tailor therapy accordingly (165). Review of data from opioid-tolerant patients participating in clinical studies of fentanyl buccal tablet (FBT) for breakthrough pain revealed that 11% had aberrant behaviors related to FBT, and 6% had aberrant behaviors that were not (166). Inadequate pain relief may prompt some patients to manifest aberrant drug-related behaviors, such as aggressively complaining about the need for more drugs, drug hoarding, unsanctioned dose escalations or other forms of noncompliance; these behaviors subside once adequate pain control is achieved. Forging prescriptions, stealing or borrowing drugs, frequently losing prescriptions, and resisting changes to medications, despite adverse effects, are more predictive of opioid misuse (167). Prescription shoppers and patients with chronic nonmalignant pain problems are the main people who constitute a small but problematic group. The main drugs they seek are benzodiazepines and opioids (168). Participants in a study by Morasco and Dobscha (169) who had a substance use disorder history were significantly more likely than participants without a substance use disorder history to report borrowing pain medications from others (OR = 6.62, 95% CI = 1.4-30.7) and requesting an early refill of pain medication (OR = 3.86, 95% CI = 1.5-9.6).

4.3 Risk Factor Stratification

The purpose of stratifying patients into risk categories is to determine the intensity and frequency of monitoring and clinical vigilance for all patients based on their risk of drug abuse. Risk stratification should not be used to deny pain treatment to high risk patients. All patients should receive at least the minimal level of monitoring, the intensity increasing as the risk level increases from low risk to moderate or high risk. Physicians must be empathetic, caring, and nonjudgmental, but willing to set and implement treatment boundaries. White et al (170) used medical and prescription drug claims data to develop models that identify patients at risk for prescription opioid abuse or misuse. Factors (measured over a 12-month period) that were associated with a risk for prescription opioid abuse or misuse were: age 18 to 24 years, male, 12 or more opioid prescriptions, opioid prescriptions from 3 or more pharmacies, early prescription opioid refills, escalating morphine dosages, psychiatric outpatient visits, hospi-

tal visits, diagnoses of nonopioid substance abuse, depression, posttraumatic stress disorder, and hepatitis.

4.4 Opioid Assessment Screening Tools

Several opioid-specific screening tools are available for screening and monitoring of abuse (Table 2). Many screening tools contain items on personal and family history of addiction and other risk factors such as age, sexual abuse, and psychological disease (3,4,171-191). Some tools are specific to pain management, while others assess risk factors for addiction in general. Some of these tools are geared to be used as a screening aid before initiating COT while others are geared to be utilized to monitor patients already on COT over time. Passik and Weinreb (171) described a mnemonic for following relevant domains in patients with chronic pain on COT. The so-called 4 A's (analgesia, activities of daily living, adverse events, and aberrant drug-taking behaviors) reflect significant domains in monitoring these patients over time; however, it has not been validated in large studies (171). These instruments aid clinical decision making and should not be viewed as necessarily diagnostically accurate. Many of the questionnaires have not been validated and the psychometric properties of these instruments are considered to be weak (143). Selection of the appropriate tool is based on time availability, physician expertise and understanding of the tools, and the clinical situation. The formatting characteristics, including linguistic problems and high readability of several opioid assessment screening tools (OAST) statements or questions may hinder many patients' ability to accurately complete and comprehend OASTs independently (171). Some instruments are lengthy and impractical to administer in a busy clinic setting. Most self-report instruments are susceptible to deception by the patient. As a result, they may not identify substance abusers who intentionally give false responses. Another disadvantage is that these instruments do not specifically explore aberrant behavior during treatment.

5.0 MONITORING PATIENTS FOR OPIOID ABUSE

All patients who receive opioid therapy for chronic pain must be regularly assessed to ensure safe and effective use of opioid analgesics. Periodic adherence monitoring is recommended to identify current drug use and any drug-related adverse effects, justify ongoing treatment, evaluate compliance, investigate misuse and abuse, and ensure sound and proper pain management (5,11). The frequency and intensity of monitoring

Opioid Abuse Predictors

Table 2. Screening instruments for opioid risk assessment.

