Opioid Analgesics

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Abstract

Chronic pain is an international health issue of immense importance that is influenced by both physical and psychological factors. Opioids are useful in treating chronic pain but have accompanying complications. It is important for clinicians to understand the basics of opioid pharmacology, the benefits and adverse effects of opioids, and related problematic issues of tolerance, dependence, and opioid-induced hyperalgesia. In this article, the role of psychiatric comorbidity and the use of validated assessment tools to identify individuals who are at the greatest risk for opioid misuse are discussed. Additionally, interventional treatment strategies for patients with chronic pain who are at risk for opioid misuse are presented. Specific behavioral interventions designed to improve adherence with prescription opioids among persons treated for chronic pain, such as frequent monitoring, periodic urine screens, opioid therapy agreements, opioid checklists, and motivational counseling, are also reviewed. Use of state-sponsored prescription drug monitoring programs is also encouraged. Areas requiring additional investigation are identified, and the future role of abuse-deterrent opioids and innovative technology in addressing issues of opioid therapy and pain are presented.

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Chronic pain is a serious international problem of immense proportion that can negatively impact every facet of daily living.[1,2] It has been estimated that annually more than 100 million Americans have chronic pain.[3] Chronic pain affects more individuals than diabetes, cancer, and heart disease combined and is the major reason people visit their primary care physicians. Chronic pain can interfere with sleep, employment, social life, daily activities, and overall quality of life. Chronic pain can also have a negative effect on mood, appetite, energy level, and sexual activities and can contribute to recurrent worried

thoughts about finances, family interactions, and future disability.[4-6]

The usefulness of opioids in the treatment of acute and cancer-related pain has been confirmed by several studies.[7] An estimated 5 to 8 million Americans use opioids for chronic pain.[8] Yet, many physicians and other health care professionals are reluctant to support the use of opioid medication for patients with chronic noncancer pain because of concerns regarding adverse effects, tolerance, and addiction.[9,10] Addiction, in particular, is of prime concern given its intensely negative consequences and its relatively broad prevalence. Over the past decade, there has been a steady increase in use of prescription opioids in the United States, which has been the main contributing factor to the skyrocketing incidence of opioid abuse. The number of opioid prescriptions written for pain increased from 76 million in 1991 to an estimated 219 million in 2011.[11] This increase has paralleled the increase in opioid-related overdoses and hospitalizations.[12] Because of increased availability, prescription opioids have become the most abused class of drug in the United States, with more deaths related to opioid abuse than to cocaine and heroin combined.[12] Many drug abusers prefer prescription opioids not only for their easier availability compared with street drugs but also for their greater purity due to their regulated manufacture.[12,13] In fact, patients in the United States consume 80% of all opioid prescriptions worldwide, and prescription drug abuse is perceived to be the fastest growing drug problem in America.[12] Unfortunately, most clinicians are not adequately prepared to properly diagnose, treat, and closely monitor patients with chronic pain who are prescribed opioids, even though studies have shown that those patients who are at greater risk for misuse of opioids are most likely to be prescribed opioids.[13]

In this article, we present a current review of the pharmacology of opioids and its uses and discuss misuse and abuse issues that are often present when treating patients prescribed opioids for chronic pain. We will also provide an overview of assessment and treatment strategies designed to improve adherence to opioid prescriptions and briefly explore unresolved clinical questions and future considerations.

OVERVIEW OF OPIOIDS FOR PAIN

Opioid Clinical Pharmacology

The term *opioid analgesics* refers to a broad class of drugs including (1) alkaloids extracted from poppy seeds (morphine, codeine) and their semisynthetic derivatives (oxycodone, hydromorphone, oxymorphone) and (2) synthetic phenylpiperidines (meperidine, fentanyl) and synthetic pseudopiperidines such as methadone.[14] Opioid analgesics act on 3 major classes of receptors: μ, δ, and κ receptors. Each of these classes of receptors has its representative endogenous ligand (eg, endorphin for the μ receptor and dynorphin for the κ receptor). These classes of opioid receptors are widely distributed throughout the central and peripheral nervous system as well as other systems such as the gastrointestinal tract. On the basis of their pharmacodynamic profiles, opioid analgesics can also be classified as a full agonist at opioid receptors (eg, morphine, fentanyl) or an agonist-antagonist such as buprenorphine.[15]

