

The Economics of Opioids: Abuse, REMS, and Treatment Benefits

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Economic Burden of Opioid Misuse and Abuse

The use of opioids for chronic non-cancer pain (CNCP) has increased in the last 2 decades; in turn, so has the misuse and abuse of these medications, which has resulted in increased healthcare costs. In an attempt to ensure the safe use of opioids, the FDA has implemented a classwide Risk Evaluation and Mitigation Strategy (REMS) program requiring prescriber and patient education.¹ Educating prescribers and patients on the proper use of opioids, monitoring patients at high risk for abuse, and encouraging the use of abuse-deterrent formulations (ADFs) could potentially reduce healthcare costs associated with opioid misuse.^{1,3}

Economic Impact on Prescribers, Payers, and Patients

Opioid misuse is the use of opioid medication in a manner other than that intended by the prescriber, either by ingesting higher doses, or by ingesting doses more or less frequently.

According to the *Diagnostic and Statistical Manual of Mental Disorders (DSM) 5*, opioid use disorder includes the following⁴:

- recurrent use that results in failure to fulfill major role/obligation at work, home, or school
- recurrent use in physically hazardous situations
- important social, occupational, or recreational activities are given up or reduced because of use
- continued use despite persistent or recurrent social or interpersonal problems that are caused or exacerbated effects of the substance

For the purpose of this article, the term abuse will be used to refer to both the misuse and abuse of prescription opioid therapies. The opioids most commonly abused are oxycodone, hydromorphone, and hydrocodone. Although the true cost of opioid abuse is considered difficult to assess because many instances of abuse go unreported, studies have estimated the cost to society at more than \$53 billion in the United States annually.⁵

Abstract

Since the 1990s, there has been a 10-fold increase in the use of opioid analgesics, which has placed a significant financial burden on the healthcare system. Extra costs include time lost from work, multiple emergency department (ED) and ambulatory clinic visits, frequent office visits, doctor-shopping, prescriptions, and rehabilitation facilities. In an attempt to ensure the safe use of extended-release (ER) and long-acting (LA) opioids, including methadone, the FDA has enacted a classwide Risk Evaluation and Mitigation Strategy (REMS) program mandating prescriber and patient education to encourage proper patient screening and appropriate monitoring. The REMS components require a time and financial commitment for both healthcare providers and payers. Although physicians have said they are willing to comply with REMS mandates, many have said they would be reluctant to prescribe opioids covered under REMS. The FDA does not have adequate data on the effectiveness of the current opioid REMS, so evidence is lacking to confirm its utility in diminishing opioid abuse. Payers could play an important role by reimbursing healthcare providers for the time spent issuing opioid risk tools, implementing patient and caregiver education risk stratification, providing naloxone reversal prescriptions with appropriate education, and monitoring overall. Furthermore, payment for abuse-deterrent formulations might also help to mitigate risk, but at a significant cost to society.

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According to the CDC, there has been a 10-fold increase in the use of opioid analgesics during the last 20 years.⁶ Increased opioid use has resulted in increased healthcare costs, with patients who abuse opioids having direct healthcare costs 8 times those of nonabusers.² Costs include time lost from work, multiple emergency department (ED) and ambulatory clinic visits, frequent office visits, doctor-shopping, prescription costs, and rehabilitation facilities.^{7,9}

A 2007 review of administrative claims data from privately insured patients who abused opioids, along with their caregivers (individuals sharing the same plan as an opioid abuse patient), indicated that the abuse accounted for \$25 billion in direct healthcare costs—44.9% of total US societal costs related to opioid abuse. Patients were identified as the source of 92% of excess medical and drug costs, with caregivers contributing the remainder.⁸

A 2008 Drug Abuse Warning Network report stated that approximately 1 million ED visits were attributable to nonmedical use of prescription or over-the-counter (OTC) drugs, comparable to the number of visits resulting from illicit drug use (eg, heroin, cocaine). Of the prescription and OTC drugs reported, opioids were the most common, with 306,000 ED visits. By comparison, heroin accounted for 201,000 ED visits; cocaine, 482,000. The top 3 drugs responsible for unintentional drug overdose deaths were opioids, cocaine, and heroin, with opioid deaths totaling more than those of cocaine and heroin combined.⁶ It should also be noted that the majority of opioid deaths involve concomitant use of benzodiazepines, alcohol, and/or sedative hypnotics. Moreover, although methadone accounts for less than 5% of all prescribed opioids, it accounts for about 30% of all opioid deaths.¹⁰

