

Current status and evolving role of abuse-deterrent opioids in managing patients with chronic pain

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ARTICLE INFO

Keywords:

opioid
abuse
abuse resistant
abuse deterrent
chronic pain
risk evaluation

Article history:

Received 8 November 2010
Received in revised form 27 January 2011
Accepted 27 February 2011
DOI:10.5055/jom.2011.0066

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ABSTRACT

Opioids are widely used for the treatment of patients with chronic pain; yet, the increase in their abuse, misuse, and diversion is an ongoing focus of regulatory, governmental, and legal scrutiny. As a consequence, clinicians are faced with numerous challenges in an effort to use opioids in appropriate patients with pain while minimizing the potential for opioid abuse, misuse, and diversion. Policies and programs such as state prescription monitoring programs, which have been in existence for decades, are but one attempt to address some of the issues regarding the prescribing of opioids. Another is a risk evaluation and mitigation strategy for opioids under consideration by the US Food and Drug Administration. At the clinical level, a universal precautions and risk management package that includes risk assessment and patient monitoring is a recommended approach. This approach can also include the use of abuse-deterrent and abuse-resistant formulations designed to reduce the non-medical use of opioids. Several of these opioid formulations have been approved or should soon be on the market for use in the United States; however, their role and other questions regarding their use remain unanswered. The authors offer their clinical perspective on several of these key questions.

BACKGROUND

Pain is part of the human condition; relief of pain is an important goal of healthcare professionals. Amidst recent concerns of the undertreatment of pain, there has been much focus on the appropriate diagnosis and more aggressive treatment of pain, particularly chronic pain. Once used primarily for acute pain and cancer pain, the opioids have become an important treatment option for many types of chronic pain,¹⁻⁵ although some controversy remains with respect to efficacy.⁶ With this greater role in pain management, the number of prescriptions for opioids has escalated. From 1998 to 2007, the number of prescriptions through US outpatient retail pharmacies increased from 63.6 to 123.3 million for hydrocodone (94 percent increase), 15.9 to 42.2 million for oxycodone (66 percent increase), and 468,000 to 4.2 million for methadone (797 percent increase).⁷ The number of units (tablets and capsules) dispensed from 1998 to 2007 increased from 2.68

billion to 7.28 billion (172 percent increase) for hydrocodone and from 725 million to 3 billion (314 percent increase) for oxycodone.⁷

Although the increased focus on pain and the greater use of opioids has undoubtedly led to improved management of pain, unwanted consequences have also occurred. Among these is the nonmedical use of pain relievers, especially opioids. In 2008, an estimated 4.7 million persons (1.9 percent) aged 12 years or older in the United States reported using a prescription pain reliever nonmedically at least one time in the previous month.⁸ Of these persons, 70 percent reported obtaining the drug from a family member or friend, and 56 percent for free. Of those obtained for free, 82 percent indicated that their family member or friend had obtained the prescription pain reliever from one physician. Another 4.3 percent obtained a prescription pain reliever from a drug dealer or other stranger, and 0.4 percent bought the drug on the Internet.⁸ Indeed, diversion

of drugs for nonmedical uses occurs in many ways between the point of manufacture and consumption, including theft, the illegal sale of prescriptions by physicians and pharmacists, “doctor shopping,” and prescription forgery or alteration.⁹⁻¹² In 2007, 5 percent of all admissions for treatment of chemical dependency were for opioid abuse (other than heroin), up from 1 percent in 1997.¹³ The number of emergency department (ED) visits related to the nonmedical use of opioids in the United States increased from 172,726 in 2004 to 366,815 in 2008, resulting in an increase in the rate from 59 to 121 per 100,000 population.¹⁴ ED visits due to hydrocodone increased from 39,844 to 89,051 (123 percent increase) and oxycodone from 41,701 to 105,214 (152 percent increase) from 2004 to 2008. Furthermore, the number of unintentional deaths due to an opioid overdose increased to 175 percent from 2001 to 2006, with 3,994 to 11,001 deaths.¹⁵

The economic cost resulting from the nonmedical use of opioids is large as well. The total cost of prescription opioid abuse in the United States was estimated at \$8.6 billion in 2001, including workplace, healthcare, and criminal justice expenditures.¹⁶ Thirty percent of these costs were attributed to healthcare goods and services, of which 95.2 percent was for excess medical costs (the average cost of medical care for a patient with a prescription opioid abuse disorder minus that for a patient without such disorder). On an individual basis, analysis of a Medicaid population (age \geq 12 years; N = 200,648) found that the total cost of care over 12 months (2002-2003) was 2.8 times higher for persons who abused opioids when compared with those who did not (\$23,556 vs \$8,436, respectively).¹⁷ Another retrospective analysis of an insurance database from 1998 to 2002 found that the mean annual direct healthcare costs for opioid abusers were more than eight times higher than for nonabusers (\$15,884 vs \$1,830).¹⁸ Both inpatient and outpatient medical and behavioral health costs have been found to be higher for substance abusers than for nonabusers.¹⁹ In addition, medical costs increased with age at a faster rate in persons with a substance abuse disorder. Finally, the costs of care for opioid-dependent persons treated with methadone maintenance have been reported to be half the costs for persons with two or more outpatient addiction treatment visits without methadone maintenance over at least a 9-month period from 2000 to 2004 (\$7,163 vs \$14,157, respectively).²⁰

These data demonstrate that despite regulatory, policy, and educational efforts, the nonmedical use of opioids continues to rise dramatically in the United States, resulting in a large societal burden.