Name	Completed by	Purpose	Description	Results	Limitations
Prescription abuse check list (173)	Physician	Evaluate prescription opioid abuse: misuse by patient in chronic pain vs. use unrelated to chronic pain.	5 criteria: overwhelming focus on drugs; pattern of ≥ 3 early refills; lost or stolen drugs; drugs obtained from multiple providers, ER or illegal sources.	Opiate abuser = $\geq 3/5$ criteria.	Evaluated in veterans, not replicated in other settings; methodologic limitations (11).
Prescription Drug Use Questionnaire (PDUQ) (174)	Physician	Identify / monitor aberrant drug-related behaviors in patients treated with opioids.	42 items structured interview with questions regarding the pain condition, opioid use, social and family history and psychiatric issues.	A score of > 15 indicates substance use disorder. 3 items are accurate in detecting substance use disorder: tendency to increase analgesic dose or frequency, preference for a specific route of administration, considering oneself as addicted.	Lengthy. Key criteria identified as predicting addiction have not been validated to predict addictive tendency (11).
Screening Tool for Addiction Risk (STAR) (175)	Physician	Identify chronic pain patients at risk for subsequent problems with opioid treatment.	14 true or false questions.	History of treatment in drug or ETOH rehab program predicts addiction with positive predictive value of 93% and negative predictive value of 5.9%.	Fewer linguistic problems. Methodologic limitations not replicated (11).
Screening Tool for Abuse (176)	Physician	Identify / monitor aberrant drug-related behaviors in patients treated with opioids.	6 items High risk = ≥ 4 Low risk = < 4	High risk = ≥ 4 Low risk = < 4 Sensitivity: 0.77 (CI 0.68-0.84). Specificity: 0.84 (CI 0.76-0.91).	Results replicated in 2 studies in a private interventional pain practice setting (177). Methodological limitations (5).
Pain Assessment and Documentation Tool (PADT) (180)	Physician	Identify / monitor aberrant drug-related behaviors in patients treated with opioids.	4 domains: analgesia, adverse effects, activities of daily living, aberrant behavior. Original PADT tool had 59 items; in the revised PADT tool 18 items were deleted.	Descriptive tool to assist documentation. Reliability and validation of individual items and sections of PADT needed. Predictive validity missing.	Pragmatic tool; utility not evaluated in studies (11).
Pain Medication Questionnaire (PMQ) (181)	Patient	Identify / monitor aberrant drug-related behaviors in patients treated with opioids.	26 items. 5 point Likert scale. High risk: with scores in upper 1/3. Low risk: with scores in lower 1/3.	High PMQ scores indicate decreased biopsychosocial function, substance abuse (2.6x), early refill (3.2x), perceived disability vs. low scores (170).	Need replication studies. Long test to administer and evaluate (11).
Screener and Opioid Assessment for Patients with Pain (SOAPP) (183)	Patient	Predict risk of aberrant drug-related behaviors (ADRB).	24 items, a 5 and 14 item questionnaire also. Classifies into high- or low-risk; higher scores indicate a greater risk of addiction.	Cutoff score of ≥ 8 . High scores weakly increased likelihood for future ADRB. Low scores moderately decreased likelihood for future ADRB (5).	Diagnostic accuracy: fair to poor evidence. Methodologic limitations Not replicated in multiple settings.
Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R) (184)	Patient	Predict ADRB.	24 items.	High scores weakly increased likelihood for future ADRB. Low scores moderately weakly decreased likelihood for future ADRB (5).	The low cutoff score makes it less vulnerable to the possibility of deception. Need validation studies in primary care settings.

Table 2 (cont.). *Screening instruments for opioid risk assessment.*

Name	Completed by	Purpose	Description	Results	Limitations
Opioid Risk Tool (ORT) (185)	Patient	Predict risk of ADRB.	5-item tool with different weights for historical and psychiatric variables. Scores of 0-3 = low risk 4-7 = moderate risk ≥ 8 = high risk.	≥ 8 = high risk. Strongly increased likelihood for future ADRB in high risk group and strongly decreased likelihood for future ADRB in low risk group (5).	Limited evidence. Methodologic shortcomings in studies; non-standardized outcomes; need validation outside pain clinics (11); (5).
Scoring System to Predict Outcome (DIRE) (186)	Physician	Predict outcomes and compliance with long-term opioid treatment.	4 domains, 7 items: diagnosis, intractability, efficacy, and 4 subcategories of risk (psychological, chemical, reliability, social support).	≤ 13 = unsuitable candidate. ≥ 14 = good candidate. Higher scores = greater possibility of successful opioid prescription.	Easy to use, takes < 2mins to complete. Validation study was retrospective. Need prospective validation in homogenous pain population.
Addiction Behaviors Checklist (ABC) (187)	Physician	Identify / monitor aberrant drug-related behaviors in patients treated with opioids.	20 items. Cutoff score ≥ 3 of 20.	Sensitivity: 0.88. Specificity: 0.86.	Tool validated in veterans. Did not use a valid reference standard for ADRB.
Current Opioid Misuse Measure (COMM) (188)	Patient	Identify / monitor aberrant drug-related behaviors in patients already being treated with opioids.	40 items.	Cut off score ≥ 10. Sensitivity: 0.74 (CI 0.63-0.84). Specificity: 0.73 (CI 0.65-0.80). High scores weakly increase likelihood of current ADRB. Lower scores weakly decrease likelihood of current ADRB (5).	Validated in chronic noncancer pain patients. Fair to poor evidence. Not replicated.
Prescription Opioid Misuse Index (POMI) (189)	Physician	Identify / monitor aberrant drug-related behaviors in patients treated with opioids.	6 items. Developed to identify OxyContin abuse in pain patients.	High sensitivity and specificity. 2 or more of 6 items classifies at risk for misuse.	No data on its application in diverse pain population.
Prescribed Opioid Difficulties Scale (PODS) (24)	Patient	Identifies common difficulties ascribed to opioid therapy by patients.	15 items scale, consisting of problems subscales and concerns subscales.	24% reported elevated psychosocial problems and 36% reported elevated concerns about controlling their use of prescribed opioids.	Does not screen or identify problem patients. Provides an entry point and a framework for a patient-centered clinical dialog about the pros and cons of taking opioid medicines.

