Foundations of Opioid Risk Management

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Abstract: Increased abuse and diversion of prescription opioids has been a consequence of the increased availability of opioids to address the widespread problem of undertreated pain. Opioid risk management refers to the effort to minimize harms associated with opioid therapy while maintaining appropriate access to therapy. Management of these linked public health issues requires a coordinated and balanced effort among a disparate group of stakeholders at the federal, state, industry, practitioner, and patient levels. This paper reviews the principles of opioid risk management by examining the epidemiology of prescription opioid abuse in the United States; identifying key stakeholders involved in opioid risk management and their responsibilities for managing or monitoring opioid abuse and diversion; and summarizing the mechanisms currently used to monitor and address prescription opioid abuse. Limitations of current approaches, and emerging directions in opioid risk management, are also presented.

Key Words: opioid analgesics, risk management, epidemiology, substance abuse, drug diversion

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Affecting at least 75 million Americans each year, acute and chronic pain remain inadequately treated, despite the availability of effective treatment options for many sufferers.[1] Opioids play a central and incontrovertible role in the management of acute pain and pain secondary to cancer. Indeed, accumulated evidence indicates that opioid analgesics yield well-tolerated and adequate pain relief in 70% to 90% of patients with cancer pain.[2] Government agencies involved in healthcare policy, such as the US Department of Health and Human Services (HHS) and the Agency for Healthcare Research and Quality, and professional organizations, such as the American Pain Society and American Academy of Pain Medicine, recognize the benefits of adequate pain management and the pivotal palliative role for opioids in the treatment of chronic cancer pain and moderate-to-severe acute pain.[3]

A 1986 case series study by Portenoy and Foley[4] revealed that long-term opioid therapy, in some cases lasting more than 7 years, can be a safe and effective treatment option in selected patients with noncancer pain. Other, more recent studies, have confirmed these findings in chronic noncancer pain populations, including subpopulations with neuropathic pain.[5–7] In carefully selected patients, opioid therapy can provide at least partial analgesia without intolerable side effects or the development of aberrant drug-related behaviors.[2] Yet, many primary care physicians and specialists remain uncomfortable prescribing opioid analgesics, a potential barrier to the effective treatment of chronic pain.[8] Physician lack of comfort may be related to insufficient understanding about the abuse potential and side effects of the agents, insufficient methods for detection of possible diversion and abuse by patients, or concern with the criminal justice aspects of interdiction with abuse and diversion.[9] Additional factors may include limited data on the long-term safety and efficacy of opioid analgesics, including the risk of addiction, creating legitimate uncertainties about the risk-benefit ratio of long-term opioid therapy.

In recent years, the expanded use of opioid analgesics for the treatment of chronic noncancer pain and the introduction of high-dose, extended-release opioid formulations with high oral bioavailability have, while improving access to analgesia for many patients, magnified opportunities for diversion and abuse. As the legitimate and clinically prudent use of prescription opioid analgesics has grown, 2-fold for fentanyl and 4-fold for oxycodone, for example, from 1997 to 2002, prescription opioid abuse as a percentage of all drug abuse cases has also increased from 5.75% to 9.85% over the same period.[10] Looked at another way, this increase

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has been associated with a sharp increase in the incidence of the nonmedical use of opioid analgesics, up to 4-fold since 1990 among youths and young adults.[11] Prescription opioid abuse has become an increasingly significant public health issue, with an abuse incidence now surpassing that for most conventional street drugs, including heroin.[11,12] The total financial costs associated with prescription opioid abuse, including healthcare costs and lost productivity, has been estimated at approximately $10 billion annually.[13]

Efforts to address prescription opioid abuse may have the undesirable consequence of diminishing legitimate access to opioids; conversely, actions to improve access to opioids for legitimate pain may fuel the prescription opioid abuse problem. The risks for opioid diversion and abuse must be addressed in an effective and medically prudent manner, coordinated among the various stakeholders, without hindering the legitimate use of opioid analgesics for patients in whom this modality has demonstrated benefits—the so-called "balanced" approach. The same considerations apply to efforts to promote greater access to analgesics for the treatment of pain.[14]

This paper, which is based on a March 2005 conference entitled "Opioid Risk Management," sponsored by Tufts Health Care Institute, will identify key stakeholders in opioid risk management and their respective responsibilities in managing opioid abuse and diversion. Moreover, this paper will examine the epidemiology of opioid abuse and diversion, as well as the mechanisms in place to monitor and understand the nature of opioid abuse in the US. In addition, balanced strategies for reducing opioid abuse and diversion while maintaining optimal analgesic treatment will be explored.

