

REVIEW ARTICLE

Strategies to Prevent Opioid Misuse, Abuse, and Diversion That May Also Reduce the Associated Costs

Kathryn L. Hahn, PharmD, DAAPM, CPE

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Background: The use of prescription opioid drugs has the potential to lead to patient abuse of these medications, addiction, and diversion. Such an abuse is associated with increased costs because of excessive healthcare utilization. Finding ways to minimize the risk for abuse and addiction can enhance patient outcomes and reduce costs to patients and to payers.

Objective: To review current strategies that may reduce the risk for misuse and abuse of opioid medications, which in turn can enhance patient outcomes and lower costs to health insurers and patients.

Discussion: Implementing approaches that will encourage the use of safe practices (universal precautions) in pain management by providers can reduce the risk for abuse and misuse associated with chronic pain medications, especially opioids. These approaches include, but are not limited to, extensive physician and patient education regarding these medications and their associated risks for abuse; the development of prescription monitoring programs to detect physician or pharmacy shopping; the detection of inappropriate prescribing and medical errors; the use of physician-patient contracts concerning opioid treatment; the requirement of presenting a photo identification to pick up an opioid prescription at the pharmacy; urine drug toxicology screening; provisions for safe disposal of unused opioids; referrals to pain and addiction specialists; and potentially encouraging the use of opioid formulations aimed at reducing abuse.

Conclusion: Supporting such approaches by health insurers and educating providers and patients on the risks associated with chronic pain medications can help minimize the risk of prescription opioid abuse, addiction, and diversion; reduce health services utilization associated with opioid abuse; improve patient outcomes; and reduce overall costs.

It is well known that the use of prescription opioid medications, more than other medications, is associated with risks for misuse, abuse, and diversion.¹⁻³ The government and pharmaceutical companies have addressed this issue by implementing specific strategies to minimize the risks associated with prescription drugs in general and with opioids in particular.

In 2005, the US Food and Drug Administration (FDA) published 3 guidances for the pharmaceutical industry on risk management activities for drug and biologic products.^{4,6} In these publications, the FDA outlines several components of risk management, including “(1) assessing a product’s benefit-risk balance, (2) developing

and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.”⁴

In 2007, the FDA Amendments Act was passed into law, establishing the requirements for Risk Evaluation and Mitigation Strategies (REMS) for drugs with safety concerns. These REMS requirements are accompanied by stipulations for physician and pharmacist training and certification, and patient registries for some medications, including opioids.⁷

Currently, risk management strategies, including REMS, are used by the government and by pharmaceutical companies to minimize the risks associated with prescription opioid use, namely, the potential for abuse, addiction, and diversion. Risk management tools can

Dr Hahn is Affiliate Faculty, Oregon State University College of Pharmacy, and Pharmacy Manager, Bi-Mart Corp, Springfield, OR.

KEY POINTS

- The use of prescription drug opioids is associated with a risk for abuse and addiction.
- Between 1997 and 2006, retail sales of opioids have increased dramatically; sales of hydrocodone increased by 244%, oxycodone by 732%, and methadone by 1177%.
- These trends have coincided with increased rates of abuse and mortality associated with prescription opioid abuse.
- The financial cost is also substantial, resulting from increased healthcare utilization.
- One study reported that healthcare costs for opioid abusers were 8 times higher than for nonabusers, with an average per-person cost of \$15,884 to payer for abusers compared with \$1830 for nonabusers.
- Educating providers and patients on these drugs can minimize opioid abuse; current approaches include prescription monitoring programs, preventing prescription/medical errors, checking patient identification at the pharmacy, referral to pain specialists, and the use of abuse-deterrent opioid formulations.
- These strategies can improve patient outcomes, prevent abuse, and reduce overall healthcare utilization and costs.

also benefit health plans, by minimizing the potential health and economic risks associated with prescription opioid use for members who are using these medications.

In this article, after reviewing the available information on the prevalence of prescription opioid abuse (the most abused of all prescription medications) and the resulting economic costs, the author outlines strategies that have the potential to minimize the risks associated with prescription opioid use and could enhance the patient's health and reduce costs to health plans and patients.