A recent study by Zedler et al identified risk factors for increased morbidity (ie, life-threatening opioid-related respiratory/central nervous system depression) and mortality associated with opioid abuse. The strongest risk factors were the opioid dose that the patient was taking in a 24-hour period, hospitalization due to toxicity or overdose within the previous 6 months, and a history of opioid dependence. Other significant risk factors included use of ER or LA opioids, liver disease, and a morphine-equivalent daily dose of 20 mg or more.¹¹

ED visits are financially taxing: a 2010 study showed the mean cost for patients not admitted to the hospital following an ED visit to be \$4121, and the mean cost for those admitted to be \$29,669.¹²

Of course, the increased use of healthcare services because of opioid abuse places a significant economic

burden on managed care organizations and payers. One study reports that Medicaid patients and their caregivers account for one-third of excess medical and drug costs due to opioid abuse, with privately insured and uninsured patients and their caregivers each contributing smaller portions to the total cost.⁸

A review of claims for 611,801 privately insured patients in a single Midwestern state reported that chronic opioid users accounted for more healthcare services than other patients. Patients with chronic opioid use filed 5% of medical claims and received 45% of all opioids prescribed in the state. Although it is not known whether these factors are directly attributable to opioid use, this population also had more physician office visits, ED visits, non-pain-related physical disorders, and psychiatric comorbidities.¹³ In addition to the acute services made necessary by opioid misuse, admissions to publicly funded treatment facilities have increased healthcare costs, growing from 98,909 in 2007 to 186,986 in 2011, for an increase of 89%.⁵

One study that looked at the monetary impact of opioid abuse reported that both privately and publicly insured patients who abused opioids had significantly higher mean annual healthcare costs than nonabusers. The study cites excess costs per patient at \$20,546 for privately insured and \$15,183 for publicly insured patients.¹⁴

Another costly aspect of opioid use is drug diversion, broadly defined as distribution from a legitimate legal source, such as a licensed medical professional, into the black market for purposes other than originally intended.¹⁵ While the common perception of drug diversion involves illegal channels, one widespread variety is “doctor shopping,” where patients obtain prescriptions from multiple healthcare providers who are unaware of the patient’s preexisting opioid prescriptions or other healthcare providers.¹⁶ It is estimated that drug diversion costs payers \$72.5 billion each year, with two-thirds of that cost coming from Medicare and Medicaid.^{9,17}

A nationwide sample of all opioids sold during 2008 showed that 1 out of every 143 patients obtained opioids from more than 1 prescriber, with 31% seeing 1 prescriber, 14% seeing 2 prescribers, 3% seeing 5 to 9 prescribers, 0.35% seeing 10 to 19, and 0.04% seeing 20 or more.¹⁶ Doctor shopping is often associated with covert behavior, and it is often assumed that patients will pay cash for multiple prescriptions to avoid detection. However, many patients will still utilize insurance to pay for their multiple prescriptions. For example, in the aforementioned study, patients who were identified as doctor shoppers

and who used insurance had prescriptions written by an average of 8 different healthcare providers.¹⁶ Another study obtained a 20% random sample of prescription data from 2010 of the 37 million Medicare Part D beneficiaries. Of the 1,808,355 beneficiaries who filled at least 1 opioid prescription, 23.1% filled prescriptions from 2 different healthcare providers, 9.5% from 3 healthcare providers, and 7.9% from 4 or more providers. There were 1,208,100 beneficiaries who filled more than 1 prescription, which resulted in even higher numbers of beneficiaries demonstrating doctor-shopping behavior, with 34.6% of beneficiaries obtaining prescriptions from 2 healthcare providers, 14.2% from 3, and 11.9% from 4 or more.¹⁸

Obtaining opioids from multiple prescribers has been associated with increased annual hospital admissions, with one report stating patients who received opioids from 4 or more healthcare providers had twice the annual rate of admissions.¹⁸ These doctor shoppers generate unnecessary prescriptions and healthcare costs that burden the payer and result in higher premiums paid by all those in the insurance plan.

The Drug Enforcement Administration estimated the economic burden of opioid misuse at \$53 billion in 2011.⁵ Specifically, employed persons who misuse opioids account for 64.5% of medically related absenteeism and 90.1% of disability costs. Comparatively, caregivers of those with opioid issues are responsible for 35.5% of absenteeism and 9.9% of disability costs. Monetarily, opioid abuse is responsible for \$25.6 billion annually in lost work productivity.⁸ It can be assumed, although the reports do not specify it, that there are direct healthcare costs (ie, office visits, prescription costs) related to absenteeism and disability.