The term "prescription drug abuse" is defined differently among various stakeholders. This paper defines drug abuse using the criteria for "abuse" and "dependence" from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, Text Revision (DSM-IV-TR), which include symptoms such as withdrawal, tolerance, use in dangerous situations, trouble with the law, and interference in major obligations at work, school, or home during the past year,[15] although problems with the validity of this usage in patients with pain have been put forth.[16] The term "nonmedical use" refers to the "use of prescription-type drugs not prescribed for the respondent by a physician or used only for the experience or feeling they caused."[17] For the purposes of this paper, any instance of taking the drug for nonmedical purposes can be defined as abuse, and the 2 terms are used interchangeably, although it is recognized that agreement on more precise terminology is needed.

STAKEHOLDERS' PERSPECTIVES AND RESPONSIBILITIES

No single governmental or private entity has responsibility for overseeing opioid risk reduction programs. Instead, this responsibility is spread among disparate groups. Chief among them are federal and state agencies, as well as the pharmaceutical industry and healthcare payers, and, finally, clinicians and patients themselves. Each of these stakeholders has different goals and responsibilities with regard to opioid risk management. These goals and responsibilities are often split between those oriented toward optimizing pain relief and those oriented toward minimizing opioid abuse and diversion.

Federal Agencies

For more than 90 years, the federal government has exerted an important influence on opioid analgesic use.[18,19] The US Food and Drug Administration (FDA) and the US Drug Enforcement Administration (DEA) share the primary federal regulatory authority and responsibility for opioid risk management. The US Substance Abuse and Mental Health Services Administration (SAMHSA), which includes the Center for Substance Abuse Treatment, plays a key role in surveillance of drug abuse and supports delivery of addiction treatment services, and the US National Institute on Drug Abuse (NIDA) supports drug abuse research.

FDA

The FDA's essential mandate is to protect public health, which includes regulating the marketing of prescription drugs. The statutory foundation for the FDA's responsibilities related to drug safety in this area springs from the Federal Food, Drug, and Cosmetics (FD&C) Act, especially as amended in 1962. The FD&C Act does not provide authority for the FDA to regulate the practice of medicine, which is a responsibility of the states.[20] Based on the FD&C Act of 1962, the FDA exercises critical oversight over prescription drugs by regulating approval for marketing based on efficacy and safety data—including their potential for abuse—submitted by the drug's sponsor, usually the manufacturer. In the development of a new drug, the FDA evaluates a drug's potential for abuse based on a composite profile of the drug's chemistry, pharmacology, clinical actions, and similarity to other drugs in its class.[21] If evidence of abuse potential emerges, the FDA requires the sponsor to provide all data relevant to abuse at the time of New Drug Application submission. If the benefits of a new drug are deemed to outweigh the risks, and if the labeling instructions permit the safe use of the product in the indicated treatment population, the FDA typically considers the drug safe for marketing.[21]

The FDA performs an initial assessment of the drug's abuse liability, but the responsibility for controlling the distribution of drugs lies with a separate federal agency, the DEA, as discussed in the next section. Responsibility for assigning a drug to a controlled substance schedule, an important element of risk management, is shared between the 2 agencies.

The FDA's role does not end with premarketing assessment; instead, it extends over the entire life cycle of

the product and, in the case of drugs that pose a high risk of diversion and abuse, includes the oversight of risk management strategies and educational activities the sponsor has implemented to reduce the risk for abuse and diversion. For instance, oxycodone (OxyContin, Purdue Pharma LP, Stamford, CT) was approved by the FDA in 1995 based on evidence that suggested the abuse liability of the product would be no greater than that of similar controlled-release opioid analgesics in its class, chiefly morphine sulfate (MS Contin, The Purdue Frederick Company, Norwalk, CT). At the time of approval, the widespread subsequent abuse of oxycodone was not predicted from the data available to the FDA. In response to reports of OxyContin abuse, the FDA worked with the manufacturer to devise a risk management plan that included a black box warning in the label, educational initiatives directed at healthcare professionals that addressed the product's potential for abuse, and a surveillance system to monitor abuse.[21]

In addition, the FDA is charged with reviewing drug labeling that meets the needs of the target patient population and, since 1962, reviewing launch and postmarketing promotional materials for consistency with the approved labeling. Labeling and promotion are considered important elements of risk management of pharmaceuticals.

