Issues in Long-term Opioid Therapy: Unmet Needs, Risks, and Solutions

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Both chronic pain and prescription opioid abuse are prevalent and exact a high toll on patients, physicians, and society. Health care professionals must balance aggressive treatment of chronic pain with the need to minimize the risks of opioid abuse, misuse, and diversion. A thorough, ongoing assessment can help fashion a multimodal therapeutic plan, stratify patients by risk, and identify those who may exhibit aberrant behaviors after receiving opioid therapy. Appropriate safeguards (eg, urine drug screens, pill counts) may be used when necessary. Because not all aberrant behaviors have the same origins or implications, physicians must consider a differential diagnosis and tailor therapy accordingly. Opioid formulations designed to deter and resist abuse are currently in late-stage clinical development and address some but not all aspects of inappropriate opioid use. By incorporating physical and pharmacological barriers to obtaining the euphoric effects of opioids, these novel formulations may minimize problematic opioid use. The formulations use a variety of strategies, for example, combining opioids with naltrexone or niacin or incorporating the opioid in a high-viscosity matrix designed to resist physical and chemical extraction. Nonopioid medications as well as cognitive, behavioral, and interventional techniques should be considered for all patients with chronic pain, particularly for those who are unable to safely take their opioids in a structured fashion. The aim of this article was to help physicians prescribe opioid medications safely and successfully to patients who need them. A PubMed literature search was conducted using the keywords *risk management, assessment, aberrant behavior, addiction, prescription abuse,* and *abuse-deterrent*.

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NSAID = nonsteroidal anti-inflammatory drug; ORT = Opioid Risk Tool; SISAP = Screening Instrument for Substance Abuse Potential; SOAPP-R = Screener and Opioid Assessment for Patients with Pain–Revised; UDT = urine drug test

Prescription opioid abuse is increasing and exacts a high toll on patients, physicians, and society. Nonmedical users of prescription pain relievers are perhaps the most troublesome population of individuals who abuse opioids; their number more than quadrupled from 1990 to 2000, with abuse of oxycodone and hydrocodone products particularly common.[1,2] Escalating prescription drug abuse is associated with higher rates of comorbidities and drug-related mortality.[3,4] The overall cost of prescription opioid abuse in the United States has been estimated at $9.5 billion (in 2005 US dollars), including health care, criminal justice, and workplace costs.[5] Physicians who prescribe opioids must maintain extensive documentation and may be subject to investigation by the Drug Enforcement Administration.[6-8] This review article aims to help physicians prescribe opioid medications safely and successfully to patients who need them. A PubMed literature search was conducted using the keywords *risk management, assessment, aberrant behavior, addiction, prescription abuse,* and *abuse-deterrent*. Articles published between January 1, 1980, and December 31, 2008, were selected by relevance to the clinical use of prescription opioids in the treatment of chronic noncancer pain.

Chronic pain and prescription opioid abuse are both highly prevalent. Chronic pain affects approximately 50 million Americans each year,[9] whereas 48 million Americans 12 years or older have used prescription drugs for nonmedical reasons in their lifetimes.[1] Among the most potent analgesics available, opioids have a recognized role in the treatment of cancer- and noncancer-related chronic pain conditions.[7,10] Yet many physicians, concerned that their patients will become addicted, are reluctant to prescribe these agents, contributing to the widespread undertreatment of chronic pain.[7] Physicians must realize that patients exhibit a continuum of behaviors in response to opioid therapy[11] (Figure 1). In practice, prescription opioid users are in heterogeneous categories that include extreme cases of medical and nonmedical abusers. However, most patients who take prescription opioids are somewhere in between, ranging from those with pain who adhere to their treatment regimen to those who purposefully abuse their medications or from nonmedical users who self-medicate by taking illicit opioids to those who abuse opioids recreationally.

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Family physicians likely see many patients with chronic pain in their practices. When evaluating and treating a patient with chronic pain, the family physician must balance the need for aggressive treatment with minimizing the risks of treatment. Numerous medical (opioid, nonopioid, interventional) and nonmedical (eg, physical therapy, acupuncture, cognitive-behavioral therapy) treatment options are available.[12,13] This article reviews the use of opioid

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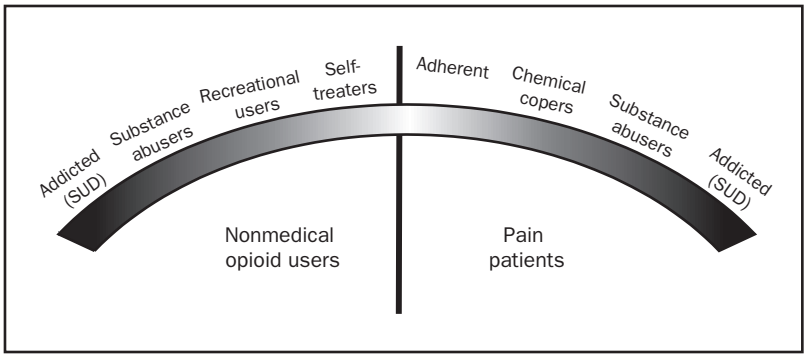