The Scope of the Problem

Abuse of Prescription Opioid Drugs in the United States

The increasing prevalence of prescription opioid abuse and its emergence as a major public health concern have been extensively documented.^{1,3} According to 2007 data from the National Survey on Drug Use and Health, an estimated 5.2 million persons aged ≥12 years (approximately 2.1% of the US population) abused prescription opioids within the past month, and 2.1 million individuals initiated nonmedical use of prescription opioids.¹ A survey of 8th-, 10th-, and 12th-grade students

showed that in 2008, the annual rate of narcotic drug use other than heroin for twelfth-graders was 9%.⁸ When students were asked the source of the drugs, approximately 56% reported obtaining them for free from friends or from relatives, 9% reported buying them from friends or relatives, and 18% reported obtaining them by prescription from a physician.¹

The nonmedical use of prescription opioids is dangerous, because the repeated recreational use of these medications can lead to addiction or death. Most abuse occurs by oral administration—swallowing the tablet or capsule whole, or chewing it and then swallowing.⁹⁻¹¹ Chewing disrupts some of the extended-release opioid formulations and releases large amounts of the drug rapidly, increasing euphoria.¹² Oral abuse, if frequent and at high doses, can lead to medication addiction.¹³

However, a significant subset of abusers progress to other, more sophisticated routes of ingestion, such as snorting (62% of abusers) or intravenous injection (26% of abusers).⁹ Snorting and parenteral delivery increase the rate and amount of delivery of the opioid and result in a greater euphoria than swallowing whole or chewing.¹² Abuse through smoking is common for some drugs (approximately 50% of fentanyl abusers smoke it), but it is relatively uncommon with prescription opioids (only 2.3% of abusers smoke prescription opioids).³ Furthermore, although it has not been conclusively proved, it has been suggested that nonmedical prescription opioid use can be a gateway to abuse of other, equally dangerous drugs, such as heroin and crack cocaine.¹⁴

The frequency of abuse and addiction in patients with chronic pain who are treated long-term with opioids is unclear. A meta-analysis of 24 studies comprising 2507 patients treated with long-term opioid therapy for chronic, nonmalignant pain showed an overall abuse/addiction rate of 3.27%.¹⁵ However, studies that include routine urine toxicology screening as an objective method of testing drug abuse tend to show higher rates—ranging from 16% to 47%—of abuse or misuse among patients with chronic pain.¹⁶⁻¹⁹ Therefore, although many patients with chronic pain can safely benefit from prescription opioid treatment, some of these patients are vulnerable to abuse and addiction.

Healthcare Utilization and Costs: Prescription Opioid Abuse

During the past decade, the treatment of noncancer pain with opioids has expanded.²⁰ Between 1997 and 2006, retail sales of opioids (grams per 100,000 population) have increased²⁰:

- Sales of hydrocodone increased by 244%
- Oxycodone by 732%
- Methadone by 1177%.

These trends have coincided with increased rates of abuse and mortality associated with prescription opioid abuse.^{1,20,21}

The financial impact on payers from prescription opioid abuse is also substantial. White and colleagues demonstrated that compared with nonabusers receiving prescription opioids, prescription opioid abusers had significantly more physician visits, mental health inpatient and outpatient services, hospital admissions, emergency department visits, motor vehicle accidents, cases of trauma, and substance abuse treatment.²² Healthcare costs for opioid abusers were 8 times higher than for nonabusers—average per-person healthcare cost to payer was \$15,884 for abusers compared with \$1830 for nonabusers ($P < .01$).²² Hospital inpatient visits were the largest contributor to increased cost—\$7239 for opioid abusers compared with \$310 for nonabusers ($P < .01$).