CHALLENGES POSED BY NONMEDICAL USE OF OPIOIDS

The growing nonmedical use of prescription opioids and other drugs has and continues to present a major challenge to healthcare professionals, regulatory agencies, law enforcement, manufacturers, policy makers, and, indeed, society as a whole. The enormity of the challenge may be best demonstrated by the annual back-to-school survey of teens and their parents conducted in 2009 by The National Center on Addiction and Substance Abuse at Columbia University. In recent years, the survey showed that more than half of the parents believe that the goal of making schools drug free is unrealistic.²¹ This viewpoint is troubling, especially in light of the laws, policies, education, and other initiatives by all levels of government as well as public and private organizations working on these issues at an annual cost of billions of dollars in the United States.²²

This situation raises the question: “What are the barriers in solving the problem of nonmedical use of opioids?” The answer depends on with whom you talk.

Individuals

The increase in the nonmedical use of opioids is part of a growing culture of alcohol, tobacco, and other substance abuse.⁸ Social, economic, genetic, and other factors such as the ready availability of prescription drugs in schools and at home likely contribute to this epidemic.^{21,23} Parental and peer use, as well as parental acceptance of drugs in schools, are significant factors as well.^{8,21} Identifying patients who are at increased risk of nonmedical use of opioids remains a clinical challenge because of the many contributory factors and drug-related behaviors.^{24,25}

Clinicians

Clinicians face many challenges when treating patients with a pain disorder with opioids. One study that involved interviews and focus groups with primary care, addiction specialist, pain specialist, and rheumatologist physicians showed that many were reluctant to prescribe opioids to persons with a history of substance abuse who experienced chronic noncancer pain.

Physicians' fears included addiction, misuse, or diversion of medications by patients.²⁶ A survey of 248 primary care physicians also found that the main barrier to prescribing opioids was physicians' concern that patients would abuse their prescriptions.²⁷ Similarly, another study involving inpatients with recent active drug use found that physicians feared being deceived by drug-using patients.²⁸ In caring for these inpatients, physicians were also observed to lack a standard approach, especially the assessment and treatment of pain with opioids and opioid withdrawal. A general lack of knowledge and uncertainty about prescribing opioids was also a common finding of the survey of 248 primary care physicians.²⁷ In fact, the ambiguity in all diagnostic and therapeutic decisions perceived by providers treating patients with pain and comorbid addiction caused the majority of providers in another study to adopt one of two decision-making approaches.²⁹ The first approach emphasized the destructive consequences of abusing illicit drugs or prescription medications such that the prescriber perceived that management of chronic pain with opioids would increase illicit drug use. The prescriber's response to drug diversion by the patient was to terminate the relationship with the patient, while expecting some type of disciplinary consequence from the medical board. The second approach emphasized the destructive consequences of untreated pain whereby the prescriber perceived that chronic opioid therapy would decrease illicit drug use. The prescriber's relationship with the patient would be maintained despite drug diversion by the patient, and with little concern for disciplinary consequences from the medical board. In general, because of the ambiguity of the disorder of coexisting addiction and pain, primary care clinicians feel unprepared to diagnose and treat coexisting substance abuse and chronic noncancer pain.³⁰⁻³²

Factors that make diagnosing substance abuse more difficult include the variety of terms used within the context of the nonmedical use of opioids, such as abuse, misuse, diversion, and addiction, as well as the lack of consensus regarding the definition of these terms. For the purpose of this review, we have chosen to adapt definitions from commonly cited sources (Table 1).³³⁻³⁶

Developers, manufacturers, and regulatory agencies

Developers and manufacturers of opioids face several challenges in overcoming the nonmedical use of opioids. The first is to eliminate the diversion

of opioids during their manufacture and distribution. The second is to identify and manufacture analgesics that are effective for severe pain but that have minimal abuse or addiction potential.

Two additional challenges are shared with regulatory agencies. The first is to develop analgesics that retain their full analgesic properties but are less likely to be abused by both the medical and nonmedical users. Product development must be focused on the medical user; however, the implicit goal is that the drug may be less abused by nonmedical users. This must be accomplished without any additional risk or adverse effect to the patient even if the adverse effect is trivial, benign, and the deterrence to nonmedical users is potentially significant. The second challenge shared by manufacturers and regulatory agencies is to develop risk evaluation and mitigation strategies (REMS) based on sound scientific principles whose impact can be objectively measured.^{37,38} The general objective of REMS is to ensure that a drug's benefits outweigh its risks in clinical practice. The implementation of REMS by manufacturers can be required by the Food and Drug Administration (FDA) at any time. REMS components include medication guides, patient package inserts, a communication plan for healthcare providers, and elements to ensure safe use including requirements for those who prescribe, dispense, or use the drug.³⁹ Although REMS have increasingly been required by the US FDA since the mid-1990s, they are only in early stages of development. Consequently, there is a lack of data that assesses the value of REMS programs in reducing the abuse and misuse of prescription drugs.

Given the numerous challenges faced by these and other stakeholders, a wide variety of approaches are under investigation or development to reduce the nonmedical use of prescription opioids.