FIGURE 1. Prescription opioid users and continuum of behavior. SUD = substance use disorder. From *Exp Clin Psychopharmacol*.[11]

pharmacotherapy in the management of chronic pain. Emphasis is on the risks of opioid abuse, misuse, and diversion when these agents are prescribed and identification of methods to assess the risk for such behaviors and reduce their likelihood. The primary care physician can strike the necessary balance by treating chronic pain appropriately, including the use of opioids when indicated, while using risk management strategies to minimize risk.[6,7] Such strategies include risk assessment, risk stratification, and ongoing monitoring for aberrant drug-taking behaviors. Abuse-deterrent and abuse-resistant opioid formulations that incorporate physical or pharmacological barriers to common routes of abuse present an emerging set of tools to be used as part of a comprehensive risk management plan.[14,15] However, the potential public health benefits of these formulations will not be evident until they are approved and accessible to patients in need.

THE ROLE OF OPIOIDS IN CHRONIC PAIN

Treatment options for chronic pain include nonpharmacological and pharmacological modalities. Choice of therapy should be guided by a comprehensive assessment, including history (eg, pain history, medical history, family history, psychosocial history, medications, past interventions), physical examination, and appropriate diagnostic studies. Underlying conditions, if present, such as a tumor or vertebral fracture causing spinal cord compression, should be treated as directly as possible while also treating the pain caused by these conditions. Successful treatment of the underlying condition does not guarantee complete pain relief, and pain relief does not guarantee elimination of the psychosocial issues that often accompany chronic pain conditions. The physician-patient relationship may be well served by a discussion of these matters at the onset of treatment so that expectations and goals can be managed. The therapeutic plan should be tailored to the individual and to the presenting problem, with analgesics properly selected to achieve the optimal balance between maximum analgesia and minimum adverse effects. Depending on the complexity of the patient's condition, such as in patients with active substance abuse disorder or those with a personal history of substance abuse, consultation with a pain specialist or

TABLE 1. **Nonpharmacological Options for Treating Chronic Pain**

Option type	Example
Physical	Self-administered therapies
	Bandage wraps
	Corsets
	Counterirritant creams
	Exercise
	Heat or cold application
	Limitation of activities
	Postural changes
	Physical medicine
	Deconditioning
	Hydrotherapy
	Massage therapy
	Mechanical devices (eg, splints)
	Physical and occupational therapy
	Range-of-motion programs
Psychological	Attention control exercises
	Biofeedback
	Cognitive-behavioral therapy
	Desensitization
	Distraction
	Goal-setting and pacing strategies
	Guided imagery
	Hypnosis
	Patient education
	Psychotherapy for comorbid conditions, such as depression and anxiety
	Relaxation training
Interventional	Bracing
	Injection and radiation therapy
	Nerve blocks
	Neurodestructive surgical techniques
	Transcutaneous electrical nerve stimulation
	Vertebroplasty

Data from reference 9.

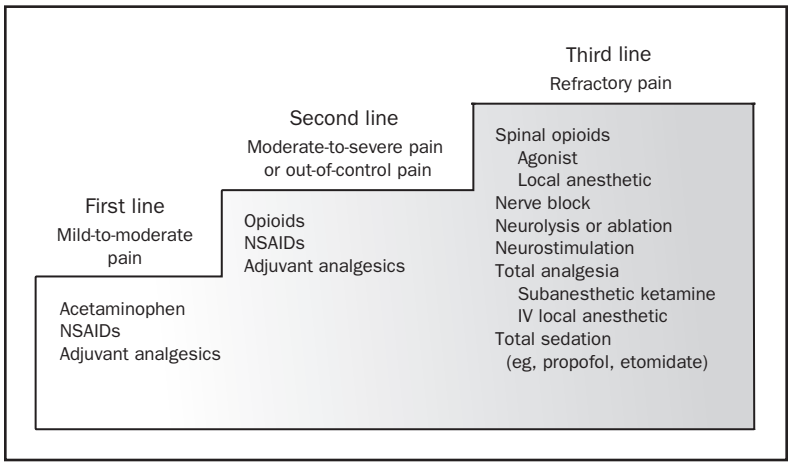

FIGURE 2. Stepladder approach to pain control. In this approach to treating pain, based on the WHO stepladder, treatment options are matched to level of pain. Opioids are considered for moderate-to-severe pain or out-of-control pain. For refractory pain, spinal opioids are among the options considered. IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs. Adapted from *Anesth Analg,*[17] with permission.

psychologist may be recommended, particularly if these issues are outside the physician's core expertise.[9,13,16]