The Economic Impact of Implementing REMS to Prevent Opioid Misuse

Educating both physicians and patients on the safe use of opioids is a presumed way of reducing risks associated with abuse.² The FDA Amendments Act of 2007 (FDAAA; PL 110-85) established the FDA's role in ensuring that the benefits of certain therapeutics outweigh their risks through the REMS program.¹⁹ Between 2007 and August 2014, over 200 REMS programs were approved by the FDA and 144 were released, leaving 68 approved REMS programs and 6 single, shared-system REMS programs. In a single, shared system REMS, multiple drugs follow the same program.²⁰ The ER/LA Opioid REMS initiative is the largest shared REMS to date.¹⁹ The goal of this program is to "reduce serious adverse outcomes

resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting" opioids. The FDA released the REMS elements in April 2011. They require all manufacturers of ER and LA opioids, including methadone, to provide prescriber education through accredited continuing education, as well as information prescribers can use to educate patients on the risks and benefits of opioids. Although methadone is rightfully included, it is technically neither an ER or LA opioid but rather an opioid with a long and variable half-life. According to the FDA blueprint, the expected result of healthcare education in a REMS is an understanding of¹:

- Patient assessment for treatment with opioid therapy, including when to refer to a pain management specialist
- Initiating therapy, modifying doses, and discontinuing use
- Ongoing management of opioid therapy
- How to educate patients regarding safe use
- General and product-specific drug information

It is imperative that healthcare providers have an understanding of, and are comfortable with, prescribing opioids and undertaking the associated risk assessment that comes along with responsible prescribing. Despite the abundance of available education on the subject, many physicians remain uncomfortable prescribing opioids for non-cancer-related pain, especially in patients who have a history of substance abuse. It could be theorized that the educational goals of the REMS program could give providers greater confidence in identifying appropriate patients for opioid therapy and initiating at the correct therapeutic dose. In addition, schools of medicine, pharmacy, and nursing education must help clinicians by laying a solid foundation for understanding the proper use and potential abuse of opioids.

Before starting a patient on opioid therapy, clinicians should conduct a comprehensive benefit-to-harm evaluation, which includes a medical history (including psychological factors and family history), physical exam, and risk assessment.²¹ In addition, evaluation of the underlying pain condition is recommended in order to determine if treatment with an opioid is the best course of action.²⁰ Only after all non-opioid alternatives are ruled out should opioids be considered. If the decision to start opioid therapy is made, the clinician and patient should discuss treatment goals and expectations that include how opioids will be prescribed and taken and any required follow-up. This should constitute an ongoing dialogue with the patient throughout treatment. In part because strong evidence in

support of opioids for CNCP has been criticized as lacking, it is highly recommended that a written treatment plan be created to ensure clarity for the patient, patient's family, and any other healthcare providers who may be involved in the patient's care. The written treatment plan and a consent for long-term opioid use may specify that the patient must obtain opioid prescriptions from a single provider, fill prescriptions at a single pharmacy, undergo random urine drug testing, and undergo scheduled office visits.²¹ One approach to patient identification is the Screening, Brief Intervention, and Referral to Treatment (SBIRT) model that employs community screening to reduce substance abuse. The model calls for using standardized screening tools to assess patients for substance abuse behaviors. Healthcare providers offer substance abuse education to those patients who are identified as being at risk, and if patients need additional help, they are referred to therapy or treatment.²²

Patient screening is important for the identification of appropriate patients for opioid therapy and for determining the correct therapy and dose. However, the requirements to conduct screening and create a written treatment plan can be time consuming and tedious. Healthcare providers may find that the financial constraints are barriers to committing time and office resources to risk management.³ Assessing and educating patients about the proper use of opioids may tax already time-constricted healthcare resources. Currently, Medicaid, Medicare, and Current Procedural Terminology (CPT) codes exist to reimburse substance abuse screening.³ Therefore, it is important for payers to encourage the use of screening tools to identify high-risk patients, facilitate the education of these patients, and reimburse healthcare providers for the time involved.³ Distribution of patient counseling information and Medication Guides as directed under the REMS program should help patients understand how to properly use opioids (including identifying signs of a potential overdose, contacting their physician before changing dose, and safely storing and disposing of the medication), which could reduce abuse and subsequent healthcare costs to payers.

An important part of understanding how to properly prescribe opioids includes being aware of federal and state regulations.¹ A survey of state medical board members showed that only 32% thought that physicians adequately understood regulations surrounding the prescription of controlled substances.²³ This understanding is important to healthcare providers because they are vulnerable to regulatory investigation and discipline.

However, healthcare providers often have limited knowledge of the policies governing opioid therapy, which can impact healthcare services in a number of ways.²¹ It takes time to become educated and comfortable with the regulations, time that physicians may not have. On the other hand, a lack of understanding may prevent physicians from providing proper pain management because of a refusal to prescribe opioids.