POTENTIAL SOLUTIONS

The numerous challenges faced by stakeholders require a wide variety of approaches to reduce the nonmedical use of opioids. President Obama's 2010 National Drug Control Strategy outlines a comprehensive 5-year plan to reduce drug abuse and its consequences and promotes collaboration among governmental, regulatory, law enforcement, healthcare, and other agencies and organizations.²² Specific objectives of these proposed programs that are of particular relevance to clinicians are as follows: increase screening for substance abuse; expand prescription drug

Table 1. Definitions

Term	Definition
Aberrant behavior ^{33,34}	Behaviors ranging from mildly problematic, such as hoarding medications to be able to use extra doses during times of more severe pain, to felonious acts such as selling medications. In its simplest use, any medication-related behaviors that depart from strict adherence to the prescribed plan of care.
Abuse ^{33,34}	Any use of an illegal drug or the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, eg, getting high.
Abuse-deterrent formulation ³⁵	Drug product to which one or more pharmacologically active ingredients have been added to reduce the reward when the dosage form is physically or chemically manipulated in search of the high sought by recreational and other nonmedical users.
Abuse-resistant formulation ³⁵	Drug product to which a physical barrier has been introduced to minimize the chance that an abusable portion of active pharmaceutical ingredient can be extracted through physical or chemical manipulation.
Addiction ³³	Addiction is a primary, chronic, neurobiological 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.
Diversion ^{34,36}	Intentional removal of a medication from legitimate distribution and dispensing channels. Diversion also involves the sharing or purchasing of drugs between family and friends or individual theft from family and friends.
Misuse ^{33,34}	Use of a medication (with therapeutic intent) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.
Physical dependence ^{33,34}	State of adaptation that is 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.

monitoring programs to improve communication among states and to provide links to electronic health records; and achieve consensus standards on opioid analgesic prescribing in collaboration with physicians. Similar objectives have been described in the National Prescription Drug Abuse Prevention Strategy developed in 2009 by the Center for Lawful Access and Abuse Deterrence (CLAAD) and Human Resources Development Institute, Inc. (HRDI).⁴⁰ One of the core strategies supported by CLAAD/HRDI is the development of opioid formulations designed to reduce their nonmedical use and that are to be used as part of universal precautions in prescribing (see later). Before focusing on these formulations, this article will highlight some other strategies intended to reduce the non-medical use of opioids.

Prescription monitoring programs

Prescription monitoring programs (PMPs) have been in existence for decades as a diversion control

instrument for schedule II medications. Originally developed using multiple copy prescription programs (MCP), PMP in many states now use electronic data transfer (EDT) of prescription information for schedule II, III, and IV medications; many states also monitor schedule V medications. The electronic nature of EDT programs is intended to provide “real-time” patient-specific prescription drug information to help identify and deter or prevent drug abuse and diversion. However, the use of PMP raises concerns regarding privacy and stigmatization. Generally administered by state health agencies instead of state law enforcement agencies as with MCP, EDT programs have several additional objectives, including not interfering with medication availability and effective patient care.⁴⁰⁻⁴² Along these same lines, the inclusion of schedule III and IV medications in current PMP is intended to curb the underprescribing of schedule II opioids by physicians who previously avoided prescribing schedule II opioids so as to steer clear of regulatory scrutiny.⁴³

As of April 2010, legislation authorizing a PMP has been enacted in 41 US states, of which 33 were operational.⁴⁴ One limitation of state-run PMP is that they do not enable the identification of persons who may doctor shop or obtain opioids in more than one state. This may be especially problematic in border towns. Consequently, some states have begun to share information. Another limitation is that the state-run PMPs do not enable the identification of persons receiving an opioid from a Veterans Affairs hospital or through a methadone maintenance treatment program. This will require greater cooperation between agencies.

Recent evidence suggests that improvements in PMP are effective in reducing the nonmedical use of opioids and in improving public health and patient care.⁴⁵⁻⁴⁸ However, the use of state-run PMP data by physicians during the treatment selection process is limited because many PMPs do not provide data in “real time” or are not accessible to physicians.⁴⁵

Universal precautions and the risk management package

The potential for opioid abuse, misuse, and diversion by each patient should be managed by employing a risk management program. As there is a degree of risk with every patient, a universal precautions approach is recommended. The strategy of universal precautions has been advocated to help prescribers implement and modify opioid therapy in a safe and controlled manner based on relevant information rather than “gut feeling.”⁴⁹ The universal precaution strategy parallels the manner in which physicians often manage patients with chronic pain and involves procedures and tools covering the spectrum of risk assessment, opioid selection, monitoring, and actions to be taken if abuse and/or addiction is detected or treatment failure is observed.⁵⁰ These tools and the overall approach can be more or less structured depending on the level of abuse risk. A more structured approach might involve more frequent visits, fewer doses of opioid per prescription, the use of abuse-deterrent opioids, urine screening, and pill counts.⁵⁰ The universal precautions approach was found to be clinically useful in assessing and monitoring prescription opioid abuse and misuse in a prospective, open-label trial involving 268 primary care physicians and 1,542 patients treated with extended-release morphine over 4 months.⁵¹ However, it

should be realized that the use of a universal precautions approach or any of the procedures and tools such as screening tools or opioid agreements may reduce but does not prevent abuse.

Risk assessment. A wide variety of tools have been developed to enable a prescriber to determine a patient’s level of risk for substance and/or opioid abuse prior to prescribing. With the level of risk for abuse identified, an appropriate treatment plan can be developed and implemented. Examples of screening tools are the Prescription Drug Use Questionnaire, the Screening Instrument for Substance Abuse Potential, the Screener and Opioid Assessment for Patients with Pain, Opioid Risk Tool, and Pain Medication Questionnaire. During opioid therapy, the Current Opioid Misuse Measure,⁵² which is a brief self-report measure of current aberrant drug-related behavior, can be used.