Treatment of comorbidities—which have a higher prevalence rate in opioid abusers—is also an important contributor to the higher costs; comorbidities, such as nonopioid poisoning, other substance abuse, hepatitis, pancreatitis, psychiatric illnesses, and chronic cirrhosis or acute liver disease occur 78.0, 43.0, 36.0, 21.0, 8.5, and 7.6 times more often, respectively, in abusers than in opioid users who are not abusers. Prescription costs in this study were also 5 times greater for abusers compared with nonabusers (mean costs, \$2034 vs \$386, respectively; $P < .01$).²²

Birnbaum and colleagues reported similar findings; prescription opioid abuse resulted in approximately \$9500 in annual medical costs per patient in 2001, which was 3 times more than that for matched nonabusers, amounting to a total healthcare cost of \$2.6 billion for prescription opioid abuse that year.²³ However, prescription opioid abuse costs went beyond healthcare costs; they also included \$1.4 billion in criminal justice costs and \$4.6 billion in workplace costs—totaling \$8.6 billion in 2001.²³

Prescription opioid abuse/misuse is also associated with increases in:

1. Visits to the emergency department²
2. Number of fatal opioid-related poisonings²⁴
3. Admissions to addiction treatment centers.³

According to one study, the number of visits to emergency departments because of prescription opioid overdose increased approximately 43% between 2004 and 2006—from an estimated 172,726 to 247,669 visits.² In addition, a 143% increase in mortality rates from prescription opioids occurred between 1999 and 2004—from 1.22 to 2.96 deaths per 100,000.²⁴ Starting in 2004, prescription opioids have been more often shown to be involved in fatal overdoses than overdoses resulting from cocaine or heroin.²⁴ The number of admissions to sub-

stance abuse treatment programs for primary prescription opioid abuse increased by 342% from 1996 to 2006 (from 16,605 to 73,439).³

Insurance fraud by prescription drug abusers imposes additional costs on the healthcare system. Drug diversion costs to health insurers are estimated at \$72.5 billion per year (including \$24.9 billion for private insurers).²⁵ The costs include fraudulent claims for prescriptions for spurious pain conditions, costs that accrue if individuals taking the diverted drugs become addicted, and costs as a result of additional comorbidities that occur in drug abusers.

Risk Minimization Approaches to Abuse

Many approaches, which are detailed below, that can be promoted and supported by employers and health plans to control the abuse and diversion of prescription opioids are not new; they are part of a series of measures that have been recommended by various stakeholders to reduce the incidence of prescription opioid abuse in the United States. Some of these policies (detailed below) have already been put in place; others are still in the planning stage.

Very little data exist regarding the effectiveness of these measures, because (1) most of them have not been systematically implemented (they exist only in limited geographical areas, or are only recommended and not mandatory), which strongly limits their impact; (2) some are too recent to demonstrate a trend yet; and (3) some have not been fully evaluated for their effectiveness in reducing abuse. Data on effectiveness, if available, are provided for each approach in the appropriate subsections below. In addition, the multifactorial aspect of prescription drug abuse makes it difficult to find an adequate measure to evaluate the impact of a particular policy on abuse in the real world. Nevertheless, some measures, such as prescription monitoring programs, have been shown to decrease abuse, as discussed below; however, the data are limited.²⁶

Educating Physicians and Patients

A comprehensive approach to risk reduction includes educating physicians on safe opioid prescribing. A system of universal precautions in pain medicine has been proposed and recommended for physicians to minimize the risk for opioid abuse by their patients, while allowing physicians to appropriately treat patients with pain.^{27,28} This approach is based on a comprehensive initial assessment of the patient and regular monitoring of patients who are prescribed opioids. Because safe opioid prescribing not only serves an important public health need but also can have a significant impact on healthcare costs, payers could benefit from promoting universal precau-

tions. Payers could help to enhance this approach by providing physicians enrolled in their insurance plans with educational/training materials or training programs.

It has also been recommended by the Substance Abuse and Mental Health Services Administration that physicians be educated on Screening, Brief Intervention, Referral and Treatment (SBIRT) guidelines for patients with substance abuse disorders and for those at risk for abuse.²⁹ SBIRT measures could be promoted by providing performance initiatives in pain management (eg, SBIRT training sessions) and encouraging referrals to pain and addiction specialists when appropriate.

Establishing opioid treatment contracts has been suggested.³⁰ These are written commitments between doctors and patients stipulating the terms of treatment, in particular, patient compliance with treatment and monitoring, including the potential use of urine drug testing.³⁰

Health information on safe opioid use could also be provided to patients. Educational and training sessions could be offered to patients on how to use opioids safely, especially information about appropriate storage (eg, lock boxes) and disposal of pharmaceuticals that are no longer needed.