Benefits and Adverse Effects of Opioids

Activation of opioid receptors produces profound analgesia mediated through a combined presynaptic and postsynaptic effect. Presynaptically, opioid analgesics act on primary nociceptive afferents (inhibition of calcium channels), resulting in the reduced release of neurotransmitters such as substance P and glutamate implicated in nociceptive transmission. Postsynaptically, opioid analgesics directly inhibit postsynaptic neuronal activity by hyperpolarizing cell membranes via opening potassium channels. Other effects of opioids (eg, antitussive, reducing gastrointestinal tract motility) also have practical therapeutic use.[16]

Because of a widespread distribution of opioid receptors both within and outside the nervous system, opioid analgesics also produce a broad spectrum of adverse effects including euphoria, dysphoria, sedation, respiratory depression, constipation, suppression of endocrine systems, cardiovascular disorders (eg, bradycardia), convulsion, nausea, vomiting, pruritus, and miosis.[17] Although the extent of these adverse effects may differ among individual opioids depending on dose regimen, these effects substantially narrow

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the clinical therapeutic window for effective opioid therapy.[17] Because of these adverse effects, particularly for opioid-naive patients, it is always best to start with a low dose and gradually titrate up.[18] For patients with chronic persistent moderate to severe pain, short-acting opioids can be converted to long-acting opioids in the belief that long-acting opioids provide less fluctuation in analgesic blood levels, fewer adverse effects, and require less frequent dosing. However, there are ongoing controversies about the comparable benefits of either opioid dosing formula.[19]

Opioid Tolerance and Opioid-Induced Hyperalgesia

In addition to opioid adverse effects, the development of tolerance to opioid analgesics is a major barrier to clinical opioid therapy. Opioid tolerance is a pharmacological phenomenon caused by repeated opioid exposure that results in decreased analgesic effects.[20] Although the degree of tolerance may differ for individual opioid analgesics, this incomplete tolerance to individual opioid analgesics is considered as a rationale for opioid rotation in opioid-tolerant patients with pain. Although changing to an alternative drug may yield a better balance between analgesia and adverse effects, this process requires a working knowledge of equianalgesic doses, and the long-term efficacy of opioid rotation is questionable.[21]

Excessive opioid exposure may produce a paradoxical increase in pain sensitivity manifested as hyperalgesia (exacerbated painful response to noxious stimulation) and/or allodynia (painful response elicited by innocuous stimulation). This opioid-induced hyperalgesia (OIH) has been linked to both short-term (eg, intraoperative remifentanil infusion) and long-term opioid administration.[22,23] Although it may be clinically difficult and controversial to differentiate between opioid tolerance and OIH using subjective pain scores, OIH may be related to exacerbated preexisting pain, new onset of pain, increasing pain with opioid dose escalation, and decreasing pain with opioid dose reduction. Accordingly, opioid tolerance and OIH may be improved and exacerbated, respectively, by opioid dose escalation, although the direct clinical impact to OIH has been questioned.[18,23]

DEFINITIONS OF TERMS AND CLINICAL ISSUES

Defining key terms is important to help minimize confusion and clarify discussion about patients prescribed opioids for pain.[24-26] *Substance misuse* is defined as the use of any drug in a manner other than how it is prescribed and indicated for use. *Substance abuse* is the unlawful use of a substance or use that results in failure to fulfill major obligations or patterns of legal, social, and interpersonal problems caused by such use. *Addiction* refers to the compulsive use of a drug resulting in physical, social, and psychological harm to the user. Addiction is generally understood to be a chronic condition with an underlying neurobiological dysfunction that, once manifested, is believed to persist and is characterized by (1) an inability to consistently abstain, (2) impairment in behavioral control, (3) craving, (4) diminished recognition of major problems with one's behaviors and interpersonal relationships, and (5) a dysfunctional emotional response.[26-28] *Physical dependence* is a common phenomenon in persons taking opioids for a period of time. It is characterized by physical withdrawal symptoms when the opioid is discontinued. *Tolerance* is a common consequence of long-term opioid treatment (although individual differences in opioid tolerance vary) that is manifested by a need for increasing doses to maintain the same effect. Physical dependence and tolerance are both commonly found among patients who use opioids for chronic pain, and neither of these phenomena is necessarily related to true addiction. *Aberrant drug-related behavior* is behavior that is suggestive of a substance abuse and/or addiction disorder. Some of these behaviors include obtaining prescription drugs from nonmedical sources, "borrowing" drugs from others, selling prescriptions, seeking prescriptions from multiple clinicians, forging prescriptions, injecting oral formulations, "losing" prescriptions on multiple occasions, having evidence of deterioration in function at work, home, or in the family, and resisting any change to therapy despite evidence of psychological and physical deterioration. A list of these terms and their definitions are presented in Table 1.