Recently, the Prescription Opioid Documentation and Surveillance (PODS) System was developed to address several clinical and documentation needs for use in patients undergoing chronic opioid therapy.⁵³ In addition to identifying patients at risk for opioid addiction or abuse, the PODS System also identifies patients with other affective comorbidities related to chronic pain. Although each of these instruments is helpful for the stated purpose of identifying the level of risk for opioid abuse or actual adherence/misuse, none completely satisfies the three key requirements of simplicity, validity, and reliability.²⁵

Monitoring. An integral part of monitoring opioid therapy is ongoing assessment of the four “As” of pain treatment—analgesia, activities of daily living, adverse events, and aberrant drug-taking behaviors. The Pain Assessment and Documentation Tool (PADT) can be useful in assessing these four domains.⁵⁴ During opioid treatment, urine toxicology and pill counts can be conducted to assess treatment adherence. Although urine toxicology screening is a valid and reliable screening approach, it is important to verify which test is used by the chosen laboratory and that the substances in question can be identified. In addition, careful interpretation of the urine toxicology results must be done. Another factor to be considered in the clinical setting is the cost of urine toxicology screening as it relates to the patient’s insurance and willingness to pay.

The reviewing of the patient’s opioid supply at each visit will assist the prescriber in monitoring and

educating patients on the use of opioids. Moreover, performing pill or patch counts mid-prescription may identify binge taking, sharing, or diversion and provide an opportunity for the prescriber to readjust the prescribing of opioids.⁵⁵ When available, accessing data through PMPs can also provide valuable information about opioid adherence, as well as the use of other prescribed medications.

Formulations designed to reduce the non-medical use of opioids. An emerging component of an opioid risk management program involves efforts to reduce their abuse by persons seeking a rapid euphoric effect. This abuse is achieved by physical or chemical manipulation of the opioid formulation so as to both shorten the time to maximum drug concentration and to increase the maximum concentration of the opioid. To reduce their potential for abuse, several opioids have or are being reformulated so that an abuser would not be able (abuse resistant) or want (abuse deterrent) to manipulate the opioid to provide the rapid euphoric effect. Abuse-resistant and abuse-deterrent opioids that are in late-stage clinical development are listed in Table 2. The misuse of opioids by persons who overconsume their prescribed opioid for various reasons remains less of a focus.

Abuse-resistant formulations incorporate physical barriers intended to reduce the chance that the opioid can be altered by physical (chewing, crushing, grinding) or chemical (extracting) manipulation, thereby preventing shortening of the time to maximum drug concentration and increase of the maximum drug concentration. Another type of abuse-resistant opioid is a prodrug that is pharmacologically inactive until converted to an active form intracellularly or extracellularly. Extracellular conversion commonly occurs in the digestive fluids, in the systemic circulation, or both. Prodrugs that require conversion, usually via hepatic metabolism, to be active (unlike codeine, for example, which is active prior to conversion to morphine) cannot produce euphoria when taken into the body through unintended routes, eg, snorting, smoking, or injecting.

Abuse-deterrent formulations contain an opioid antagonist that is released when the dosage form is physically manipulated, thereby reducing the rapid euphoric effect of the opioid. In addition, physical dependence is significantly lessened with some abuse-deterrent formulations, while analgesia comparable with the opioid alone is maintained.^{56,57} The addition of naloxone to pentazocine (Talwin NX)

and buprenorphine (Suboxone) are examples currently available. Other abuse-deterrent formulations in development contain an added ingredient intended to break the stimulus-reward cycle by causing unpleasant effects when the opioid is taken in excess or physically manipulated. In addition to reducing abuse, these latter formulations may also be useful to curb misuse by persons who overconsume a prescribed opioid.

The effectiveness of some of these new opioid formulations in reducing abuse has been investigated in clinical trials. Several trials have shown a reduction in abuse potential or patient preference,⁵⁷⁻⁶⁰ whereas another trial has not.⁶¹ A summary of the published clinical trials is given.

The efficacy of morphine with naltrexone extended-release capsules (Embeda) has been demonstrated in patients (N = 113) with osteoarthritis pain.⁶² A 14-day, crossover, open-label comparison with extended-release morphine demonstrated the two products to provide similar reductions in pain intensity and comparable safety. Another study compared the drug-liking (a standard method of evaluating the abuse potential of psychoactive drugs) and euphoria effects of whole and crushed morphine sulfate with naltrexone extended-release capsules with morphine sulfate oral solution and placebo in a randomized, double-blind, crossover study in experienced, nondependent opioid users.⁵⁹ The maximum euphoric effect was lower and flatter with both whole and crushed morphine with naltrexone when compared with morphine sulfate oral solution.

In a phase III double-blind clinical trial, 719 patients with chronic low back pain ($\geq 5/10$) were randomly assigned to receive oxycodone four times daily, oxycodone with naltrexone (Oxytrex) two or four times daily, or placebo.⁵⁷ Doses were escalated weekly from 10 mg/d to 80 mg/d until adequate pain relief was achieved ($\leq 2/10$) or tolerable side effects occurred. Following 12 weeks of stable therapy, comparable analgesia (pain intensity $\leq 2/10$) was observed by patients receiving active treatment. The mean daily drug dose was 34.7 and 34.5 mg in the oxycodone with naltrexone two and four times daily groups, respectively, when compared with 39.0 mg for the oxycodone group ($p = 0.03$ for both comparisons). In addition, symptoms of physical dependence were significantly lower (55.8 percent) on the first day after drug discontinuation for the oxycodone with naltrexone twice daily group when compared with the oxycodone group ($p = 0.009$). Although symptoms of