DEA

The Controlled Substances Act (CSA) of 1970 charges the DEA with regulating the production and distribution of controlled substances to control their nonmedical use. Under the provisions of the CSA, the DEA schedules controlled substances; sets production quotas; regulates prescribers, dispensing pharmacies, manufacturers, distributors, importers, researchers, etc.; and plays a role in law enforcement activities to stem drug abuse and diversion. The CSA is not intended to supersede the FD&C Act. The CSA provides for a closed system of distribution, encompassing manufacturers, distributors, pharmacies, and physicians, by which the distribution of prescription drugs with the potential for abuse can be controlled.

All drugs with a potential for abuse, termed controlled substances, are placed into one of 5 schedules (schedules I to V) based on their medical usefulness and potential for abuse. Schedule I drugs (eg, heroin, LSD) manifest a high potential for abuse and no medically recognized therapeutic value in the US (Table 1). Prescription drugs with a potential for abuse, that is, controlled substances with approved medical uses, are placed into schedules II to V, based on their abuse potential. Schedule II includes those pharmaceuticals with the highest potential for abuse. The placement of a drug into a particular schedule is not irrevocable; controlled drugs can move from one schedule to another, based on new information related to abuse. The DEA, HHS, or private petitioners, including the drug's manufacturer, can each initiate proceedings to add, delete, or change the schedule of a specific drug.[22] By statute, the FDA and DEA consider 8 factors when determining whether a drug will be scheduled or removed from scheduling (Table 2).[23] HHS has the power to veto scheduling of a drug.[19]

TABLE 1. CSA Schedule of Controlled Substance

Schedule	Description	Example
I	• The drug or other substance has a high potential for abuse • The drug or other substance has no currently accepted medical use in treatment in the US • There is a lack of accepted safety for use of the drug or other substance under medical supervision	Ecstasy, heroin, LSD
II	• The drug or other substance has a high potential for abuse • The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions • Abuse of the drug or other substances may lead to severe psychologic or physical dependence	Cocaine, methadone, oxycodone and oxycodone combinations, morphine, fentanyl
III	• The drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II • The drug or other substance has a currently accepted medical use in treatment in the United States • Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychologic dependence	Anabolic steroids, buprenorphine, hydrocodone combinations, ketamine, nalorphine
IV	• The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III • The drug or other substance has a currently accepted medical use in treatment in the United States • Abuse of the drug or other substance may lead to limited physical dependence or psychologic dependence relative to the drugs or other substances in Schedule III	Alprazolam, diazepam, lorazepam, modafinil, pentazocine/nalaxone, sibutramine, eszopicilone
V	• The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV • The drug or other substance has a currently accepted medical use in treatment in the United States • Abuse of the drug or other substance may lead to limited physical dependence or psychologic dependence relative to the drugs or other substances in Schedule IV	Guaifenesin/codeine, atropine/difenoxin

To control diversion from the excess manufacture of controlled substances, the CSA confers authority on the DEA to set production quotas.[19] Production quotas, however, must be sufficient to meet legitimate demands for medical and scientific use. The DEA uses the Automation of Reports and Consolidated Orders System (ARCOS), an automated system developed by the DEA, to monitor the flow of selected controlled substances. By law, the DEA must provide analyzed ARCOS data to state agencies. State agencies should use these data to monitor trends and identify discrepancies in drug distribution.[22]

The DEA does not regulate clinical practice or prescribing decisions made by clinicians. Rather, the states are charged with that responsibility as part of the overall responsibility to protect public health and safety.[19] Essentially, the DEA has 2 central responsibilities: to prevent, detect, and investigate the diversion, abuse, and trafficking of controlled substances, and to ensure an adequate and uninterrupted supply of these substances to meet the legitimate medical and commercial needs in the United States.