Another time-consuming dictate of the REMS requirement is the ongoing management of opioid therapy. Approximately 84% of primary care physicians who were surveyed said that their primary concern about prescribing opioids was abuse; few took action to deter this from occurring. The majority of respondents did not conduct urine drug testing either before prescribing opioids or after, and only 55.9% had an established protocol to track patients on opioids.²⁴ Furthermore, in order for urine drug testing to have a positive effect on treatment outcomes, clinicians must be aware of how testing is conducted at the laboratory they use. For example, many laboratories do not test for semisynthetic or synthetic opioids unless requested, and more detailed testing using mass spectroscopy may be needed to identify opioid metabolites.²⁵ These additional tests could result in added expense.

Having an ongoing management plan in place is important for insuring the proper use of opioid therapy. In 2010, the American Pharmacists Association convened a stakeholder meeting to discuss improvement of current REMS communication. The panel stated that the most effective patient safety programs are those that require contacting patients either by phone, by e-mail, or in person, and that this can be done by a panel of nurses, pharmacists, or physicians. The best intervention should not increase the burden on office or administrative staff. Although the educational activities specified in the REMS program are directed to opioid prescribers, pharmacists should also be included in the ongoing management of opioid therapy. Pharmacists provide an important point of contact with patients, from which they can educate, identify problems, monitor therapy, and communicate with other healthcare professionals about a patient's opioid use.¹⁹

The FDA blueprint states that educational activities should take approximately 3 hours for physicians, but it is clear that the ongoing screening, educating, and monitoring of patients as required by the REMS program have the potential to be time-consuming and costly above and beyond the minimal requirements.¹

Overall View of REMS

In a survey of 201 physicians showing varying attitudes, physicians who treat chronic pain stated a concern about the impact that REMS requirements will have on their practice and patients. Although physicians thought the Elements to Assure Safe Use (ETASU) associated with REMS would have a positive impact on patient care, they also thought that any implementation system that monitored or evaluated whether the ETASU are being observed would have a negative impact. Physicians stated that any requirement for patients to complete education would be a significant barrier and that the increased requirements may not improve patient education or reduce abuse or misuse.²⁶ The opinion of healthcare providers appears divided as to whether they would continue prescribing opioids if they were required to undergo education or provide patient education, with 50.2% saying they would continue to prescribe opioids under those circumstances versus 49.8% who would not.²⁷

The views of this small sample of physicians may reflect concerns that are warranted. The Office of Evaluation and Inspections of the Office of the Inspector General for HHS conducted a survey to determine if the FDA has adequate data to assess the effectiveness of REMS programs. The survey reviewed the 199 REMS programs approved by the FDA from 2008 to 2011.²⁸ The FDA requires manufacturers to submit assessments of REMS effectiveness at 18 months, 3 years, and 7 years after implementation, with failure to comply resulting in financial penalties.²⁰ In addition, the FDA must evaluate the ETASU for 1 drug each year. The goal is to assure safe use, patient access, and minimal burden on the healthcare system. Between 2008 and 2011, the FDA approved 32 REMS with ETASUs, but as of the end of 2011 had only evaluated 1 drug. The FDA stated that it was unable to evaluate a REMS with ETASU because for the first 3 years, it was developing and implementing the REMS program, and the program must be in place for a sufficient amount of time before it can be properly evaluated. For the programs identified by the FDA as not meeting REMS goals, the most often identified issue was patient or prescriber lack of risk awareness. The report found 2 factors lacking in the FDA's REMS program. First, the FDA does not have a plan in place to identify, develop, validate, and assess the effectiveness of REMS components. Second, the FDA cannot compel sponsors to provide assessment data to the agency, and without those data, it is impossible for the FDA to monitor the performance of REMS programs and ensure that patients are protected from the potential risks associated with therapeutics.²⁸

The economic impact of the REMS program is not clear. The cost implications for the healthcare industry are widespread, including costs to pharmaceutical companies for the development, implementation, and monitoring of the REMS program. While the government has mandated REMS programs, it is severely lacking in the resources needed to effectively review them. And then there are the healthcare providers and payers. The goal of the REMS program is to insure that opioids are prescribed to clinically appropriate patients and are used properly; by increasing the awareness of abuse and fraud, healthcare costs could theoretically be reduced.²⁹ But in order to comply with a REMS, healthcare providers must carry most of the burden, because they are responsible for going through training and taking time to educate and monitor patients, and payers are impacted by the time that is billed to assess and educate patients.²⁰