Use of Prescription Monitoring Programs

Prescription monitoring programs are data collection systems that determine the number of physicians who prescribe opioids for each patient and the number of pharmacies where opioids are dispensed for that patient.²⁶ Prescription monitoring programs are administered on a state-by-state basis and are currently operational in 33 states, and are at various stages of implementation in 7 more states.³¹ Prescription monitoring programs collect information on the prescriber, pharmacy, product name, concentration, dose, and amount of medicine dispensed.²⁶ Although the data are limited, they so far suggest that such programs reduce abuse practices.²⁶

Prescription monitoring program threshold reports can be used to limit the prescribing of opioids to “doctor-shoppers” and “pharmacy-shoppers.”³² Once a patient reaches the determined threshold, action can be taken, including notifying all the physicians who have prescribed an opioid to the patient, limiting the number of pharmacies used by the patient to one, notifying the patient of the knowledge of the suspicious activity, and if appropriate, referring the patient to law enforcement for investigation.^{25,32}

Preventing Inappropriate Prescribing and Medical Errors

An important aspect of risk minimization relevant to opioids is detecting inappropriate prescribing of opioids and medical errors, including incorrect patient selection

(opioid-naïve patients), off-label use, incorrect indication (eg, “as needed” use of extended-release formulations), incorrect dosage, and conversion errors. This could be accomplished by establishing algorithms that identify mismatches between diagnoses and medication/dose. The purpose of such measures should not be to prosecute prescribers (unless, of course, unlawful behavior is clearly proved), but to educate prescribers who made honest errors in safe opioid prescribing practices and ultimately help them to avoid malpractice lawsuits.

Setting up systems in prescribers’ offices, such as electronic prescribing, may promote safe opioid prescribing and reduce medical errors.

The US Drug Enforcement Administration issued a regulation effective June 1, 2010, approving the use of electronic prescribing for controlled substances in the United States.³³ The regulation is expected to add another barrier to the diversion of prescription drugs by reducing prescription forgery. Moreover, it is intended to reduce the number of prescription errors caused by illegible handwriting, thereby enhancing safety. Implementation of the regulation is expected to take up to 18 months, because some operational issues need to be resolved and prescribing software must be updated.

Checking Patients’ Photo Identification at the Pharmacy

Pharmacists may require that photo identification be presented by patients when they are picking up their opioid prescriptions at the pharmacy, because an increasing number of cases of abuse have involved identity theft. This could be achieved by mandating that the patient’s identification be checked before accepting a claim for prescription opioid medication. Some states, such as Virginia, are currently considering passing a bill that will require individuals to present a photo identification to pick up prescriptions for controlled substances.³⁴ To reduce insurance fraud, the Government Accountability Office also recommends that insurers remove deceased patients and physicians from their systems to avoid paying claims for fraudulent prescriptions for controlled substances purportedly written by deceased physicians or to deceased patients.³⁵

Referral to Pain Specialists

Encouraging referrals to multidisciplinary pain management programs and referral resources for addiction specialists is another option. In addition, although reimbursing for services such as routine urine drug tests and referral to specialists may be more costly in the short-term, the ability of these services to help detect and correctly manage patients at risk for prescription opioid abuse may reduce costs in the long-term.

Table Abuse-Deterrent Opioid Formulations

Trade name	Opioid	Mechanism	FDA status
OxyContin	Oxycodone	Hard plastic polymer that renders the tablet difficult to crush or dissolve	Approved in 2010
Remoxy	Oxycodone	Very viscous liquid intended to resist crushing, dissolution, injection, or inhalation	Under FDA review
Suboxone	Buprenorphine	Contains sequestered naloxone (an opioid antagonist), which is released when product is chewed/crushed and cancels the euphoric effects of buprenorphine	Approved in 2002
Embeda	Morphine	Contains sequestered naltrexone (an opioid antagonist), which is released when the product is chewed/crushed and cancels the euphoric effects of morphine	Approved in 2009
Acurox	Oxycodone (immediate release)	Contains an aversive agent (niacin) that causes unpleasant effects when injected, inhaled, or taken orally in high doses	Under FDA review

FDA indicates US Food and Drug Administration.