The FDA and DEA meet regularly to discuss new ways to prevent prescription drug abuse and diversion. In addition to assisting one another with scheduling, risk management programs and criminal investigations, these agencies are currently working together on several initiatives, including addressing the diversion of pharmaceutical controlled substances via the Internet.[24] Often their missions are complementary yet distinct. For instance, both agencies have responsibilities involving the abuse and diversion of opioid analgesics; however, the FDA focuses on clinical issues, whereas the DEA focuses on law enforcement approaches. Depending on the nature of the restrictions imposed by these federal agencies, manufacturers may be dissuaded from developing opioid-based products, or healthcare providers may perceive barriers to use of potentially beneficial agents.[25]

Office of National Drug Control Policy

Established by the Anti-Drug Abuse Act of 1988, the White House Office of National Drug Control Policy (ONDCP) sets up policies, priorities, and objectives for the nation's drug control program. ONDCP goals include reducing illicit drug use, manufacturing, and trafficking, as well as drug-related crime and violence and negative, drug-related health consequences. To achieve these ends, the director of ONDCP has been charged with the responsibility to develop the National Drug Control Strategy, which directs national antidrug abuse efforts and establishes guidelines for cooperation among federal, state, and local entities. Key elements of this program include student drug testing, drug prevention educational programs, improved drug abuse treatment delivery, and bolstering enforcement nationally and internationally to disrupt the illicit drug market.[26] The ONDCP continues to work with the other agencies, including the FDA and DEA, as a part of a national task force focused on methods for dampening the illicit sale of controlled prescription drugs.[21]

TABLE 2. Eight Factor Determination for Scheduling Required by CSA

1. Its actual or relative potential for abuse
2. Scientific evidence of its pharmacologic effect, if known
3. The state of current scientific knowledge regarding the drug or other substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Its psychologic or physiologic dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled under this title

SAMHSA

Established in 1992, SAMHSA, a part of the US Department of HHS, is the lead federal agency addressing substance abuse and mental health services. SAMHSA administers competitive and block/formula grant programs and collects and evaluates data related to drug abuse.[27] SAMHSA includes 3 centers—the Center for Mental Health Services, the Center for Substance Abuse Prevention, and the Center for Substance Abuse Treatment. The SAMHSA Office of Applied Studies (OAS) is the focal point for the collection, analysis, and dissemination of national data on practices and issues related to substance abuse and mental disorders.

Since 1992, the OAS has been responsible for Drug Abuse Warning Network (DAWN) operations. An ongoing national public health surveillance system, DAWN collects information on drug-related visits to emergency departments (ED) from a national probability sample of hospitals and on drug abuse-related deaths reviewed by medical examiners and coroners.[28] OAS/SAMHSA is also responsible for the National Survey on Drug Use and Health (NSDUH), the primary source of statistical information on the incidence and prevalence of drug abuse in the US population.

National Institute on Drug Abuse

The mission of the NIDA is "to lead the nation in bringing the power of science to bear on drug abuse and addiction."[29] Established in 1974, NIDA became part of the National Institutes of Health, Department of HHS, in October 1992. NIDA supports, through grants, over 85% of the world's research on the health aspects of drug abuse and addiction. NIDA-supported science addresses a broad range of research efforts directed at understanding fundamental questions about drug abuse, focusing on filling current gaps in knowledge. NIDA also advances the rapid and effective transfer of scientific data to policy makers, drug abuse practitioners, other healthcare practitioners, and the general public. Providing information to the public on drug abuse is a key educational activity of NIDA, and much of this information can be easily obtained from its website at http://www.nida.nih.gov/. Current NIDA initiatives in the area of prescription opioid abuse include a request for

applications on the intersection of pain and opioid abuse (http://grants.nih.gov/grants/guide/notice-files/NOT-DA-05-009.html).