Table 2. Abuse-deterrent and abuse-resistant opioids

Compound (Company)	Trade name	Mechanism
Controlled-release oxycodone (King Pharmaceuticals)	Remoxy™	Physical barrier, crush and extraction resistant.
OxyContin® tamper-resistant (Purdue Pharma)	OxyContin®	Physical barrier, crush and extraction resistant.
Sustained-release oxycodone (Intellipharma)	Rexista™	Physical barrier, crush and extraction resistant.
Sustained-release oxycodone (Collegium Pharmaceutical)	DETERx™ (COL-003)	Physical barrier using microparticles.
Controlled-release hydromorphone (Covidien Pharmaceuticals)	Exalgo®	Physical barrier, crush and extraction resistant.
Extended-release tramadol (PriCara)	Ultram® ER	Physical barrier, crush and extraction resistant.
Extended-release morphine and naltrexone (King Pharmaceuticals)	Embeda™	Agonist/antagonist combination.
Sustained-release oxycodone and naltrexone (Elite Pharmaceuticals)	OxyNal™ (ELI-216)	Agonist/antagonist combination.
Oxycodone and ultra-low-dose naltrexone (Pain Therapeutics)	Oxytrex™	Agonist/antagonist combination.
Immediate-release oxycodone and niacin (King Pharmaceuticals)	Acurox™	Unpleasant systemic (oral, IV) and local (snort) effects, extraction resistant.
Lysine-modified opioid prodrug (New River Pharmaceuticals)	NRP290	Prodrug

physical dependence for oxycodone were significantly greater than placebo for the first 3 days after discontinuation ($p < 0.001$ on days 1 and 2, $p = 0.02$ on day 3), symptoms were significantly greater for oxycodone with naltrexone than placebo only on day 2 ($p = 0.01$). A separate double-blind, placebo-controlled, crossover study that evaluated the addition of ultra-low-dose naloxone (0.0001 to 0.001 mg) to oxycodone (20 or 40 mg) found no significant differences in abuse liability when compared with oxycodone alone.⁶¹ The patients ($N = 14$) were experienced opioid abusers.

A controlled-release high-viscosity liquid matrix oxycodone (Remoxy) that resists breaking, crushing, chewing, and extraction was evaluated using the Opioid Attractiveness Technology Scaling (OATS) method, which evaluates the attractiveness of a drug for recreational use.⁶⁰ Remoxy was evaluated as having less attractive features for recreational use when compared with extended-release oxycodone (OxyContin), oxycodone with acetaminophen

(Percocet), and hydrocodone with acetaminophen (Vicodin), but similar to pentazocine with naloxone (Talwin NX).

Risk evaluation and mitigation strategy

As none of these formulations is intended to address all types of abuse or misuse, opioid reformulation is but one part of an overall REMS. At present, the US FDA is working with other stakeholders to develop a REMS for the opioid class of drugs. During a joint meeting of the US FDA's Anesthetic and Life Support Drugs and Drug Safety and Risk Management advisory committees (July 22-23, 2010), committee members voted 25-10 against a proposed REMS for extended-release and long-acting opioid analgesics after deeming the proposed plan insufficient to stop abuse of the painkillers. As of August 2010, a REMS has been approved for the following opioids: Darvon/Darvon-N/Darvocet-N,

Embeda, Exalgo, morphine oral solution, Onsolis, and OxyContin.⁶³

REMAINING QUESTIONS AND FUTURE ISSUES

As the development of formulations designed to reduce the nonmedical use of opioids is in its early stages, numerous questions exist and require investigation. Several questions are centered on the role of abuse-deterrent and abuse-resistant opioid formulations in clinical practice. Should the abuse-deterrent and abuse-resistant opioid formulations currently available be preferred over standard opioids for their respective indications? The short answer is no, not at present. There are only a handful of opioid formulations currently available designed to reduce nonmedical use. Limiting clinicians to prescribing these few opioid formulations would not provide the needed flexibility to provide the best care possible to patients with pain disorders. Further evidence is needed that these formulations are as effective as standard opioids in relieving pain. We also need evidence that these formulations are safe and do not result in unacceptable safety issues. Currently, the US FDA does not appear to be willing to support new formulations that may be a deterrent to nonmedical use, but could burden even a small subset of patients with pain with trivial, benign side effects. In our view, it would seem that if societal harm from opioid abuse threatens access to pain therapy, as has been shown, minimal side effects and increased cost from abuse-deterrent and abuse-resistant formulations would be a rational trade off.

There are additional issues to consider before determining that abuse-deterrent and abuse-resistant formulations should be preferred over standard opioids. Although available evidence indicates that abuse-deterrent and abuse-resistant formulations reduce nonmedical use, more evidence is needed,⁶⁴ ideally including data outside of clinical trials. These data should demonstrate a reduction in nonmedical use via multiple routes, such as snorting, smoking, and injecting. Prior to the filing of a new drug application, the endpoints in clinical trials must be the amount of drug diverted and the effect on liking, using tools such as the OATS method.^{60,65} After a drug is approved, the endpoints must be part of long-term epidemiological studies assessing the change in amount and type of drugs abused.