Use of Abuse-Deterrent Formulations of Opioids

Opioid manufacturers are addressing the problem of prescription opioid abuse pharmacologically by developing new opioid formulations with abuse-deterrent properties. Abuse-deterrent opioid formulations (Table) use a combination of old and new strategies that fall into 3 general categories:

- The “fortress approach,” in which the formulation maintains its extended-release characteristics despite attempts to crush or dissolve it
- The “neutralizing approach,” in which the formulation is relatively easy to alter, but tampering with the formulation results in the release of a neutralizing antagonist
- The “aversive approach,” in which the opioid is formulated with an aversive agent that results in unpleasant side effects when a large quantity of the opioid is ingested. Some of these formulations are already on the market, including Suboxone (buprenorphine), Embeda (morphine), and the new OxyContin (oxycodone). Others are still in development or are currently under FDA review, as shown in the Table.

The recently approved (April 2010) OxyContin formulation exemplifies the “fortress approach.” This new tablet is coated with a plastic polymer designed to prevent chewing, cutting, or crushing of the tablet.³⁶

Suboxone (approved in 2002) and Embeda (approved in 2009) are examples of the “neutralizing approach,” characterized by extended-release opioid agonist-antagonist combinations. Suboxone contains buprenorphine and naloxone; Embeda contains morphine and naltrexone (which is a longer acting antagonist than naloxone).

The strategy behind these products is to blunt the euphoric effects of the opioid if the formulation is altered. The antagonist agent (naltrexone or naloxone) is sequestered if the medication is taken as directed, but if it is tampered with (eg, chewed, crushed, or dissolved), the antagonist is released. A recent study has shown that Suboxone has a lower abuse liability than Subutex (buprenorphine alone).³⁷ Similarly, crushed Embeda produces less euphoria (as measured by “drug high” on a visual analog scale) in substance abusers than either intact Embeda or immediate-release morphine sulfate.³⁸

An example of the “aversive approach” is the immediate-release formulation of oxycodone containing niacin (Acurox), which is currently under FDA review (Table).³⁹ Niacin causes unpleasant side effects, such as warmth or flushing, itching, sweating, and/or chills. The formulation is designed to release no or insignificant amounts of niacin if Acurox is taken as directed, but if it is taken in higher than recommended doses, temporary unpleasant (but not harmful) effects of niacin are experienced, as demonstrated in a clinical study comparing Acurox with oxycodone.^{40,41} If and when approved, the aversive strategy will be the only strategy that could prevent abuse of a medication by swallowing excessive numbers of tablets or capsules whole; the fortress and neutralizing approaches are likely to be inefficient against this form of abuse.

Practical Considerations

A key question for payers will be the degree to which these new formulations deter abuse. The real question is whether these formulations truly reduce misuse, abuse,

addiction, and diversion on a population basis (ie, in the real world). The payer community should have a reasonable skepticism about the real-world abuse deterrence of these formulations. Indeed, in the mid-1990s, claims were made that the pharmacokinetic properties of the extended-release oxycodone were less reinforcing than immediate-release oxycodone, and therefore extended-release oxycodone would have a lower abuse potential.⁴² What was not recognized, however, was the simplicity by which the extended-release mechanism could be subverted: just breaking, chewing, or crushing extended-release oxycodone tablets could lead to the rapid release and absorption of a high dose of oxycodone.⁴² The rapid increase in OxyContin abuse after the drug was launched is a good lesson in how the abuse potential of any drug is a function of the ease with which that formulation can be subverted.