State Regulation

Neither the FDA nor the DEA has statutory authority to regulate medical practice. This responsibility lies with the individual states under the sections of state constitutions intended to protect public health and safety.[19] States can require that a drug prescription be filled within a specified amount of time after it is written, and they can classify drugs at a higher level of abuse risk than the CSA schedule or place the drug on a state-controlled substance list if not on the CSA list.[18] Similar to federal law, state-controlled substance laws prohibit nonmedical use of controlled substances; yet, unlike federal laws, many state regulations have not recognized the clinical benefits of controlled substances, including opioid analgesics, or the need to ensure their availability for medical purposes.[30]

Excessive state regulation and monitoring has the potential to hinder the appropriate management of pain by raising the specter of regulatory scrutiny and discipline for "inappropriate" prescribing, a recognized barrier to treatment. Indeed, 40% of physician members of the American Pain Society have indicated that regulatory, not medical, concerns have dissuaded them from prescribing opioids for chronic noncancer pain.[31] State policies may conflict with or hamper the implementation of current treatment guidelines for the management of pain in several ways: by limiting the amounts of opioid medications that can be prescribed; by requiring special government-issued prescription forms; by restricting access to opioid treatment for patients with a history of substance abuse, even when in pain; by using outdated terminology; by considering opioids the treatment of last resort; and even by suggesting incorrectly that the therapeutic use of opioids hastens death.[30]

State medical boards can address physician concerns about regulatory scrutiny and promote the balance between opioid benefits and risks. Before 1989, only a few state medical boards developed policies governing the use of controlled substances.[32] Subsequently, 41 states have adopted such policies, including regulations with the force of law, as well as guidelines and policy statements. State medical board regulations, guidelines, and policy statements mirror the knowledge and attitudes of the board members, and these have improved over time.[32]

Recognizing the need for consistent state policies nationwide, the Federation of State Medical Boards (FSMB) of the United States developed guidelines to promote adequate treatment, including the use of opioid analgesics, when appropriate. The FSMB recognized inconsistencies and restrictions in state pain policies as factors that may contribute to the undertreatment of pain by fostering the perception among healthcare professionals that prescribing adequate amounts of opioids will yield unnecessary scrutiny. In addition, the FSMB found that many state medical boards lack up-to-date knowledge of medical standards, research, and clinical guidelines related to optimal pain management and the risks for opioid abuse.[33] To remedy these deficiencies, the FSMB adopted a set of guidelines that are recommended when evaluating the physician's treatment of pain (Table 3). These guidelines were submitted to the states for consideration and have been adopted, at least in part, by 22 states.[32] From 2000 to 2003, 16 states improved their policies sufficiently to increase their grade for "balance."[34] Yet, achieving balanced and consistent state policies remains an elusive goal. Only about half the state medical board policies include language indicating that the medical use of opioid analgesics is *inside* the boundaries of legitimate medical practice.[30]

To assist in identifying diversion trends, "doctor shoppers" and inappropriate prescribing, 22 states have now implemented electronic prescription monitoring programs.[35] Although the initial orientation of state electronic prescription monitoring programs was toward facilitating law enforcement efforts, recent initiatives have begun to focus on assisting healthcare providers in more comprehensive monitoring of their patients and identifying those who may be in need of addiction treatment or more comprehensive pain management services.[36]

Healthcare Providers

Healthcare Professionals

Pain is the chief symptom that triggers new visits to office-based physicians.[37] As a result, primary care physicians and their medical staff are at the forefront in the daunting task of balancing effective pain treatment with the risks associated with analgesics. Clinicians have a responsibility to embrace prudent approaches to prescribing and implementing the necessary controls to minimize opioid abuse and diversion.[38] Steps to minimizing opioid analgesic risks include a complete diagnostic workup to identify the cause of pain and the appropriateness of opioid therapy; assessment of comorbid psychologic conditions to detect the presence of conditions that can exacerbate pain, such as depression or anxiety; screening patients for risk of opioid abuse; special management of patients at an increased risk of substance abuse, including using medication agreements or contracts to enhance compliance; use of urine toxicology screening to identify current abusers, carefully monitoring patients on a regular basis to detect signs of abuse and documenting each patient encounter in the medical record; and, if aberrant drug behavior surfaces, evaluating whether such behavior indicates an opioid abuse problem and managing such problems actively should they occur.[38–40] Removing from opioid therapy patients who are not benefiting, or who are persistently unable to comply with opioid therapy, is an important but underemphasized aspect of appropriate opioid prescribing.