Cost is another important consideration,³⁴ not only the acquisition cost of abuse-deterrent and

abuse-resistant opioid formulations, but more importantly, the impact on the cost of healthcare. For example, Insurance copayments and benefit coverage are increasingly larger barriers to patients being able to afford medications. Another cost consideration is the impact on societal costs such as law enforcement and judiciary. The estimated cost of diversion and abuse of opioids has been estimated to be as high as \$72.5 billion a year (2007 dollars) to public and private medical insurers in the United States. This estimate includes excess drug, hospital, physician, outpatient, and other costs of care for a person who abuses an opioid when compared with a nonabuser.⁶⁶

Another issue to be addressed is how to curb all of the methods of nonmedical use of opioids. The abuse-deterrent and abuse-resistant opioid formulations currently available or in development are generally not designed to curb the overconsumption that occurs in a large percentage of pain patients, many seeking additional pain relief. However, as noted by Budman et al., "there is no mechanism that is going to prevent abusers from taking the drug as it was meant to be taken in excess, and thereby still abusing the drug."⁶⁷ Additional deterrent approaches are needed that deliver safe and effective analgesia without rewarding effects. Simply taking a higher dose of any deterrent can be a safety concern and produce rewarding effects. Open communication between the prescriber and the patient are important in ensuring safe use of opioids, with close monitoring and early intervention when problematic use is detected.

A third major issue to be addressed is healthcare professional education. The US FDA recently underscored the importance of healthcare professional education as an important component of REMS.³⁹ Assessment of pain, risk assessment, providing a balanced approach to pain management strategies, and monitoring of opioid therapy should be core education competencies. Prescribers need to understand who is at greater risk of misuse and abuse and who can be treated and who should be referred. Similarly, better screening and monitoring tools are needed.

SUMMARY

Opioids play an important role in the management of patients with a pain disorder; however, they are subject to growing abuse and misuse. As a consequence, increased actions by numerous stakeholders are being taken to curb their abuse and misuse while striving to insure their availability and use in appropriate patients

with a pain disorder. To balance these concerns in the clinical setting, a risk management package that centers on a universal precautions approach is recommended. The risk management package involves procedures and tools covering the spectrum of risk assessment, opioid selection, monitoring, and actions to be taken if abuse and/or addiction is detected or treatment failure is observed. Although many of the screening tools currently available are helpful to assess the risk of opioid abuse and misuse, each has its limitations. Monitoring treatment adherence is a critical component of the risk management package and can include ongoing assessment of the four As (analgesia, activities of daily living, adverse events, and aberrant drug-taking behaviors), urine toxicology screening, pill/patch counts, and accessing data through PMPs. An emerging risk management strategy is the use of opioid formulations that incorporate physical and/or pharmacological barriers to manipulation. Several abuse-resistant or abuse-deterrent opioids are now available, with many more in development. These formulations have the potential to play an important role in the risk management package to deter and prevent abuse of opioids. Their specific role requires further assessment of their clinical, judicial, regulatory, economic, and quality of life impact.

ACKNOWLEDGMENTS

Funding for writing, editorial, and administrative support was provided by the Center for Lawful Access and Abuse Deterrence (CLAAD), Arlington, VA. Editorial and administrative support for this article was provided by KOL, LLC, Woodbridge, CT. Writing support was provided in part by Gregory Scott, PharmD, WriteHealth, LLC, Kennebunk, ME.

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REFERENCES

1. Dworkin RH, O'Connor AB, Backonja M, et al.: Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain*. 2007; 132(3): 237-251.
2. Pergolizzi J, Boger RH, Budd K, et al.: Opioids and the management of chronic severe pain in the elderly: Consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008; 8(4): 287-313.
3. Moulin DE, Clark AJ, Gilron I, et al.: Pharmacological management of chronic neuropathic pain—Consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag*. 2007; 12(1): 13-21.
4. Attal N, Cruccu G, Haanpaa M, et al.: EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*. 2006; 13(11): 1153-1169.
5. Tan T, Barry P, Reken S, et al.: Pharmacological management of neuropathic pain in non-specialist settings: Summary of NICE guidance. *BMJ*. 2010; 340: c1079.
6. Chou R, Fanciullo GJ, Fine PG, et al.: Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009; 10(2): 113-130.
7. Belouin SJ, Reuter N, Borders-Hemphill V, et al.: Substance Abuse and Mental Health Services Administration. Prescribing trends for opioids, benzodiazepines, amphetamines, and barbiturates from 1998-2007; 2008. Available at https://nac.samhsa.gov/DTAB/Presentations/Aug08/SeanBelouinDTAB0808_508.pdf. Accessed June 21, 2010.
8. Anonymous: Substance Abuse and Mental Health Services Administration. Results from the 2008 National Survey on Drug Use and Health: National findings; 2009. Available at <http://www.oas.samhsa.gov/nsdub/2k8nsdub/2k8RResults.pdf>. Accessed May 24, 2010.
9. Inciardi JA, Surratt HL, Cicero TJ, et al.: The "black box" of prescription drug diversion. *J Addict Dis*. 2009; 28(4): 332-347.
10. Inciardi JA, Surratt HL, Cicero TJ, et al.: Prescription opioid abuse and diversion in an urban community: The results of an ultrarapid assessment. *Pain Med*. 2009; 10(3): 537-548.
11. Joranson DE, Gilson AM: Drug crime is a source of abused pain medications in the United States. *J Pain Symptom Manage*. 2005; 30(4): 299-301.
12. Inciardi JA, Surratt HL, Cicero TJ, et al.: Prescription drugs purchased through the internet: Who are the end users? *Drug Alcohol Depend*. 2010; 110(1-2): 21-29.
13. Treatment episode data set (TEDS) highlights - 2007. National admissions to substance abuse treatment services; 2009. Substance Abuse and Mental Health Services Administration. Available at <http://www.dasis.samhsa.gov/teds07/teds07high2k7.pdf>. Accessed May 19, 2010.
14. Anonymous: Drug Abuse Warning Network. National estimates of drug-related emergency department visits, 2004-2008; 2010. Available at <https://dawninfo.samhsa.gov/data/default.asp?met=All>. Accessed May 21, 2010.
15. Anonymous: National Drug Intelligence Center, US Department of Justice. National Drug Threat Assessment 2010: Controlled prescription drugs; 2010. Available at <http://www.justice.gov/ndic/pubs38/38661/rx.htm#Top>. Accessed July 12, 2010.