Nonpharmacological approaches include physical, psychological, and interventional options (Table 1).[9] Frequently, a combination of nonpharmacological and pharmacological therapies is effective in managing chronic pain and any related physical and psychosocial impairments.[16] If medications are used, pain severity is an important criterion for choosing a therapeutic option, but it is not the only consideration. Previously, the World Health Organization stepladder approach had been criticized for treating pain solely on its intensity. A more contemporary strategy now includes treatment based on the underlying mechanism of pain. A modification of the World Health Organization stepladder approach incorporates the role of additional pain management interventions when rational trials and upward titrations of various pharmacotherapies do not effectively control pain or when the benefits of treatment are offset by burdensome adverse events. In this recommendation, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjuvant analgesics (eg, antidepressants and anticonvulsants) are suggested for the treatment of mild to moderate pain. For the treatment of moderate to severe pain or uncontrollable pain, opioids, NSAIDs, and adjuvant analgesics are recommended (Figure 2).[17]

The general thought among pain specialists is that some medications are more effective for one type of pain than another (eg, NSAIDs for nociceptive pain and anticonvulsants or antidepressants for neuropathic pain). However, few blinded comparative clinical studies have been published to support such beliefs.[18,19] Opioids are currently regarded as effective in the treatment of nociceptive pain, and there is increasing evidence from several controlled clinical studies on longer-acting opioid formulations (eg, methadone, oxycodone, levorphanol) for their utility in treating neuropathic pain as well.[7,19-21] Guidelines suggest that long-acting (controlled-release or sustained-release) opioids are useful for patients with continuous pain, whereas short-acting (immediate-release) opioids are used to manage intermittent and breakthrough pain.[9] Attentive care by a physician can often manage or even prevent the occurrence of common adverse effects caused by opioid therapy (eg, constipation, nausea, vomiting, endocrine dysfunction).[7] Often, patients develop tolerance to many of these adverse effects, although careful monitoring is always important. Despite additional treatment, some patients experience intolerable adverse effects that may be remediated by opioid rotation or multimodal treatment.

Combining drugs with different mechanisms of action (eg, an NSAID and an opioid for chronic pain associated with arthritis) can often enhance analgesia while lowering the necessary doses of drugs and reducing adverse effects. Although multidrug therapy appears to be a common practice, few formal clinical studies of this treatment concept have been published. In the only randomized controlled study of the use of such multidrug therapy, an opioid and an antiepileptic drug were administered either in combination or alone in patients with neuropathic pain. In that study, Gilron et al[22] found that a combination of morphine and gabapentin provided superior analgesia in patients with neuropathic pain at lower doses than placebo or each drug taken as monotherapy.

TABLE 2. **Spectrum of Aberrant Drug-Taking Behaviors**

More suggestive of addiction[a]	Less suggestive of addiction
Concurrent abuse of alcohol or illicit drugs	Aggressive complaining about the need for more drugs
Evidence of a deterioration in the ability to function at work, in the family, or socially that appears to be related to drug use	Drug hoarding during periods of reduced symptoms
Injecting oral formulations	Openly acquiring similar drugs from other medical sources
Multiple dose escalations or other nonadherence with therapy despite warnings	Requesting specific drugs
Obtaining prescription drugs from nonmedical sources	Reporting psychic effects not intended by the physician
Prescription forgery	Resistance to a change in therapy associated with tolerable adverse effects accompanied by expressions of anxiety related to the return of severe symptoms
Repeated resistance to changes in therapy despite clear evidence of drug-related diverse physical or psychological effects	Unapproved use of the drug to treat another symptom
Repeatedly seeking prescriptions from other physicians or emergency departments without informing prescriber	Unsanctioned dose escalation or other nonadherence with therapy on 1 or 2 occasions
Selling prescription drugs	
Stealing or borrowing drugs from others	

[a] Documented in patient's medical chart.
Data from reference 23.

RISK ASSESSMENT

If opioid therapy is considered for a patient, the risks of opioid abuse, misuse, and diversion should be carefully assessed. The object of risk assessment is to identify the likelihood that a patient will exhibit aberrant behaviors (eg, abuse, misuse, diversion, addiction; Table 2[23]) once opioid therapy has been prescribed so that appropriate safeguards can be placed in his or her pain management plan.[3,24] Some patients are at greater risk for abuse, misuse, diversion, and addiction than others, but identifying these patients can be a complex task because there is no clear consensus on their respective definitions. On the assumption that every patient has a degree of risk, a universal precautions approach is advised, beginning with a thorough risk assessment for every patient who is to be prescribed opioid therapy for chronic pain.[6] Risk management comprises a suite of assessment, monitoring, and treatment tools that need to be considered for each patient and individualized as clinically indicated[11] (Table 3).

Patients should be assessed for known risk factors for opioid abuse, including smoking,[25] psychiatric disorders, and personal or family history of substance abuse.[24] For example, smoking is a risk factor for substance abuse because approximately 75% to 95% of patients being treated for a substance abuse disorder smoke,[26] and 2 leading screening tools have linked smoking to aberrant behaviors in patients with pain.[25,27] Patients who have risk factors or are determined through the clinical screening tools to be at high risk should not necessarily be excluded from opioid pharmacotherapy if such treatment has been determined to be the best course of action. However, these patients should begin taking an opioid medication only after a highly structured treatment plan has been created to encompass all aspects of the risk management package discussed herein, particularly strict and frequent monitoring.