is individualized and guided by risk stratification. Individuals at low risk for adverse outcomes and on stable doses of opioids can be monitored at least once every 3 to 6 months. Individuals at high risk for abuse will need more intense and frequent assessments. Monitoring should routinely include assessment and documen-

tation of pain severity, functional ability, psychological health, progress toward achieving treatment goals, treatment compliance, presence of adverse effects, aberrant drug-related behaviors, and substance use. Supplemental information from external sources such as testing of biologic material (e.g., urine), interviews

with family or caregivers, review of medical records, payer opioid prescription data, or input from prescription monitoring programs, can be helpful and should be used as needed. Adequate prescription monitoring mechanisms at the systems level are, however, inadequate or lacking, hence providers need to rely on their clinical skills and the patient's behavior pattern over time to detect problematic prescription drug misuse.

5.1 Opioid Assessment Screening Tools

Although several formal screening instruments that identify aberrant drug-related behaviors in patients on opioid therapy have been described, there is no well-tested, reliable, and easily administered screening tool to detect drug-seeking behaviors in primary care patients taking long-term opioids or being considered for such therapy. Evidence on prediction and identification of aberrant drug-related behaviors is limited; the definitions for aberrant drug-related behaviors are not standardized across studies and do not account for seriousness of identified behaviors. In general, the psychometric properties of published questionnaires and interview protocols are weak and, quite unlike other tests and protocols, have not been subjected to stringent scrutiny consistent with the practice of EBM (80-84,114-117). Furthermore, most studies that evaluated these instruments are limited by methodological shortcomings (143). In terms of tools for screening patients before initiating COT, a tool which has been described to have a reasonably high-quality deviation which may be used in conjunction with clinical assessment is the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) (192). It is suggested that OAST should be used, jointly with other measures, to guide and monitor therapy. Two tools, Pain Assessment and Documentation Tool (PADT) and COMM with strong content, face and construct validity, are recommended for these purposes (5). PADT is a simple charting device based on the "4 A's" concept and designed to help clinicians consistently document various significant domains over time (180,193).

Chou and his colleagues (5) evaluated 9 studies ($n = 1,530$) for accuracy of screening tools for identifying aberrant drug-related behavior in patients who were on long-term opioid therapy for CNCP. They found that none of the investigators were blinded to the results of the screening instruments. There was a significant variation in the aberrant drug-related behavior across the studies. Only 2 studies out of 9 made evaluations using the Pain Medication Questionnaire. Out of the 8

instruments studied, 2 were self-administered, 4 were interviewer-administered, and in the remaining 2 studies the methodology was not described. Pain scores were recorded in only one study, and none of the studies documented the doses of the opioids used. In one higher quality study, self-administered COMM was used to determine the diagnostic test characteristics of this instrument (126). It showed a sensitivity of 0.75 (95% CI, 0.63-0.84) and specificity of 0.73 (95% CI, 0.65-0.80). In another lower quality study, the interviewer-administered Addiction Behavior Checklist (ABC), showed a sensitivity of 0.88 and specificity of 0.86 (187). Screening instruments in 4 studies showed poor diagnostic accuracy.

Atluri and Sudarshan (176) developed a tool to detect the risk of inappropriate use of prescription opioids in chronic pain patients. The tool was developed for use in interventional pain management settings. Six clinical criteria were identified to predict opioid abuse:

1. Focus on opioids
2. Opioid overuse
3. Other substance abuse
4. Low functional status
5. Unclear etiology of pain
6. Exaggeration of pain.

The score is derived by counting the number of positive criteria. The total score can range from 0 to 6; a cutoff score of 3 and above predicts abuse. Patients who misused opioids scored above the cutoff of 3. In a retrospective study of CNCP patients receiving opioids, a score of 3 or above indicated abuse (OR 16.6; 95% CI: 8.3-33 and $P < 0.001$). Manchikanti et al (179) used these criteria in a prospective study of 500 patients in an interventional pain management setting and found that 100 out of 500 patients had a history of drug abuse. The authors concluded that this was a cost-effective and reliable tool for screening drug abuse potential in an interventional pain management setting. It predicted substance abuse but did not identify illicit drug use (177).