Payers and Opioid Use

There are a number of ways in which payers can have a significant impact on the use, and possible misuse, of opioids. In addition to encouraging and reimbursing costs for the use of screening tools, payers can implement formulary controls that limit reimbursement for higher-risk opioids and encourage use of tamper-resistant formulations, also known as ADFs.³

Oxycontin was approved by the FDA in 1995 with no inherent resistance to tampering, allowing people to circumvent the control of the oxycodone release by crushing the tablet. Therefore, an ADF of Oxycontin was developed that ensures bioequivalent oxycodone when ingested intact. A study of recreational opioid users evaluated the abuse potential, pharmacokinetics, pharmacodynamics, and safety of crushed, tamper-resistant Oxycontin and showed that the tamper-resistant formulation demonstrated reduced C_{max} , increased T_{max} , and lower abuse potential than the original formulation.³⁰

ADFs take longer for abusers to prepare, and in general, the end result is often undesirable. One study showed that ADF tapentadol tablets required more time to prepare for abuse, and few participants were willing to snort or inject the results: only 14% of intranasal users said they would snort the results and only 18% of intravenous users said they would inject.³¹ This suggests that tamper-resistant formulations may deter approximately 86% of intranasal and 82% of intravenous abusers.³⁰ Therefore, payers encouraging the use of tamper-resistant formulations in high-risk patients may effect reduced costs related to opioid abuse. Nevertheless, this will not deter or pre-

vent addicted patients from taking multiple ADFs orally or seeking non-ADF traditional or generic products that are more likely to be covered by third-party payers.

Before the approval of ADFs, it was estimated that they could save payers between \$0.6 and \$1.6 billion per year.³² A study examining claims data from 2009 to 2011 reported cost savings associated with the introduction of abuse-deterrent oxycodone at \$430 million³³; however, these savings were seen within the first year the formulation was on market. As ADFs become more widely prescribed, additional cost savings may become less evident or even more costly.³⁴ As mentioned earlier, a costly aspect of opioid abuse is the practice of doctor shopping, which results in numerous unnecessary prescriptions being issued by multiple prescribers. To control doctor shopping, patients may be required to obtain prescriptions from a single prescriber or pharmacy. Patient Review and Restriction Programs, or “lock-in” programs, allow state Medicaid programs to control access to opioid therapy for certain patients.¹⁹ The states employ both subjective and objective criteria to flag patients who, due to certain behavior, should be in the lock-in program, and the states will only reimburse claims for “locked-in” beneficiaries who go to a single prescriber or pharmacy.^{16,33} This allows better coordination of services and a reduction in unnecessary prescriptions and services and, in turn, a reduction in healthcare costs.^{17,35}

However, the true economic impact of ADFs and lock-in programs remains to be seen. For example, some studies have failed to show that lock-in programs can result in a reduction in overdose mortality rates or opioid consumption.³⁶ In addition, restricting prescription opioids appears to be causing an increase in heroin use. Cicero et al reported that before the 1980s, whites and nonwhites were represented equally among heroin users. However, in the last decade, 90% of people who began using heroin were white and attributed their heroin use to the fact that it was more readily accessible and less expensive than prescription opioids.³⁷

Pharmacists have the opportunity to act as gatekeepers and help identify and educate patients prescribed opioids. Community pharmacies are already active in patient education, so they should be able to seamlessly incorporate REMS education into their current practice if time allows. Pharmacists can help identify appropriate patients for opioid therapy and assist in detecting illicit drug use and poor adherence.³⁸ There is also a growing trend for pharmacists to evaluate patients and ensure

that opioids are being prescribed for legitimate medical reasons.³⁹ In addition, pharmacists can provide proper education regarding naloxone if it is prescribed to the patient, and if not, contact the healthcare provider to discuss whether naloxone is appropriate or, if state mandate allows, provide naloxone to the patient.⁴⁰ However, it is important for pharmacists to be reimbursed for the time spent educating patients and their caregivers. In addition, pharmacy computer databases can help minimize unnecessary prescriptions by flagging patients who are filling prescriptions from more than 1 healthcare provider and then notifying the physicians.¹⁸

Conclusion

It is clear that opioid abuse burdens the healthcare system and results in increased healthcare costs. While the economic viability of REMS is unclear, educating prescribers and patients on the proper use of opioids could positively impact abuse liability and reduce healthcare costs. Payers reimbursing providers for time spent educating patients will support the benefits of REMS. In addition, identifying appropriate patients for opioid therapy, prescribing ADFs for high-risk patients, providing access to naloxone reversal strategies, and if necessary, restricting opioid access for some patients, could also help control healthcare costs.

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