16. 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.
17. McAdam-Marx C, Roland CL, Cleveland J, et al.: Costs of opioid abuse and misuse determined from a Medicaid database. *J Pain Palliat Care Pharmacother*. 2010; 24(1): 5-18.
18. 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.
19. Clark RE, Samnaliev M, McGovern MP: Impact of substance disorders on medical expenditures for Medicaid beneficiaries with behavioral health disorders. *Psychiatr Serv*. 2009; 60(1): 35-42.
20. McCarty D, Perrin NA, Green CA, et al.: Methadone maintenance and the cost and utilization of health care among individuals dependent on opioids in a commercial health plan. *Drug Alcohol Depend*. 2010; 111(3): 235-240.
21. Anonymous: The National Center on Addiction and Substance Abuse at Columbia University. National survey of American attitudes on substance abuse XIV: Teens and parents; 2009. Available at <http://www.casacolumbia.org/article-files/380-2009%20Teen%20Survey%20Report.pdf>. Accessed May 24, 2010.
22. National drug control strategy. President of the United States; 2010. Available at <http://www.whitehousedrugpolicy.gov/publications/policy/ndcs10/ndcs2010.pdf>. Accessed May 24, 2010.
23. Anonymous: The National Center on Addiction and Substance Abuse at Columbia University. Under the counter: The diversion and abuse of controlled prescription drugs in the U.S.; 2005. Available at http://www.casacolumbia.org/templates/Publications_Reports.aspx#r19. Accessed May 24, 2010.
24. Passik SD, Kirsh KL, Donaghy KB, et al.: 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.
25. Turk DC, Swanson KS, Gatchel RJ: Predicting opioid misuse by chronic pain patients: A systematic review and literature synthesis. *Clin J Pain*. 2008; 24(6): 497-508.
26. Baldacchino A, Gilchrist G, Fleming R, et al.: Guilty until proven innocent: A qualitative study of the management of chronic non-cancer pain among patients with a history of substance abuse. *Addict Behav*. 2010; 35(3): 270-272.
27. Bhamb B, Brown D, Hariharan J, et al.: Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. *Curr Med Res Opin*. 2006; 22(9): 1859-1865.
28. Merrill JO, Rhodes LA, Deyo RA, et al.: Mutual mistrust in the medical care of drug users: The keys to the "narc" cabinet. *J Gen Intern Med*. 2002; 17(5): 327-333.
29. Berg KM, Arnsten JH, Sacajiu G, et al.: Providers' experiences treating chronic pain among opioid-dependent drug users. *J Gen Intern Med*. 2009; 24(4): 482-488.
30. Gunderson EW, Coffin PO, Chang N, et al.: The interface between substance abuse and chronic pain management in primary care: A curriculum for medical residents. *Subst Abuse*. 2009; 30(3): 253-260.
31. Gunderson EW, Levin FR, Smith L: Screening and intervention for alcohol and illicit drug abuse: A survey of internal medicine housestaff. *J Addict Dis*. 2005; 24(2): 1-18.
32. Wilsey BL, Fishman SM, Crandall M, et al.: A qualitative study of the barriers to chronic pain management in the ED. *Am J Emerg Med*. 2008; 26(3): 255-263.
33. Savage S, Covington EC, Heit HA, et al.: American Pain Society. Definitions related to the use of opioids for the treatment of pain. A consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine; 2001. Available at <http://www.ampainsoc.org/advocacy/opioids2.htm>. Accessed May 24, 2010.
34. Katz NP, Adams EH, Chilcoat H, et al.: Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain*. 2007; 23(8): 648-660.
35. Webster LR, Bath B, Medve RA: Opioid formulations in development designed to curtail abuse: Who is the target? *Expert Opin Investig Drugs*. 2009; 18(3): 255-263.
36. National Prescription Drug Threat Assessment 2009. National Drug Intelligence Center, Drug Enforcement Administration; 2010. Available at <http://www.justice.gov/ndic/pubs33/33775/diversion.htm#Top>. Accessed July 2, 2010.
37. McCormick CG, Henningfield JE, Haddox JD, et al.: Case histories in pharmaceutical risk management. *Drug Alcohol Depend*. 2009; 105 (Suppl 1): S42-S55.
38. Henningfield JE, Schuster CR: Risk management and post-marketing surveillance of CNS drugs. *Drug Alcohol Depend*. 2009; 105 (Suppl 1): S56-S64.
39. Guidance for industry. Format and content of proposed risk evaluation and mitigation strategies (REMS), REMS assessments, and proposed REMS modifications; 2009. US Food and Drug Administration. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>. Accessed June 15, 2010.
40. Barthwell AG, Barnes MC, Leopold VR, et al.: Center for Lawful Access and Abuse Deterrence. National prescription drug abuse prevention strategy; 2009. Available at http://claad.org/downloads/Nat_Prescript_Drug_Abuse_Prev_Strat_2009.pdf. Accessed May 21, 2010.
41. Anonymous: National Alliance for Model State Drug Laws. Prescription drug monitoring programs: A brief overview; 2009. Available at <http://www.namsdl.org/documents/PDMPsBriefOverviewApril2009.pdf>. Accessed May 21, 2010.
42. Gilson AM, Kreis PG: The burden of the nonmedical use of prescription opioid analgesics. *Pain Med*. 2009; 10 (Suppl 2): S89-S100.
43. Wang J, Christo PJ: The influence of prescription monitoring programs on chronic pain management. *Pain Physician*. 2009; 12(3): 507-515.
44. Anonymous: National Alliance for Model State Drug Laws. Status of state prescription drug monitoring programs; 2010. Available at <http://www.namsdl.org/documents/StatusofStatesApril222010.pdf>. Accessed May 26, 2010.
45. Katz N, Houle B, Fernandez KC, et al.: Update on prescription monitoring in clinical practice: A survey study of prescription monitoring program administrators. *Pain Med*. 2008; 9(5): 587-594.
46. Baehren DF, Marco CA, Droz DE, et al.: A statewide prescription monitoring program affects emergency department prescribing behaviors. *Ann Emerg Med*. 2009; 56(1): 19-23.
47. Pradel V, Frauger E, Thirion X, et al.: Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. *Pharmacoepidemiol Drug Saf*. 2009; 18(1): 36-43.