Most abuse-deterrent formulations on the market have been approved recently, and therefore no data are yet available to determine the impact of these formulations on the abuse and diversion of these opioids in the real world. Suboxone (which was approved in 2002) has some real-world abuse data. One study showed that of 64 patients switched from Subutex to Suboxone, 5 abused Suboxone intravenously (once each by 4 patients and twice by 1 patient), and all reported that it provided no euphoria or was unpleasant and that they would not repeat the experience.⁴³ However, real-world data show that buprenorphine is still widely abused and diverted. In the United States, law enforcement and pharmacists report that Suboxone is being abused successfully when snorted,⁴⁴ and data from the National Forensic Laboratory Information System, which tracks drug seizures by law enforcement, suggest that diversion of buprenorphine has been steadily rising despite the introduction of Suboxone.⁴⁵ Data from 2003 to 2005 from US Poison Control Centers show that Subutex and Suboxone rates of abuse are similar,⁴⁶ and a study in Malaysia showed that the introduction of Suboxone did not reduce the rate of intravenous buprenorphine abuse in that country.⁴⁷

Conclusion

Many approaches are currently in various stages of implementation to help decrease the incidence of prescription opioid misuse, abuse, and diversion. For each measure, health plans, employers, and other payers may have to consider (1) the feasibility of implementing the measure; (2) the cost of implementation versus the ultimate cost-savings; (3) the additional burden on the healthcare system (ie, physician, pharmacist, and insurer) that the measure creates; (4) the potential negative consequences on the appropriate treatment of pain

(chilling effect); and (5) the true impact of the measure on misuse, abuse, and diversion of opioid medications. Therefore, policies and recommendations should come from consensus decisions from various stakeholders. The effectiveness of these programs will have to be evaluated and adapted for optimal reduction of prescription opioid abuse and diversion. ■

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STAKEHOLDER PERSPECTIVE

Just Say No

PAYERS/PROVIDERS: “Just say no to drugs.” Do you remember this phrase during the popular anti-drug abuse campaign created in the 1980s as part of the US “War on Drugs”? What you may not know is that marijuana use by high school seniors dropped from 50.1% before that campaign to 12% in 1991.¹ In addition, cocaine use by the same demographic group dropped from 12% to 10%, and heroin use dropped from 1% to 0.5%, during the same time period.¹

Critics, nevertheless, believed that the solutions to the drug abuse problem were never addressed by this campaign, and that the problem was reduced to a very costly catch phrase.

There are many psychological, physical, and social factors that lead to drug abuse problems. Psychological and emotional factors, such as depression and schizophrenia, are linked to the development of drug abuse problems. Physical challenges, such as

Continued

STAKEHOLDER PERSPECTIVE (Continued)

chronic pain or improper or undertreated pain, can lead to drug abuse. And social factors, such as stress, unemployment, poverty, and lack of education, can also lead to drug abuse.

In her article in this issue, Dr Hahn provides an overview of several strategies that can be employed to prevent opioid misuse, abuse, and diversion. Strategies such as education of physicians and patients, use of prescription-monitoring programs, checking photo identification at the point of sale, referral to pain specialists, and use of abuse-deterrent opioid formulations are all legitimate strategies, and these should be used by healthcare stakeholders, such as payers and providers, but is it enough?

Well, the catch is, we do not know. Dr Hahn correctly points out in the article that very little data exist regarding the effectiveness of these measures for many reasons, such as a lack of systematic implementation of these measures, some of the strategies are too new, and some have not been fully evaluated regarding their effectiveness.

However, in addition to answering the questions regarding effectiveness of the various strategies that Dr Hahn lists, we must also remember the other causes for the development of drug abuse, because these other causes must be addressed if we want to prevent

misuse, abuse, and diversion. We can no longer only focus on “policing” patients who are treated with and providers who prescribe opioids. We must also address the underlying causes that lead to drug abuse.

Effectively treating depression, schizophrenia, and chronic pain is as, if not more, critical than changing the formulation of an opioid if the goal is to prevent opioid misuse and abuse. Improving the education and financial future of our nation is as, if not more, critical than checking photo identification at the point of sale if we want to prevent drug diversion.

POLICYMAKERS: We have a drug abuse problem in this country. If we want to prevent opioid misuse, abuse, and diversion, we need a comprehensive strategy that can be measured appropriately to truly understand whether we are having a positive effect on this problem. We may even want to consider a catch phrase as part of our comprehensive strategy as long as we can measure the results.

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Atheer A. Kaddis, PharmD
 Vice President, Managed Markets
 Diplomat Specialty Pharmacy

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