Several earlier studies suggested that most individuals prescribed opioids for the treatment of pain typically do not develop

addiction or substance abuse,[27] although the reported incidence of addiction from prescription opioids has been variable. Most patients receiving long-term opioid therapy experience physical dependence and tolerance to the medication. It has also been suggested that some persons with chronic pain who are undermedicated manifest drug-seeking behaviors by overusing their prescription medication in an attempt to find relief. This concept, known as *pseudoaddiction*, identifies those patients who, once adequately relieved from the pain, discontinue all drug-seeking behaviors.[29]

RISK FACTORS FOR PRESCRIPTION OPIOID MISUSE

Efforts to improve health care professionals' ability to identify abuse and diversion of controlled substances have been strongly recommended by the US Department of Justice.[30] In particular, seeking prescriptions from multiple physicians, using illicit drugs, snorting or injecting medications, selling and diverting prescription drugs, and using drugs in a manner other than its intended use have been identified as particularly problematic. Despite the need to identify misuse of opioids and limit inappropriate prescribing, health care professionals also struggle with providing appropriate pain relief for patients who present with legitimate pain problems.[31,32]

There are particular problems associated with long-term use of opioids. Some patients become psychologically dependent on the medication,[33,34] while others may have signs of impaired cognition,[35] difficulties with psychomotor performance,[36] and over time, development of OIH.[14,20,22,37-39] There is some evidence that high-dose opioids, which some define as greater than 180-mg morphine equivalent per day, can be particularly dangerous, leading to increasing risk of respiratory depression, central sleep apnea, and sleep-disordered breathing and with lower long-term efficacy.[16] There is also evidence that early misuse of opioids can increase the chance of leading to addiction,[40] supporting the need for early risk assessment, careful monitoring, and strategies to assess and improve compliance when indicated.[41]

There are some identifiable factors that are related to lower risk of misuse of opioids, including older age, stable mood, a history of being responsible and keeping appointments, not overusing medication, and, in general, presenting in a rational and pleasant manner.[2] Risk factors commonly cited in the literature as being associated with opioid misuse include (1) family or personal history of substance abuse, (2) young age, (3) history of legal problems, (4) frequent contact with high-risk individuals or environments, (5) history of previous problems with employers, family, and friends, (6) history of risk-taking and thrill-seeking behavior, (7) smoking cigarettes and regularly using other substances that lead to dependence, (8) history of major depression or anxiety, (9) multiple psychosocial stressors, (10) history of childhood abuse, and (11) previous drug and/or alcohol rehabilitation (Table 2).[2,42-44]

It is important to understand that the determinants of opioid misuse and addiction rest with the user and that many patient-specific factors may increase susceptibility to these problems. Factors such as preexisting personality traits,[45] a tendency to self-medicate to alleviate symptoms,[46] and opioid craving[47-49] have been identified as individual factors that contribute to opioid abuse.

TABLE 1. Definition of Terms

Substance misuse—The use of any drug in a manner other than how it is indicated or prescribed
Substance abuse—The use of any substance when such use is unlawful or when such use is detrimental to the user or others
Addiction—A primary, chronic, neurobiological disease that 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. Addiction is generally understood to be a chronic condition from which recovery is possible; however, the underlying neurobiological dysfunction, once manifested, is believed to persist
Physical dependence—A state of adaptation that is manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, or decreasing blood levels of the drug and/or by administration of an antagonist
Tolerance—A state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time
Aberrant drug-related behavior—Behavior suggestive of a substance abuse and/or addiction disorder. Examples are selling prescription drugs, prescription forgery, stealing or "borrowing" drugs from others, injecting oral formulations, obtaining prescription drugs from nonmedical sources, multiple episodes of prescription "loss," repeatedly seeking prescriptions from other clinicians, evidence of deterioration in function (work, home, family), and repeated resistance to change therapy despite evidence of physical and psychological problems