TABLE 3. **Risk Management Package for Patients Undergoing Opioid Therapy**

Screening and risk stratification
Use of prescription monitoring program data
Compliance monitoring
Urine drug testing
Pill or patch counts
Education about drug storage and sharing
Psychotherapy and highly structured approaches
Abuse-deterrent or abuse-resistant strategies in opioid formulation

Data from reference 11.

Effective screening tests are available to aid in risk assessment, including the Opioid Risk Tool (ORT), the Screener and Opioid Assessment for Patients with Pain–Revised (SOAPP-R), and the Screening Instrument for Substance Abuse Potential (SISAP). ORT is a self-administered, 5-question test that measures risk factors associated with substance abuse, including personal and family history of substance abuse, age, history of preadolescent sexual abuse, and psychological diseases. ORT has a high degree of sensitivity and specificity for determining which patients are at risk for opioid abuse, misuse, and diversion.[24] SOAPP-R, a 24-item, self-administered questionnaire, also has shown validity and reliability as a measure for stratifying risk of aberrant opioid-related behavior among patients with chronic pain.[28] Patients rate questions about the frequency of behaviors such as substance abuse, the patient-physician relationship, antisocial behaviors, behaviors associated with medication, issues involving personal care and lifestyle, neurobiological need for medicine, psychiatric disorders, and psychosocial difficulties on a scale of 0 (never) to 4 (very often).[29] Of the 24 SOAPP items, 14 are apparent predictors of aberrant drug use[29]; an abbreviated version of SOAPP using the 14 items has recently been validated and published.[25] SISAP,

a 5-item, physician-administered instrument, also demonstrates good sensitivity and specificity. It identifies at-risk patients through inquiries about age and drug, alcohol, and cigarette use; however, SISAP lacks questions about psychiatric comorbidities.[27] Although many validated tools are available, the choice of the appropriate tool often depends on the needs of each practice. For example, ORT is a short, self-administered test that can be used quickly and easily in a busy primary care practice, whereas SOAPP is a slightly longer test, factoring in more complex variables that may be better suited to a specialty practice.

When available, prescription monitoring programs, which exist in 35 states and monitor when and where prescriptions are filled, can provide physicians with valuable information about prescription compliance. Urine drug tests (UDTs) can be particularly useful among patients with inadequate response to opioid therapy and patients treated with opioid analgesics on a long-term basis.[6] Prescribers who refer patients for UDTs need to be certain that the laboratory performing the testing can identify the substance(s) in question. Use of UDTs in clinical practice varies, depending on the needs of the practice. Some specialists require that patients submit to a UDT on entering the practice and periodically thereafter. Other physicians consider a UDT only after a patient has clearly transitioned to long-term opioid therapy. The optimal option may be to require a UDT for all patients and to correlate the frequency of these tests with the risk level of the patient. Although all these tools have been individually, clinically validated, the best combination of tools to use for risk assessment in a primary care setting has yet to be clearly demonstrated.

MONITORING

On the basis of risk assessment, patients can be stratified by their level of risk, and therapy can be structured appropriately to minimize risk and guide monitoring.[6,13] Patients at minimal risk can receive minimal structure, whereas those at greater risk can receive more structure, such as more frequent visits, fewer pills per prescription, specialist-level care (eg, an addiction specialist or psychotherapist), and UDTs. An opioid treatment agreement, discussed and signed by the patient before opioid therapy begins, outlines the risks and benefits, explains what is expected of the patient, educates the patient about drug storage, and helps the patient distinguish between acceptable and unacceptable drug-taking behaviors.[16,30] Refusal to sign such an agreement may indicate misuse or abuse issues but may arise from concerns or psychological issues unrelated to substance abuse or misuse. Patients must be made aware of the responsibility of safeguarding these medications against diversion by friends, family, or visitors who may have access to medications left out or in unlocked locations. Multiple studies have shown that 50% or more of prescription opioids diverted for nonmedical use are obtained from friends and family.[31,32] The physician can benefit from consulting endorsed guidelines for using opioids to treat chronic pain, available from various state medical boards and the Federation of State Medical Boards.[7,30] A recent survey showed that these techniques led to resolution of aberrant behaviors in more than 40% of problematic patients when administered by a multidisciplinary team comanaged by a pharmacist and a nurse practitioner.[33] As comanagers, pharmacists and nurse practitioners can play a critical role by directly educating and monitoring patient compliance with opioid-based treatment regimens.