5.2 Urine Drug Testing

Urine screening provides a noninvasive, low-cost monitoring strategy that will detect most drugs for 1-3 days after exposure. It provides objective documentation of treatment compliance and exposes possible drug misuse and abuse in patients on opioid therapy. Urine drug testing (UDT) can detect the presence of illicit drugs,

such as heroin or cocaine, or controlled substances not prescribed by the physician ordering the test (e.g., hydromorphone in a patient prescribed oxycodone). Self-reporting of drug use, prescribed or otherwise, among chronic pain patients treated with opioids is often unreliable. Evidence from studies suggests that behavior monitoring alone in patients on chronic opioid treatment will fail to detect potential problems revealed by urine toxicology testing; one in 5 patients who appeared to be taking opioids as prescribed by an expert clinician had a positive urine screen for an illicit drug (190,191). In another practice, abnormal UDT results triggered referral to behavioral health and addiction medicine specialists in 40% of patients and assisted with detecting drug abuse or addiction in 19.6% of patients (42). It is therefore suggested that urine drug screens should be routinely employed in monitoring patients on opioid therapy, whether or not the patient has any signs or symptoms of drug misuse. The results of UDT should be used as a part of the overall clinical strategy in pain management, because both false-positive and false-negative results can occur on occasion. In addition, some compounds are not typically found in standard urine screens and specific and expensive urine, blood, or hair testing may need to be ordered (41). Despite the evidence in favor of urine screens, UDTs are not routinely used in monitoring opioid therapy. A survey of attendees at the American Congress of Pain Medicine in 2008 revealed wide variability in the motivations for urine testing and testing practices; urine testing was not used consistently and testing was motivated more by a desire to detect undisclosed substances than to evaluate appropriate opioid use. Some respondents never tested the urine of their opioid patients, and about two-thirds of respondents had no formal training in urine testing of patients on opioid therapy. Most respondents did random, rather than scheduled, testing and few had any urine testing protocol (194). Christo et al (9) extensively reviewed the role of UDT in adherence monitoring and recommended an algorithmic approach based on well controlled diagnostic accuracy trials (30,34).

5.3 Monitoring of Prescribing Practices

Passik and Kirsh (195) described a unique concept of prescribing opioids and called it "in and out of the box" prescribing. According to these authors, providers should regularly evaluate whether their opioid prescribing patterns match those of their peers. Prescribing "in the box" refers to prescribing opioids in a usual and customary fashion similar to that of their colleagues. Pre-

scribing "out of the box" refers to opioid prescribing practice that deviates from the usual prescribing habits of the majority of physicians prescribing opioid analgesics. Although it is not wrong to prescribe "out of the box," there must be sound reasons to justify the practice. It is expected that this model will alert physicians when they are not in line with usual practice and therefore may decide to increase the degree, amount, or rigor of documentation. Factors that indicate "out of the box" prescribing are the type of pain condition where opioid use is controversial (e.g., headaches), there is a complicating active psychiatric condition (e.g., depression, bipolar disorder, impulse control disorder, substance use disorder), contact with nonmedical users, a young age, and prescribing > 180 mg/d of MSO4 equivalents. A daily dose of 180 to 200 mg morphine or morphine equivalent is considered by consensus as the upper dose limit for appropriate prescribing in CNCP (5,196). It is suggested that the "out of the box" opioid therapy group should be carefully reevaluated for any change in their medical or social condition and/or consultation with a pain specialist should be obtained to identify factors that led to "out of box" prescribing. Some of the therapeutic strategies that may work include opioid rotation, multidrug therapy (nonsteroidal anti-inflammatory drugs [NSAIDs], anticonvulsants, antidepressants, topical analgesics), multimodal or multidisciplinary treatment with rehabilitation therapies (modalities, orthosis, exercises), behavioral interventions, injections and other interventional treatments, neuromodulatory treatments, and complementary and alternative medicine therapies (11,29,31,32,33,35,37,114-117,196-214). While this concept needs to be refined further, providers must recognize that good pain management should lead to some decreases in pain perception for the patient combined with a corresponding increase in the ability to function. Ongoing reports of poorly controlled pain and or failure to improve functioning should prompt reassessment and review of treatment with opioid analgesics (196).

5.4 Payer Opioid Prescription Data

Among patients with chronic nonmalignant pain, requests for increasing opioid doses need careful assessment to discover any nonmedical factors that may be at play. In addition to reviewing medical records, a prescription database and payer data check can be useful in identifying patients who receive larger than expected numbers of opioid prescriptions and the issues associated with larger prescription numbers. A retrospective review of payer opioid prescription data and

patient charts from a rural family medicine group identified patients with 3 or more prescriptions (average 8.4; standard deviation [SD] = 5.5, range 3-28) from 2 or more providers (average 3.7; SD = 1.8, range 2-10) over a 6-month period. Patients using nonopioid analgesics had 3.2 fewer prescriptions per 6 months and were less likely to have 6 or more prescriptions (OR=0.24, 95% CI=0.08-0.73) than those on opioids alone. Concurrent use of nonopioid analgesics, escalating opioid dosage, and number of providers were the best predictors for the number of opioid prescriptions (215).