Data from the American Academy of Pain Medicine,[24] the American Society of Addiction Medicine,[25] and the American Psychiatric Association.[26]

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ISSUES OF NEGATIVE AFFECT AND OPIOID USE

Many patients with chronic pain have accompanying psychiatric comorbidity expressed as depression, anxiety, irritability, and negative affect.[50-53] Also, surveys of patients with chronic pain have revealed a high incidence of physical or sexual abuse and early childhood trauma.[54-56] Among patients treated in a specialty pain center, studies suggest that between 50% and 80% of patients with chronic pain have signs of psychopathology, making psychiatric problems the most prevalent comorbidity in these patients.[57-59] In an earlier survey study conducted by Arkinstall et al,[60] patients prescribed opioids were found to have a 50% prevalence of a mood disorder. It has also been reported that physicians are more likely to prescribe opioids for chronic pain on the basis of pain behavior and increased affective distress rather than the patient's self-reported pain severity or objective physical pathology.[53] Furthermore, patients with chronic pain who have major psychopathology are more likely to report greater pain intensity, more pain-related disability, and higher levels of emotional distress associated with their pain than those who do not have evidence of psychopathology.[61,62]

Follow-up studies of patients with chronic pain who have notable psychopathology have revealed poorer treatment outcomes (eg, greater pain and disability) compared with patients who present with minimal psychopatholgy.[63,64] In particular, those with elevated ratings of anxiety and depression tend to have considerably worse return-to-work rates 1 year after injury compared with those without any mood disorder.[57,65] One study investigating the effects of intravenous morphine found a 40% greater reduction in pain among patients with minor psychopathology compared with a matched group with major psychopathology.[64] Taken together, the literature suggests that patients with chronic pain and a high degree of negative affect benefit less from opioids and any other treatments designed to control their pain compared with those with minimal negative affect.[52]

Many patients with affective disorders also have substance use disorders. Treating an affective disorder may result in decreased substance abuse behaviors, although patients are at risk of relapse.[47] Some studies have found that patients with high-level negative affect are 2 to 3 times more likely to misuse opioid medications than patients with low-level negative affect.[53,66,67] Hasin et al[68] found that some patients abuse their opioid pain medication to alleviate their psychiatric symptoms. Similarly, a study by Wasan et al[48] indicated that comorbid depression and/or anxiety disorders were associated with greater opioid misuse, even in those with no history of a substance use disorder.

TABLE 2. Risk Factors for Opioid Misuse

- Family history of substance abuse
- Personal history of substance abuse
- Young age
- History of criminal activity and/or legal problems including DUIs
- Regular contact with high-risk people or high-risk environments
- Problems with past employers, family members, and friends (mental disorder)
- Risk-taking or thrill-seeking behavior
- Heavy tobacco use
- History of severe depression or anxiety
- Psychosocial stressors
- Prior drug and/or alcohol rehabilitation

DUI = driving under the influence.

RISK ASSESSMENT TOOLS

Many physicians struggle with providing appropriate pain relief for patients while minimizing the misuse of opioid analgesics, and in response, concerted efforts have been made to identify individuals at risk for abuse of prescription opioids.[33,34] Numerous regulatory and professional organizations have released recommendations and guidelines related to the use of opioids among patients with chronic pain.[10,69,70] These guidelines emphasize the importance of opioid risk assessment before initiation of long-term opioid therapy. In addition to obtaining a thorough medical history, reviewing past medical records, and performing a medical examination, an opioid risk assessment using validated screening tools should be conducted. Structured interview measures based on *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria have been useful in assessing alcoholism and substance use disorders,[71] but often these measures lack validation in persons

with chronic pain. Using traditional substance abuse measures increases the likelihood that tolerance and dependence will be identified when no abuse exists. Some of the most commonly recommended tools include the Screener and Opioid Assessment for Patients with Pain — Revised,[72-74] the Opioid Risk Tool,[75,76] the Diagnosis, Intractability, Risk, and Efficacy scale,[77] and the Screening Instrument for Substance Abuse Potential.[78] Validated ongoing assessment measures have also been useful in identifying current opioid abuse (Current Opioid Misuse Measure[79,80] and Opioid Compliance Checklist[81]). Scores on any of these measures are not necessarily a reason to deny opioids but instead allow clinicians to identify patients in whom close monitoring might be required to minimize their likelihood of opioid abuse and addiction. Brief descriptions of these assessments and other tools are provided in Table 3.