When using opioids to treat chronic pain, physicians should be observant of aberrant drug-taking behavior, which can prompt them to suspect deeper problems with abuse or diversion of opioids. Ongoing assessment of the 4 A's of pain treatment is helpful. The 4 A's—analgesia, activities of daily living, adverse events, and aberrant drug-taking behaviors—can structure assessment and serve as a means by which to record patient response to therapy. The Pain Assessment and Documentation Tool is useful for evaluating outcomes in those 4 domains.[34] Documentation of all aspects of patient care, from the initial examination to later visits, reduces the risk of regulatory sanction and is an important part of risk management.[6,35] However, not all instances of aberrant drug-taking behavior are related to abuse or addiction on the part of the patient. For example, a patient taking more medication than indicated may be doing so to obtain adequate analgesia, indicating that he or she has become tolerant to the medication (Table 4). Diversion of prescription opioids may be unintentional on the part of the patient, such as a case in which an adolescent who uses drugs recreationally takes prescription opioids from a parent or grandparent's medicine cabinet (Table 4). Certainly, frank abuse and criminal diversion of opioid medications may also occur.

Aberrant drug-taking behaviors may occur along a spectrum from those less suggestive of addiction, such as occasionally increasing the dose, to those that may be more suggestive of addiction, such as crushing and injecting oral medications (Table 2).[23] The former behaviors are more common and more likely to be clinically observable. Although they generally do not call for an extreme clinical change in response, they may signal an abuse problem if part of a pattern of repeated rule breaking. Passik et al[36] used the Pain Assessment and Documenta-

TABLE 4. **Case Examples of Aberrant Drug Use**

Case	Description
Case 1 (unintentional diversion)	A 45-year-old woman with chronic low back pain and no history of substance abuse is suspected of aberrant drug-taking behavior when she frequently runs out of medication before the refill date. On consultation, the patient insists she is compliant and takes her pills exactly as directed. The patient states she suspects her adolescent son may be taking her medication. Her son tests positive for opioids on a urine drug test and is referred to a substance abuse program.
Case 2 (misuse)	A 75-year-old man with chronic, severe pain due to metastatic colon cancer is prescribed a long-acting opioid to be taken twice daily. He takes an average of 3 tablets per day to get adequate pain relief. When he runs out of the medication prematurely, he informs the prescriber how he has been using the medication and that the regimen is effective.
Case 3 (addiction)	A 30-year-old male smoker with a history of substance abuse and generalized anxiety disorder is prescribed a long-acting opioid for chronic pain due to a work-related low back injury. The patient frequently loses his prescription or loses his pills. He frequently requests more medication because of stated inadequacy of analgesia provided by his prescription. He has been caught forging at least 1 prescription so that he would have a greater quantity of medication. Opioid urine drug test results are frequently positive for the prescribed drug, but on 1 occasion the screening result is positive for a nonprescribed opioid. The patient is referred to a substance abuse treatment center for treatment of opioid addiction.
Case 4 (tolerance)	A 52-year-old patient with a history of low back pain and lumbar radiculopathy due to degenerative disk disease taking a stable dose of long-acting morphine notes that the medication has gradually lost its effectiveness during a 2-year period and assertively requests a higher dose.

tion Tool to study aberrant drug-taking behaviors in 388 patients with noncancer pain receiving opioid therapy. During a 6-month period, 45% exhibited 1 or more aberrant behaviors, and 11% exhibited 5 or more aberrant behaviors. Interestingly, the behaviors were judged as aberrant by the patients' treating physicians in only 1 of every 5 instances.[37] These findings suggest a need for a clearer understanding of and greater agreement for the characterization of these behaviors.

TABLE 5. **Glossary of Terms Related to Aberrant Opioid Use**

Term	Definition
Addiction (substance dependence)	Substance abuse involving out-of-control, compulsive use of a drug despite harm
Chemical coping	Reliance on a drug for psychological stability
Diversion	Redirection of a prescription drug from its lawful purpose to illicit use; can be done with criminal intent
Misuse	Inappropriate use of a drug, whether deliberate or unintentional
Physical dependence	Condition in which abrupt termination of drug use causes withdrawal syndrome
Pseudoaddiction	Condition characterized by behaviors, such as drug hoarding, that outwardly mimic addiction but are in fact driven by a desire for pain relief and usually signal undertreated pain
Self-medication	Use of a drug without consulting a health care professional to alleviate stressors or disorders such as depression and anxiety
Substance abuse	Maladaptive pattern of substance use leading to considerable impairment or distress
Tolerance	Phenomenon in which analgesia decreases as the body grows tolerant to a given dosage of a drug

Data from references 37-40.

In diagnosing aberrant drug-taking behaviors, differentiating among conditions that are often confused is important (Table 5[37-40]). For example, a patient who is hoarding drugs may be showing signs of pseudoaddiction, caused by undertreatment of pain.[38] Undiagnosed or untreated psychiatric comorbidities may also be the cause of aberrant drug-taking behaviors.[13]

Patients in recovery from substance abuse represent a unique challenge in pain management. Nonopioid therapies should be the first choice in the treatment of these patients and, even then, they need to be monitored carefully. However, with appropriate structure, patients who have an active substance abuse problem may be able to receive opioid treatment for chronic pain.[13] Currently, in phase 2 clinical trials, Project Pain (Medication Adherence Therapy for Opioid Abusing Pain Patients) is an initiative aimed at developing and pilot-testing novel interventions to address prescription opioid abuse and pain concurrently. The programs developed include adherence therapy, which involves education, drug tests, pill counts, and supportive counseling; motivational adherence therapy, which includes the steps of adherence therapy along with homework, behavioral analysis of lapses, and self-monitoring through a diary; and methadone therapy, which includes pharmacotherapy (with conversion of all opioids to methadone) and adherence interventions.[41]