5.5 Prescription Monitoring Programs

Prescription monitoring programs (PMPs) collect statewide data about prescription drugs and track their flow (216,217). These programs have 3 components. The first is data collection for prescriptions. They show the physicians who wrote them and the pharmacies that dispensed them. Pharmacies are required to report the data by law. Physicians are encouraged to report but are not mandated to do so. The second component is a central repository for this data; and lastly there should be a protocol in place describing how this data from the central repository can be made available to appropriate authorities and agencies. To date, 38 states have PMPs, but there is a significant difference in the manner and frequency with which the data is collected.

President George W. Bush signed into law the National All Schedules Prescription Electronic Reporting Act (NASPER) in 2005 which was created by the American Society of Interventional Pain Physicians and enacted by Congress (218). This law requires states to collect prescription information for Schedule II, III, and IV medications. It also requires states to have the capability to share this information with one another. This can decrease cross-border narcotic trafficking.

At one point, only 3 states allowed physicians access with physician-friendly programs to monitor drug utilization. These included Kentucky, Utah, and Idaho. Now, with the enactment of NASPER and/or other funding from the Harold Rogers Prescription Monitoring Program, multiple states are operating physician-friendly programs where pain physicians can identify the risk of overuse and abuse (61,216-221). Adherence monitoring has been shown to increase compliance and reduce drug abuse (222-225).

5.6 Opioid Treatment Agreement

The purpose of an opioid treatment agreement (OTA) is to inform patients about the risks and benefits

of opioid therapy, facilitate a mutually agreed upon course, enhance the therapeutic relationship, improve patient adherence to opioid therapy by documenting treatment parameters, and establish procedures should problems arise. OTAs are commonly used in pain clinics and reported to improve care through better adherence to opioid therapy and reduce opioid analgesia misuse (222-235). Yet OTAs are controversial and questions are raised regarding their intent, elements, language and tone, readability, physician responsibility, and legal risk (226-229). The evidence that OTAs are effective in reducing opioid misuse is relatively weak and OTAs have not been proven to improve adherence, improve patient care, or protect the rights of patients or physicians (228-230). One systematic review evaluated the association of treatment agreements and UDT with opioid misuse outcomes in outpatients with CNCP and found no high quality studies. All of the studies were observational and were of poor to fair quality; there was a modest reduction in opioid misuse (7% to 23%) after treatment agreements with or without UDT (231). The Federation of State Medical Boards suggests that there may be circumstances in which the use of a written OTA may be necessary. Some states suggest, and others mandate, a written OTA. It is advised that physicians review the policies of their state regarding OTAs and controlled substances and carefully consider the purpose and methods when developing and implementing an OTA.

5.7 Universal Precautions

The term "universal precautions" is derived from the infectious disease approach to potentially life threatening infections where it is recognized that it is often impossible to tell early in the treatment phase who is infected with human immunodeficiency virus (HIV) or hepatitis C, so that everyone is treated as potentially infected and the appropriate minimum level of precautions is applied to all patients. Similar to infectious disease, it is impossible to identify "at-risk" individuals in chronic pain management. In order to reduce stigma, improve patient care, and contain overall risk, Gourlay et al (232) proposed the "universal precautions" approach to assessment and ongoing management of chronic pain patients. Universal precautions are a unified 10-step process of 1) establishing a diagnosis and treating treatable causes including any comorbid psychiatric illness; 2) psychological assessment including risk of addictive disorder; 3) informed consent that includes anticipated benefits and foreseeable risks; 4) a treatment agree-

Table 3. *Ten-step process: An algorithmic approach for long-term opioid therapy in chronic pain.*