INTERVENTIONS FOR HIGH-RISK PATIENTS

Opioid Therapy Agreements

Controlled substance agreements have been used in clinics to document the expectations and roles of patients and physicians concerning the use of prescription opioids. The goal of these agreements is to use informed consent in order to address potential problems with opioid use and to improve patient adherence with opioid medication. Often, these documented agreements are used to educate patients as well as inform them of their responsibilities when using prescribed pain medication.

An opioid therapy agreement identifies the conditions required of patients to be prescribed opioids for pain. Patients are often aware of the risks and complications associated with opioids, and termed conditions are needed to document that the patients are being responsible and benefiting from prescription opioids for pain.[81] Typical sample conditions state that (1) patients should only use their prescribed medications as directed by their physician, (2) they agree to only receive prescription pain medication from one physician, (3) they will only use one pharmacy to fill prescriptions, (4) they will not receive additional medication if their prescription runs out early, (5) they will be unable to receive replacement medication if lost or stolen, (6) they agree to submit to periodic urine screens and pill counts to verify adherence, (7) they will be responsible in maintaining their

TABLE 3. Opioid and Medication Abuse Screening Assessments Tools

Name of questionnaire	References	Purpose of questionnaire
Screener and Opioid Assessment for Patients with Pain — Revised	Butler et al,[72] 2004; Butler et al,[73] 2008; Butler et al,[74] 2009	24- Item self-administered screening tool designed to predict aberrant medication-related behaviors for patients with chronic pain being considered for long-term opioid therapy. Opioid risk cutoff score is 18. The reliability and predictive validity were high
Current Opioid Misuse Measure	Butler et al,[79] 2007; Butler et al,[80] 2010	17-Item self-report assessment developed for identifying patients with chronic pain who are currently misusing prescription opioids. Opioid risk cutoff score is 9. The reliability and predictive validity were high
Opioid Risk Tool	Webster and Webster,[75] 2005; Webster and Dove,[76] 2007	5-Item checklist that allows the physician to determine if a patient will display aberrant drug-related behaviors. Opioid risk cutoff score is 8
Diagnosis, Intractability, Risk, and Efficacy score	Belgrade et al,[77] 2006	Predicts the feasibility of long-term opioid treatment for noncancer pain. Also used to pinpoint beneficial factors, if any, of an individual's opioid use. Opioid risk cutoff score is 14
Screening Instrument for Substance Abuse Potential	Coambs et al,[78] 1996	5-Item self-report screening questionnaire for substance abuse potential intended mostly for alcohol abuse
Opioid Compliance Checklist	Jamison et al,[81] 2014	12-Item questionnaire developed to assess adherence in patients with chronic pain receiving long-term prescription opioids. Five items were found to best predict subsequent aberrant behaviors based on multivariate logistic regression analyses
Pain Assessment and Documentation Tool	Passik et al,[82] 2004	41-Item questionnaire that provides extensive documentation of the patient's progress and objectively monitors the patient's care. There is no numerical scoring method for this assessment
Prescription Drug Use Questionnaire	Compton et al,[83] 2008	42-Item questionnaire used to identify patients who are likely to be nonaddicted, substance abusing, or substance-dependent

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appointments, (8) they agree to participate in all aspects of treatment (eg, physical therapy, psychotherapy, and behavioral medicine), and (9) if pain and daily function have not improved with their prescription pain medication, the physician has the right to taper the patient off the medication.[2,44,81]

Each of the elements of the opioid therapy agreement should be clarified so that patients know exactly what is expected of them. By signing the agreement, they are acknowledging their consent to the proposed treatment plan and agree to adhere to the specific conditions and responsibilities set by the clinic. It is recommended that every patient prescribed opioids for pain read and sign a controlled substance agreement. Periodic use of an opioid adherence checklist can also be used to remind patients of their responsibilities when using opioids.[81] For some, a violation of this agreement would mean tapering and eventually discontinuing prescription opioids. Unfortunately, violations of this agreement can go unreported, and often, the treating physician has difficulty in tracking and verifying adherence.[2]