ABUSE-DETERRENT AND ABUSE-RESISTANT APPROACHES

Opioid formulations that incorporate barriers to common forms of manipulation are an emerging component of risk management. Novel subclasses of opioid formulations, incorporating pharmacological strategies and physical barriers, are designed to deter or resist misuse and abuse by making it difficult to obtain euphoric effects from opioid use. To obtain euphoric effects, most individuals who abuse opioids crush the tablets or capsules and snort or inject them, increasing opioid bioavailability.[42] In this way, a long-acting formulation can be made to release its full dose immediately. When extraction of the active drug is difficult because of the inclusion of physical barriers, the attractiveness of an opioid for abuse may be reduced.[8,15] As pharmacologically proactive tools, these formulations use either pharmacodynamic or physical mechanisms to make opioids unattractive to individuals who abuse them, as well as present barriers to unintentional or deliberate misuse. However, the true ability of these formulations to reduce misuse and abuse will be unknown until they are approved, and widespread epidemiological data regarding their abuse become available.

PHARMACOLOGICAL STRATEGIES

Pharmacological strategies have developed as either agonist-antagonist or agonist–additional active ingredient combinations. Agonist-antagonist formulations can be considered pharmacodynamic strategies because they act to reduce reward at the receptor level.[43] An example of such a strategy is Embeda (King Pharmaceuticals, Bristol, TN), which combines morphine with an antagonist. If this formulation is ingested normally, the naltrexone remains latent; if it is crushed, the naltrexone is released and reduces the effects of the morphine.[44] This opioid-naltrexone combination is distinctly different from Oxytrex (Pain Therapeutics Inc, South San Francisco, CA), a combination of oxycodone with ultralow-dose naltrexone. The addition of ultralow-dose naltrexone has shown potential to enhance opioid analgesia and reduce physical dependence and tolerance but was not designed to be an abuse deterrent.[43,45-47] The value of naltrexone combination formulations needs to be assessed clinically because of physician concerns of withdrawal or diminished pain control caused by naltrexone leakage in patients. In addition, extractability studies are needed to determine how easily this formulation can be modified for misuse or abuse.[48]

Another added-ingredient approach is the use of the vitamin niacin, which is designed to induce unpleasant, but temporary, symptoms if too many tablets are consumed.[44] The efficacy of agonist-antagonist and agonist–additional active ingredient formulations in reducing misuse and abuse of opioids in the real world is still untested. However, these approaches represent incremental advantages in the reformulation of opioid therapies.

ABUSE-RESISTANT STRATEGIES

Abuse-resistant mechanisms use physical strategies that make extracting the active drug from its formulation more difficult. One such formulation is a controlled-release oxycodone, Remoxy (King Pharmaceuticals), formerly known as PTI-821, which sequesters oxycodone in a high-viscosity matrix. This investigational drug is intended to resist physical manipulation and chemical extraction used to alter drug delivery to unintended routes, such as injection, snorting, and other common methods of abuse. The evidence suggests that this gel cap formulation provides a stable 12-hour dose of oxycodone and is difficult to extract by chewing, crushing, freezing, and crushing or dissolving in water, alcohol, or other common beverages.[49,50] These extractability studies establish an inherent difficulty in defeating the controlled-release mechanism of this formulation. In its pivotal phase 3 trial, this abuse-resistant formulation of oxycodone was found to significantly decrease pain intensity (P=.007), as well as secondary end points such as global assessment (P=.007) and quality of analgesia (P=.004), in patients with moderate to severe pain due to osteoarthritis compared with placebo.[39]

Opioids with a reduced abuse potential are one of the most important unmet needs in the management of chronic pain. Whether through pharmacodynamic or physical means, abuse-deterrent and abuse-resistant formulations may help to meet that need, although their actual impact will not be known until postmarketing data can be collected. This could restore the confidence of physicians in prescribing long-acting opioids and present an opportunity to increase access to opioid medications in minority and low-income communities, where such access has been limited.[51] Of course, access to these medications also will depend on their cost and the willingness of health care and prescription organizations to include them on formularies. As part of a comprehensive risk management plan, these formulations may help physicians to better balance optimal analgesia with reduced risk of prescription misuse and abuse.

Each component of a risk management package—assessment through screening and risk stratification, use of prescription monitoring programs, compliance monitoring, patient education, referral, psychotherapy, and new pharmaceutical formulations—can be individually tailored to each patient. Some health care professionals may not have

access to a prescription monitoring program or an addictionologist for a high-risk patient. In these cases, physicians must rely more on other components, such as thorough screening, frequent UDTs, and pill counts. These basic tools can be used to develop an optimal treatment plan to suit a patient's current needs. Moreover, these tools allow for flexibility over time so that the level of structure can be adapted as needed to manage changes in patient behavior.