STEP I	Comprehensive initial evaluation
STEP II	Establish diagnosis <ul style="list-style-type: none"> ◆ X-rays, MRI, CT, neurophysiologic studies ◆ Psychological evaluation ◆ Precision diagnostic interventions
STEP III	Establish medical necessity (lack of progress or as supplemental therapy) <ul style="list-style-type: none"> ◆ Physical diagnosis ◆ Therapeutic interventional pain management ◆ Physical modalities ◆ Behavior therapy
STEP IV	Assess risk-benefit ratio <ul style="list-style-type: none"> ◆ Treatment is beneficial
STEP V	Establish treatment goals
STEP VI	Obtain informed consent and agreement
STEP VII	Initial dose adjustment phase (up to 8-12 weeks) <ul style="list-style-type: none"> ◆ Start low dose ◆ Utilize opioids, NSAIDs and adjuvants ◆ Discontinue <ul style="list-style-type: none"> • Lack of analgesia • Side effects • Lack of functional improvement
STEP VIII	Stable phase (stable – moderate doses) <ul style="list-style-type: none"> ◆ Monthly refills ◆ Assess for four A's <ul style="list-style-type: none"> • Analgesia • Activity • Aberrant behavior • Adverse effect ◆ Manage side effects
STEP IX	Adherence monitoring <ul style="list-style-type: none"> ◆ Prescription monitoring programs ◆ Random drug screens ◆ Pill counts
STEP X	Outcomes <ul style="list-style-type: none"> ◆ Successful – continue <ul style="list-style-type: none"> • Stable doses • Analgesia, activity • No abuse, side effects ◆ Failed – discontinue <ul style="list-style-type: none"> • Dose escalation • No analgesia • No activity • Abuse • Side effects • Noncompliance

MRI = magnetic resonance imaging; CT = computed tomography; NSAID = nonsteroidal anti-inflammatory drug

ment that describes the expectations and obligations of both patient and provider and also establishes appropriately set boundary limits to enable early identification and intervention around aberrant behavior; 5) pre- and post-intervention assessment of pain level and function; 6) an appropriate trial of opioid therapy with or without adjunctive medications; 7) reassessment of pain score and function; 8) regular assessment of the “four A’s” of pain medicine and affect; 9) a periodic review of the pain diagnosis and comorbid conditions, including addictive disorders; and 10) careful and thorough documentation to reduce medicolegal exposure and risk of regulatory sanction. In addition, a triage scheme of risk stratification was described. By placing patients into risk categories of low, medium, or high (Groups I, II, and III), it is possible to recommend to primary care practitioners those patients whom they might confidently manage on their own, co-manage with specialty support, or refer to specialty clinics with more experience and resources to tackle challenging cases (1,233-236). Universal precautions as a concept should be based upon mutual trust and respect between patient and practitioner, both of whom should be committed to setting and achieving realistic goals in both cancer and noncancer pain patients.

Trescot et al (3) and Manchikanti et al (4) described a 10-step process for managing chronic opioid therapy as illustrated in Table 3.

6.0 TACKLING OPIOID ABUSE AND DIVERSION

Effective strategies are needed to reduce diversion of opioids for nonmedical use. These strategies should be combined with education, behavioral interventions, and monitoring. A concerted effort to improve education and research about the rational management of chronic pain is needed to preserve the right of patients with chronic pain while reducing the catastrophic effects of opioid misuse, abuse, and overdose. Novel opioid formulations designed to reduce nonmedical use are being marketed to deter abuse. Future studies will demonstrate if these formulations play a vital role in limiting abuse and diversion. Implementation of prescription monitoring programs may curtail abuse and diversion, but has been limited by a lack of federal and state funding for these programs. New regulations have been introduced by the Food and Drug Administration (FDA) in an attempt to limit opioid-related adverse effects, specifically misuse, addiction, overdose, and death.

6.1 Educating Patients and Providers

Patients need to be educated in the areas of safeguarding medications, disposing unused medications, and understanding the consequences of manipulating physicians and selling their medications (46). In 2008, the Utah Department of Health added 12 questions to the state's Behavioral Risk Factor Surveillance System (BRFSS) survey to better understand how state residents obtain and use prescription pain medication. Findings from the survey indicated that an estimated 20.8% of Utah adults aged 18 or older had been prescribed an opioid pain medication during the preceding 12 months. Of those prescribed an opioid pain medication, 3.2% reported using their medication more frequently or in higher doses than had been directed by their doctor; 72.0% reported having leftover medication, and 71.0% of those with leftover medication reported that they had kept the medication. Approximately 1.8% of all adults reported using prescription opioids that had not been prescribed to them. In 2009, the Utah Department of Health published a set of guidelines to reduce morbidity, mortality, and disability associated with misuse or abuse of prescription drugs, especially narcotics. The guidelines include recommendations that providers counsel patients to dispose of unused medication properly once the pain has resolved and prescribe no more than the number of doses needed based on the usual duration of pain severe enough to require opioids for that condition (233). Physician education should be focused on considering a patient's risk for opioid misuse before initiating opioid therapy; recognizing that a patient is misusing and/or diverting prescribed medications; and understanding the variation in the abuse potential of different opioid medications currently on the market. Other strategies for providers include changing behavior and practice patterns, saying "no" to unreasonable patient demands, and adopting a universal precaution approach toward all patients prescribed drugs of addiction.