A rational systematic approach in the treatment and management of chronic pain with opioid therapy known as *universal precautions* has received strong support from pain societies and clinicians alike.[84] This approach, borrowed from infectious disease paradigms, includes a means of identifying and monitoring patients at risk for misusing prescription opioids. Gourlay et al[84] recommended the following steps when considering a patient for long-term opioid therapy: (1) establish a diagnosis with the appropriate differential, (2) obtain a psychological assessment, including risk potential for addictive disorder, (3) complete an informed consent and treatment agreement, (4) assess level of pain and function, (5) begin an opioid therapy trial if indicated, (6) periodically reassess pain, function, and behavior (eg, analgesia, activities of daily living, adverse events), (7) obtain at least annual urine screens, (8) review the primary diagnosis and comorbidities on every follow-up visit, and (9) thoroughly document all information. Additional evaluation and treatment planning can be provided by members of a comprehensive pain management center and communicated to the referring physician. Some pain management specialists prefer to incorporate a trilateral agreement with the patient's primary care physician. After the patients have been followed up by a pain specialist and their condition stabilized with a particular opioid regimen, they may be referred back to the primary care physician. If issues of opioid nonadherence occur or there is a change in the pain diagnosis, the pain specialists could offer a reevaluation and consider additional treatments or changes in the medication regimen if necessary.

Urine Toxicology Screening

Urine toxicology screens are particularly useful in determining patients' adherence to their prescribed opioid medication. Immunoassay urine screens can be helpful in determining if a particular class of drug is present in the urine, but gas chromatography/mass spectrometry is the most sensitive and specific type of urine screen and is particularly helpful in quantifying a particular prescription medication. Gas chromatography/mass spectrometry screens are also helpful in determining creatinine levels used to identify possible drug tampering/adulteration as well as the presence of illegal substances and/or absence of prescribed medications. Objectively documenting adherence by obtaining a urine screen for every patient receiving opioid therapy at least yearly is recommended.[85]

Random urine toxicology screening in patients with chronic pain who have been prescribed opioids has revealed a high incidence of abnormal results. In a study of 122 patients, 43% of the sample had an abnormal result.[86] Another study found that 21% of the study patients had evidence of an illicit drug or a nonprescribed medication even though no obvious behavioral issues had been observed by their physicians.[87] These results were replicated in a study of 226 patients with chronic pain, which revealed that 46.5% of the sample taking prescribed opioids had abnormal urine toxicology screen results.[88] These studies suggest that risk assessment alone may not always identify patients who misuse pain medication and underscore the importance of regular urine toxicology screening along with behavioral observation and incorporation of self-report measures. Many clinics use immunoassay urine screens as the first line of analysis and then obtain results from gas chromatography/mass spectrometry testing when it is important to

detect the specific level of drug metabolite in the urine.[88]

Prescription Drug Monitoring Programs

Potential solutions to the continuing increase in opioid abuse, misuse, and diversion have become an ongoing focus in regulatory, legal, and governmental action. Prescription drug monitoring programs (PDMPs), one of the first diversion control tools established, monitor and analyze electronic prescription data transferred from pharmacies and practitioners. Prescription drug monitoring programs are one facet of a universal precautions approach that has been implemented clinically over recent years. Universal precautions assume a degree of risk for each patient and include risk assessment strategies as well as close patient monitoring in order to initiate and modify therapy in a safe and controlled manner.[84] For instance, if a patient is screened and deemed to be at higher risk for opioid misuse, more frequent follow-up may be indicated as well as signing an opioid treatment agreement, prescribing fewer doses of opioids per prescription, requiring frequent urine screening, using pill counts, and regularly checking the PDMP. The goals of this plan also include an expansion of PDMPs among states and an objective to achieve consensus standards for prescribing of opioids.[89]

Behavioral Interventions for Opioid Adherence

Patients with chronic pain who have evidence of nonadherence with prescription opioids are sometimes dismissed from clinical practice. Being "fired" as a patient at a clinic is not optimal because these patients often seek treatment elsewhere by going to the emergency department of a local hospital or engaging in illegal activity. A randomized study was conducted to examine the benefits of close monitoring and cognitive behavioral motivational counseling in improving adherence with prescription opioid use among patients with noncancer back pain at high risk for opioid misuse.[44] The results revealed that adherence training paired with careful monitoring of high-risk patients can be incorporated into a multidisciplinary pain program. Additionally, opioid adherence among high-risk patients could be improved to that of low-risk patients. This encouraging study documents the value and importance of risk assessment, frequent monitoring with monthly urine screens and opioid adherence checklists, and motivational counseling to help improve adherence with opioids. An ancillary component of this trial was the reduced number of patients who were discharged from treatment because of the attention and measures taken among patients prone to misuse of prescription opioids.