48. Simeone R, Holland L: An evaluation of prescription drug monitoring programs; 2006. Simeone Associates, Inc. Available at <http://www.simeoneassociates.com/simeone3.pdf>. Accessed May 27, 2010.
49. Webster LR, Fine PG: Approaches to improve pain relief while minimizing opioid abuse liability. *J Pain*. 2010; 11(7): 602-611.
50. Passik SD: Reducing risk: Practical strategies for prescribing analgesics. Paper presented at the American Conference on Pain Medicine, New York, NY, April 5, 2008.
51. Lee KW, Brown JW, Strehlow MD, et al.: ACCESS 2008: Assessing risk of opioid abuse in primary care. Paper presented at the American Academy of Pain Medicine, San Antonio, TX, February 3-6, 2010.
52. Butler SF, Budman SH, Fernandez KC, et al.: Development and validation of the Current Opioid Misuse Measure. *Pain*. 2007; 130(1-2): 144-156.
53. Wilsey BL, Fishman SM, Casamaluapa C, et al.: Documenting and improving opioid treatment: The Prescription Opioid Documentation and Surveillance (PODS) System. *Pain Med*. 2009; 10(5): 866-877.
54. 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.
55. St. Marie B: Coexisting addiction and pain. In St. Marie B (ed.): *Core Curriculum for Pain Management Nursing*. 2nd ed. Dubuque, IA: Kendall Hunt, 2010: 626-627.
56. Wang HY, Friedman E, Olmstead MC, et al.: Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling. *Neuroscience*. 2005; 135(1): 247-261.
57. Webster LR, Butera PG, Moran LV, et al.: Oxytrex minimizes physical dependence while providing effective analgesia: A randomized controlled trial in low back pain. *J Pain*. 2006; 7(12): 937-946.
58. Coleman JJ, Bensinger PB, Gold MS, et al.: Can drug design inhibit abuse? *J Psychoactive Drugs*. 2005; 37(4): 343-362.
59. Stauffer J, Setnik B, Sokolowska M, et al.: Subjective effects and safety of whole and tampered morphine sulfate and naltrexone hydrochloride (ALO-01) extended-release capsules versus morphine solution and placebo in experienced non-dependent opioid users: A randomized, double-blind, placebo-controlled, crossover study. *Clin Drug Investig*. 2009; 29(12): 777-790.
60. Butler SF, Black R, Grimes Serrano JM, et al.: Estimating attractiveness for abuse of a not-yet-marketed "abuse-deterrent" prescription opioid formulation. *Pain Med*. 2010; 11(1): 81-91.
61. Tompkins DA, Lanier RK, Harrison JA, et al.: Human abuse liability assessment of oxycodone combined with ultra-low-dose naltrexone. *Psychopharmacology (Berl)*. 2010; 210(4): 471-480.
62. Katz N, Sun S, Johnson F, et al.: ALO-01 (morphine sulfate and naltrexone hydrochloride) extended-release capsules in the treatment of chronic pain of osteoarthritis of the hip or knee: Pharmacokinetics, efficacy, and safety. *J Pain*. 2010; 11(4): 303-311.
63. Approved risk evaluation and mitigation strategies (REMS); 2010. US Food and Drug Administration. Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>. Accessed May 28, 2010.
64. Katz N: Abuse-deterrent opioid formulations: Are they a pipe dream? *Curr Rheumatol Rep*. 2008; 10(1): 11-18.
65. Butler SF, Benoit CM, Budman SH, et al.: Development and validation of an opioid attractiveness scale: A novel measure of the attractiveness of opioid products to potential abusers. *Harm Reduct J*. 2006; 3(1): 5.
66. Mahon WJ: Coalition Against Insurance Fraud. Prescription for peril. How insurance fraud finances theft and abuse of addictive prescription drugs; 2007. Available at <http://www.insurancefraud.org/downloads/drugDiversion.pdf>. Accessed August 5, 2010.
67. Budman SH, Grimes Serrano JM, Butler SF: Can abuse deterrent formulations make a difference? Expectation and speculation. *Harm Reduct J*. 2009; 6: 8.