6.2 Behavioral Interventions

Most often treatment is discontinued for chronic pain patients who show aberrant drug-related behavior and are noncompliant with their use of opioids for pain. These patients then seek out another provider ("doctor-shopping") to obtain opioids, or borrow from friends or family, or use other illicit means to obtain drugs from the street. The end result is the individual continues to experience poorly controlled pain and the problem of abuse and diversion continues to fester in

the community. Behavioral interventions with close monitoring and cognitive behavioral substance misuse counseling could increase overall compliance with opioids in noncompliant chronic pain patients as demonstrated by Jamison et al (130) in a trial of patients with noncancer back pain who were prescribed opioids and demonstrated opioid misuse or were at-risk. Patients considered high-risk for opioid misuse were randomized to either standard control (High-Risk Control) or an experimental compliance treatment consisting of monthly urine screens, compliance checklists, and individual and group motivational counseling (High-Risk Experimental). In addition, a low-risk control group (Low-Risk Control) was recruited. Patients were followed for 6 months and the percentage with a positive DMI was estimated. The DMI score, a composite score of self-reported drug misuse, physician-reported abuse behavior, and abnormal urine toxicology results, was significantly different among the groups with 73.7% of the High-Risk Control patients demonstrating positive scores on the DMI compared with 26.3% from the High-Risk Experimental group and 25.0% from the Low-Risk Controls ($P < 0.05$) (130).

6.3 Managing Pain in Patients with Substance Abuse

Physicians are "reluctant" to prescribe opioids to patients with CNCP and a history of substance abuse for fear of addiction, misuse, or diversion of the medications. In one study, individual interviews and focus groups were conducted with general practitioners, addiction specialists, pain specialists and rheumatologists. Many exhibited "distrust" that such patients were experiencing "genuine pain," resulting in patients often being considered guilty until proven innocent. Such negative regard toward these patients was based on previous manipulative "drug seeking" encounters and often resulted in the undertreatment of pain. Potential "flags" were identified that alerted physicians to the potential for abuse or diversion of their prescription, including: doctor shopping, losing prescriptions, and early requests for prescription refills. Physicians reported different management approaches and stricter prescribing regimes for patients with a history of substance abuse to limit the potential of addiction, misuse, and diversion. Examples of poor pain management were described where drug users had been undertreated as a result of negative attitudes or the inexperience of staff (234). Interdisciplinary pain management, the use of universal precautions in all patients, and special atten-

tion to the structure of care in those at higher risk for opioid misuse may improve outcomes in this population (235).

6.4 Abuse Deterrent Formulations

Opioid formulations designed to deter and resist abuse address some, but not all, aspects of inappropriate opioid use. By incorporating physical and pharmacological barriers to contain the euphoric effects of opioids, these novel formulations make the drug less convenient or less desirable to abusers and may curb problematic opioid use.

The formulations use a variety of strategies, for example, combining opioids with naltrexone or incorporating the opioid in a high-viscosity matrix designed to resist physical and chemical extraction. These drugs include extended-release morphine with sequestered naloxone (Embeda), controlled-release oxycodone in a high-viscosity hard gelatin capsule (Remoxy), and tamper-resistant, once-daily hydromorphone extended release (OROS hydromorphone). Extended-release morphine with sequestered naltrexone offers a pharmacological barrier in that pellets of morphine surround an internal core of naltrexone (ratio 100: 4 of morphine to naltrexone), which is released if the tablet is compromised by chewing or crushing. Severe opioid withdrawal due to misuse of Embeda was recently reported (236). As of November 17, 2011 Pfizer withdrew Embeda from the U.S. market because the manufacturers failed to meet some of the prespecified stability requirements. Remoxy's hard gelatin capsule of controlled-release oxycodone was designed to resist tampering and the drug cannot be extracted with a needle.

While these drugs hold promise, it remains unproven if they can truly curb abuse. It is possible that abuse-detering formulations may divert drug abusing individuals to find other drugs that are easier to compromise. Nevertheless, these formulations are important innovations and warrant further study to assess their appropriate role as analgesics (237,238).

6.5 Postmarketing Surveillance

The primary goal of postmarketing surveillance is to provide information for risk assessment of a drug. Drugs affecting the central nervous system (CNS), such as opioid analgesics, stimulants, sedative-hypnotics, muscle relaxants, and anticonvulsants form a unique group of products for surveillance because they are often misused, abused, and diverted. Their adverse events are difficult to monitor because there are often

attempts to conceal the misuse, abuse, and diversion of the product by the users. A postmarketing surveillance system for prescription drugs abused in the U.S. should include product-specific information that is accurate, immediately available, and geographically specific and includes all areas of the country. Most producers of branded opioid analgesic products have created systems that measure abuse from multiple vantage points: criminal justice, treatment professionals, susceptible patient populations, and acute health events. In the past, the U.S. government has not established similar requirements for the same products produced by generic manufacturers. However, the FDA Amendments Act of 2007 includes generic opioid analgesic products by requiring that all products containing potent opioid drugs perform rigorous surveillance and risk management. While general risk management guidance has been developed by the FDA, more specific analyses and guidance are needed to improve surveillance methodology for drugs which are misused, abused, and diverted (239).