The recommended criterion standard of care for all patients considered for long-term opioid therapy includes a comprehensive assessment with a thorough history and physical examination, a mandatory opioid agreement, and regular monitoring. For those patients at greatest risk for misuse of their medication, more frequent visits with urine toxicology screens, use of an adherence checklist, motivational counseling, and pill counts, if indicated, would be recommended.[2] Even though risk of opioid misuse and addiction remains, greater focus on risk screening and documentation of outcome will help to mitigate the misuse of prescription opioids.[41]

UNSOLVED QUESTIONS AND FUTURE CONSIDERATIONS

In anticipation of an ever-aging population, future emphasis will be given to adequately managing chronic pain and other medical comorbidities within the health care system. Abuse-deterrent opioids will continue to be developed, and greater attention will be given to educating physicians and patients about obtaining, storing, and disposing of opioids. Abuse-deterrent formulations are those that are hard to crush and may contain substances that are designed to make the formulation less attractive to abusers. Some products combine an opioid agonist with an antagonist released when the pills are adulterated. Several new opioid formulations that are designed to prevent or deter the abuse of opioids have been developed,[90-92] and many more are expected to be approved for marketing in years to come. The future incorporation of abuse-deterrent opioids will hopefully decrease the abuse potential of prescribed opioids.

In the future, innovative technology will play a more active role in health care. Interactive and dynamic software programs that are

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designed to educate physicians, pharmacists, and patients will continue to be developed. Recently, there has been rapid growth of mobile and electronic health (mHealth and eHealth) applications in pain assessment and management.[93] The advent of mHealth, which refers specifically to the use of mobile and wireless applications (eg, text messaging, apps, movement monitors, social media), has increasingly become a viable option for managing chronic pain. It is hoped that eHealth and mHealth applications will reduce barriers to availability and accessibility for individuals with pain. With ever-expanding technology, larger segments of the population will have access to information and personal data designed to improve pain and coping, which hopefully will lead to reduced costs and more efficient health care utilization.

Another hopeful area of investigation will be genome research and genetics testing. This area of study holds much promise for the identification of markers for potential opioid misuse. Single-nucleotide polymorphisms have been identified that seem to affect drug metabolism and opioid reception (eg, cytochrome P450, catechol-O-methyltransferase, and *ABCB*$_1$) as well as other allelic variants.[94] Future identification of markers for opioid benefit and abuse within endogenous chemical-reactive systems will also shed light on our understanding of tolerance, OIH, craving, and potential opioid misuse. Longitudinal studies investigating demographic variables or sex, ethnic origin, and personality characteristics will also help in creating empirically based practice guidelines.

Ongoing investigations into cannabinoids and cannabinoid receptors will likely impact pain treatment strategies of the future and offer understanding into new mechanisms for symptom reduction. Nanotechnology used to deliver treatment to a specific targeted area and development of other delivery strategies like topical preparations will add to the treatment armamentarium. Lastly, a mechanistic understanding behind how an acute pain problem develops into a chronic pain syndrome and the effects this process has on centralized mechanisms will help to expand the scope of interventions for pain. The ultimate long-range goal would be to offer effective, affordable, and acceptable treatments for those who suffer the most from chronic pain.

CONCLUSION

Chronic pain is a multifaceted global health problem that requires multiple modes of intervention. Despite the apparent physical pathology of pain, it has been implicated that psychiatric comorbidities such as depression and anxiety disorders substantially affect pain intensity, level of functioning, and pain outcome. Corresponding to the dramatic increase in opioid prescriptions, psychiatric comorbidity is now associated with opioid misuse, abuse, and/or diversion. Many screening assessments are useful for evaluating a patient's risk for opioid misuse. Additionally, opioid therapy agreements, urine toxicology screens, use of tamper-resistant opioids, implementation of PDMPs, and other behavioral interventions have been established to improve opioid adherence. Unfortunately, there is a paucity of studies on long-term opioid therapy and little empirical support to instruct clinicians in the best strategies for treating pain with opioids. Sponsorship of continued research in this area is critically needed.

Abbreviations and Acronyms: **OIH** = opioid-induced hyperalgesia; **PDMP** = prescription drug monitoring program

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