CONCLUSION

Chronic pain and prescription opioid abuse are common and substantially affect patients, physicians, and society. Aggressive treatment of chronic pain must be balanced with the need to minimize the risks of opioid abuse, misuse, and diversion. Ongoing assessment can aid in developing a multimodal therapeutic plan, stratifying patients by risk, and identifying patients who may have aberrant behaviors after receiving opioid therapy. Not all aberrant behaviors have the same etiology, and thus physicians must consider a differential diagnosis and tailor therapy accordingly. Opioid formulations designed to deter and resist abuse are currently in late-stage clinical development and address some aspects of inappropriate opioid use. By incorporating physical and pharmacological barriers to obtaining the euphoric effects of opioids, these novel formulations may minimize problematic opioid use. Nonopioid medications and cognitive, behavioral, and interventional techniques should be considered for all patients with chronic pain.

REFERENCES

1. National Institute on Drug Abuse (NIDA). *NIDA Community Drug Alert Bulletin—Prescription Drugs*. Bethesda, MD: US Dept of Health and Human Services; 2005. NIH Pub. No: 05-5580. http://www.nida.nih.gov/PrescripAlert/index.html. Accessed March 6, 2009.

2. Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain*. 2006;22(2):173-181.

3. White AG, Birnbaum HG, Mareva MN, et al. Direct costs of opioid abuse in an insured population in the United States. *J Manag Care Pharm*. 2005;11(6):469-479.

4. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiol Drug Saf*. 2006;15(9):618-627.

5. Birnbaum HG, White AG, Reynolds JL, et al. Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. *Clin J Pain*. 2006;22(8):667-676.

6. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med*. 2005;6(2):107-112.

7. Trescot AM, Boswell MV, Atluri SL, et al. Opioid guidelines in the management of chronic non-cancer pain. *Pain Physician*. 2006;9(1):1-39.

8. Katz NP, Adams EH, Benneyan JC, et al. Foundations of opioid risk management. *Clin J Pain*. 2007;23(2):103-118.

9. National Pharmaceutical Council I; Joint Commision on Accreditation on Healthcare Organizations. Scribd Web site. Pain: current understanding of assessment, management, and treatments. 2001. http://www.scribd.com/doc/7563477/National-pharmaceutical-council-NPC-npcnow. Accessed March 9, 2009.

10. Carr DB, Goudas LC, Balk EM, Bloch R, Ioannidis JP, Lau J. Evidence report on the treatment of pain in cancer patients. *J Natl Cancer Inst Monogr*. 2004;(32):23-31.

11. Kirsh, KL, Passik SD. The interface between pain and drug abuse the evolution of strategies to optimize pain management while minimizing drug abuse. *Exp Clin Psychopharmacol*. 2008; 16(5):400-404.

12. Argoff CE. Pharmacologic management of chronic pain. *J Am Osteopath Assoc*. 2002;102(9)(suppl 3):S21-S27.

13. Passik SD, Kirsh KL. Opioid therapy in patients with a history of substance abuse. *CNS Drugs*. 2004;18(1):13-25.

14. Woolf CJ, Hashmi M. Use and abuse of opioid analgesics: potential methods to prevent and deter non-medical consumption of prescription opioids. *Curr Opin Investig Drugs*. 2004;5(1):61-66.

15. Webster LR. PTI-821: sustained-release oxycodone using gel-cap technology. *Expert Opin Investig Drugs*. 2007;16(3):359-366.

16. American Academy of Pain Medicine; American Pain Society. The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain. *Clin J Pain*. 1997;13(1):6-8.

17. Fine PG. The evolving and important role of anesthesiology in palliative care. *Anesth Analg*. 2005;100(1):183-188.

18. Harke H, Gretenkort P, Ladleif HU, Rahman S, Harke O. The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. *Anesth Analg*. 2001;92(2):488-495.

19. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol*. 2003;60(11):1524-1534.

20. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology*. 2003;60(6):927-934.

21. Morley-Forster PK, Clark AJ, Speechley M, Moulin DE. Attitudes toward opioid use for chronic pain: a Canadian physician survey. *Pain Res Manag*. 2003;8(4):189-194.

22. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352(13):1324-1334.

23. Passik S, Portenoy RK, Ricketts PL. Substance abuse among cancer patients, part 1: prevalence and diagnosis. *Oncology (Williston Park)*. 1998;12(4):517-521, 524.

24. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005;6(6):432-442.

25. Akbik H, Butler SF, Budman SH, Fernandez K, Katz NP, Jamison RN. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). *J Pain Symptom Manage*. 2006;32(3):287-293.

26. Rohsenow DJ, Colby SM, Martin RA, Monti PM. Nicotine and other substance interaction expectancies questionnaire: relationship of expectancies to substance use. *Addict Behav*. 2005;30(4):629-641.

27. Coambs RB, Jarry JL. The SISAP: a new screening instrument for identifying potential opioid abusers in the management of chronic nonmalignant pain within general medical practice. *Pain Res Manag*. 1996;1(3):155-162.

28. Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the Revised Screener and Opioid Assessment for Patients With Pain (SOAPP-R). *J Pain*. 2008 Apr;9(4):360-372. Epub 2008 Jan 22.

29. Butler SF, Budman SH, Fernandez K, Jamison RN. Validation of a screener and opioid assessment measure for patients with chronic pain. *Pain*. 2004;112(1-2):65-75.

30. Federation of State Medical Boards of the United States, Inc. Model policy for the use of controlled substances for the treatment of pain. Published May 2004. http://www.fsmb.org/pdf/2004_grpol_Controlled_Substances.pdf. Accessed March 9, 2009.

31. McCabe SE, Boyd CJ. Sources of prescription drugs for illicit use. *Addict Behav*. 2005;30(7):1342-1350.

32. Boyd CJ, McCabe SE, Cranford JA, Young A. Prescription drug abuse and diversion among adolescents in a southeast Michigan school district. *Arch Pediatr Adolesc Med*. 2007;161(3):276-281.

33. Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal

clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med*. 2007;8(7):573-584.

34. Passik SD, Kirsh KL, Whitcomb L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clin Ther*. 2004;26(4):552-561.

35. Atluri S, Boswell MV, Hansen HC, Trescot AM, Singh V, Jordan AE. Guidelines for the use of controlled substances in the management of chronic pain. *Pain Physician*. 2003;6(3):233-257.

36. Passik S, Kirsh K, Whitcomb L, et al. Monitoring outcomes during long-term opioid therapy for noncancer pain: results with the Pain Assessment and Documentation Tool. *J Opioid Manag*. 2005;1(5):257-266.

37. Passik SD, Kirsh KL. The need to identify predictors of aberrant drug-related behavior and addiction in patients being treated with opioids for pain. *Pain Med*. 2003;4(2):186-189.

38. Weaver M, Schnoll S. Abuse liability in opioid therapy for pain treatment in patients with an addiction history. *Clin J Pain*. 2002;18(4)(suppl):S61-S69.

39. Friedmann N, Butera P, Klutzaritz D, Gilmore D, Merrigan T, Webster L. Abuse-resistant, long-acting oxycodone treats chronic pain in a large Phase III study [abstract PT224]. Presented at: 12th World Congress on Pain (WCP). August 22, 2008; Glascow, Scotland. http://www.pslgroup.com/dg/2299aa.htm. Accessed March 9, 2009.

40. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Revised 4th ed. Washington, DC: American Psychiatric Association; 2000.

41. National Institute on Drug Abuse (NIDA). Project Pain—1. http://www.clinicaltrials.gov/ct/show/NCT00249587?order=1. Accessed March 9, 2009.

42. Passik SD, Hays L, Eisner N, Kirsh KL. Psychiatric and pain characteristics of prescription drug abusers entering drug rehabilitation. *J Pain Palliat Care Pharmacother*. 2006;20(2):5-13.

43. Webster LR, Dove B. *Avoiding Opioid Abuse While Managing Pain: A Guide for Practitioners*. North Branch, MN: Sunrise River Press; 2007.

44. Gershell L, Goater JJ. Making gains in pain. *Nat Rev Drug Discov*. 2006; 5(11):889-890.

45. Chindalore VL, Craven RA, Yu KP, Butera PG, Burns LH, Friedmann N. Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: a randomized, controlled trial of Oxytrex. *J Pain*. 2005;6(6):392-399.

46. Webster LR. Oxytrex: an oxycodone and ultra-low-dose naltrexone formulation. *Expert Opin Investig Drugs*. 2007;16(8):1277-1283.

47. Spierings EL, Butera PG, Wu N, Moran LV, Friedmann N. Phase III study to assess physical dependence and analgesic efficacy of Oxytrex versus oxycodone. Poster presented: 25th Annual Scientific Meeting of the American Pain Society; May 4-6, 2006; San Antonio, TX. Poster 814.

48. Katz NP, Buse DC, Budman SH, et al. Development and preliminary experience with an ease of extractability rating system for prescription opioids. *Drug Dev Ind Pharm*. 2006;32(6):727-746.

49. Friedmann N, de Kater AW, Butera PG, et al. Remoxy, a novel drug candidate, deters oxycodone abuse in humans [abstract]. Abstract presented at: 3rd International Congress World Institute of Pain; September 21-25, 2004; Barcelona, Spain. http://www.lifetreeresearch.com/media/abstracts/RemoxyAbstract.pdf. Accessed March 9, 2009.

50. de Kater AW, Friedmann N, Butera PG, et al. Clinical pharmacokinetics of oxycodone after single and multiple doses of Remoxy, a novel, abuse-resistant long-acting oxycodone formulation [abstract]. Abstract presented at: 3rd International Congress World Institute of Pain; September 21-25, 2004; Barcelona, Spain.

51. Green CR, Ndao-Brumblay SK, West B, Washington T. Differences in prescription opioid analgesic availability: comparing minority and white pharmacies across Michigan. *J Pain*. 2005;6(10):689-699.