6.6 Regulatory Measures

The White House in April 2011 announced a plan to curb prescription drug abuse called "Epidemic: Responding to America's Prescription Drug Abuse Crises." The key elements of the plan are: expansion of state-based prescription drug monitoring programs, recommending convenient and environmentally responsible ways to remove unused medications from homes, supporting education for patients and health care providers, and reducing the number of "pill mills," and doctor-shopping through law enforcement. In concert with the White House plan, the U.S. FDA announced a new risk reduction program, called Risk Evaluation and Mitigation Strategies (REMS), for all extended-release and long-acting opioid analgesics. The new REMS concentrates on educating physicians about proper pain management, patient selection, other requirements, and improving patient awareness regarding the safe use of opioid analgesics (240). As part of the plan, the FDA directed manufacturers of certain extended-release opioids and methadone to give patients educational materials, including a medication guide that uses consumer friendly language to explain safe use and disposal. The FDA has directed makers of opioid analgesics to work together and develop a single system of implementing the REMS strategies. Physician training, patient counseling, and other risk reduction measures developed by opioid manufacturers as part of the REMS are ex-

pected to become effective by early 2012. They will be required for the various brand names of generic opioids: oxycodone, morphine, hydromorphone, oxymorphone, methadone, transdermal fentanyl, and transdermal buprenorphine. At this time physician training is not mandatory under the REMS plan. Other federal agencies are working to get Congress to link mandatory opioid physician training to the already required Drug Enforcement Administration (DEA) registration number needed to prescribe controlled substances. The FDA will also require risk management to include a way to determine if the education programs are helping to reduce problems associated with long-acting and extended-release opioids, while allowing patients who need opioids to get them (241).

6.7 Emerging Treatments

The opioid analgesics that are currently available exert their analgesic activity by binding to opioid receptors in the CNS. Centrally mediated opioid analgesia is accompanied by other CNS-mediated side effects such as respiratory depression, nausea, cognitive disturbances, tolerance and addiction. At the heart of the issue of opioid misuse is the role of opioid systems in the reward circuitry, and the adaptive processes associated with repetitive opioid use that manifest during withdrawal. An opioid drug that retains analgesic efficacy without the centrally mediated rewarding effects of μ -opioids would be the "holy-grail" for opioid research. Research is directed at developing opioid drugs with reduced deleterious side effects. Several alternatives are being investigated, such as combining μ -opioids with CB1 cannabinoid receptor antagonists or NK1 neurokinin receptor antagonists. Another alternative that holds promise is the development of peripherally acting opioid agonists without centrally mediated effects. Experimental and clinical research has revealed the existence of peripheral opioid receptors on neuronal and non-neuronal tissues (242,243). These peripherally restricted opioid receptors are activated by endogenous and exogenous opioid ligands and have a potent analgesic effect as demonstrated in experimental models of inflammatory pain (244-247). Peripherally acting opioid analgesics do not cross the blood-brain barrier and are therefore devoid of the common side effects that accompany centrally acting opioid analgesics. In the future, these drugs can potentially play a major role in providing optimal pain control and simultaneously curbing drug abuse. Emerging pharmacological insights of opioid receptors provide future hope for developing

opioid-based analgesics with reduced addictive properties and perhaps, reduced opponent processes. In addition, with the increased understanding of nociceptive circuitry and the molecules involved in transmitting pain, new therapeutic targets have become evident that may result in effective analgesics either alone or in combination with current opioid therapies (248).

7.0 CONCLUSION

Two major public health hazards are undertreatment of pain and prescription drug misuse/abuse. The widespread use of prescription opioids in recent decades has been associated with a steady increase in prescription drug abuse and an increase in opioid-related deaths. Multiple approaches to identify and manage at-risk patients have been proposed. Experts recommend combining several different strategies to identify at-risk patients, including examining the underlying origins or implications of aberrant behaviors, and tailoring treatments accordingly. Informed consent forms, treatment agreements, risk documentation tools, and regular monitoring of the 4 A's will help to educate patients and guide management based on treatment goals. The application of universal precautions and awareness of aberrant behaviors will increase physician confidence in identifying and addressing problematic behaviors. Chronic pain treatments must be multimodal and combined with nonopioid medications. There should also be cognitive, behavioral, and interventional techniques to optimize outcomes, particularly for those who are unable to safely take their opioids in a structured fashion. Opioid formulations designed to deter and resist abuse are being marketed and may address some, but not all, aspects of inappropriate opioid use. The legal and regulatory environment surrounding opioid prescribing is in flux and the FDA has adopted new approaches to control the growing problem of prescription opioid misuse and abuse. It is important that providers understand the dynamics surrounding pain management, and keep abreast of advances in opioid analgesia in order to treat pain effectively while minimizing abuse.

DISCLOSURES

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