TABLE 3. US Federation of State Medical Boards' Guidelines

Patient evaluation	• Medical history • Physical examination • Nature and intensity of pain • Current and past pain treatments • Underlying or coexisting diseases or conditions • Effect of pain on physical, psychologic function • History of substance abuse • For use of a controlled substance: medical record should document the presence of one or more recognized medical indications
Treatment plan	• Written plan stating objectives used to determine treatment success (eg, pain relief) and indicating if any further diagnostic evaluations, or treatments are planned • Adjust treatment to meet individual patient needs • Consider other treatment modalities or rehab program based on pain etiology and associated physical or psychologic impairment
Informed consent	• Written agreement for high-risk patients outlining patient responsibilities during drug therapy • Discuss risks vs. benefits of using controlled substances for pain treatment • Prescriptions should be written by one physician and filled by one pharmacy, when possible
Periodic review	• Review treatment regimen periodically to assess progress toward treatment objectives • Continue or modify pain management therapy as needed • Consider assessment of pain management from patient and from caregivers
Consultation	• Refer patient as necessary for additional evaluation and treatment • Pay special attention to patients at risk for medication misuse or diversion
Medical records to be maintained accurately and completely and ready for review	• Medical history • Physical examination • Evaluations and consultations • Treatment objectives • Discussion of risks vs. benefits • Informed consent • Treatments • Medications (including date, type, dosage, and quantity prescribed) • Instructions and agreements • Periodic reviews
Regulatory compliance	• Physician licensed in state to prescribe controlled substances • Compliance with applicable federal and state regulations as per the US Drug Enforcement Administration *Practitioner's Manual*

Healthcare Payers

For opioids and other drugs, managed care health plans and pharmacy benefit management organizations can influence utilization by imposing formulary restrictions, most commonly prior authorization, quantity limit requirements, and tiered copays.[41,42] Managed care organizations (MCOs) use prior authorization as a principal means for restricting the use of opioids perceived by the specific organization as having the greatest potential for abuse. For some MCOs, prior authorization for sustained-release opioids is required unless prescribed by a specialist. In addition, some healthcare plans impose quantity limits at the point of sale. To detect misuse and abuse, MCOs may review online claims processing to examine the dosage.

Despite these efforts, a recent national survey revealed that only a minority (18%) of the MCOs systematically implement clinical practice guidelines for pain management, and those guidelines vary widely among organizations.[42] Further, in the same survey, almost 90% of the MCOs indicated that inappropriate utilization of pain medications was a concern for the organization, with abuse and misuse of pain medications reported most commonly (77%) as the greatest challenge facing managed healthcare. This concern is supported by a recent study on the direct medical treatment costs of patients treated for opioid abuse, which found that such costs were more than 8 times higher in opioid abusers than in nonabusers.[13] Thus, MCOs have a clear need to implement programs that define the appropriate use of opioid analgesics to support adequate pain treatment while minimizing the risks and costs of prescription opioid abuse.

Pharmaceutical Industry

The pharmaceutical industry, by the very nature of its activity, has product liability responsibilities for reducing the risks for opioid analgesic abuse and diversion. The pharmaceutical industry in the United States has discussed drug safety as one of its highest priorities and, consistent with that priority, supports the concept of risk management as an essential step in fostering public safety and ensuring that risk/benefit decisions for particular drugs are based on scientific evidence.[43] In this context, safe drugs are viewed as those for which the benefits outweigh the risks when used in accordance with FDA-approved labeling. Risk management, in its ideal form, is viewed by the pharmaceutical industry as a comprehensive and proactive application of evidence-based methodologies to identify, assess,

communicate, and minimize the drug risks through its life cycle. This perspective is consistent with that of the FDA and DEA and underscores the importance of a dialogue between industry and regulatory agencies in achieving successful risk management plans for opioid analgesics.[43,44]

Some observers have pointed to the marketing and promotional practices by pharmaceutical companies as a possible driver of prescription opioid abuse.[45] In response to these concerns, the pharmaceutical industry has collaborated with federal and state agencies on developing risk management strategies, as well as education programs and other activities for physicians, pharmacists, and the public, to help detect and prevent the abuse and diversion of prescription opioids.

The US pharmaceutical industry remains under continued pressure to improve the quality of its drug risk/benefit decisions.[44] In 2002, Congress reauthorized the Prescription Drug User Fee Act III, and an aspect of this act authorized the FDA to produce industry guidance on risk management activities for drug and biologic products. To meet this goal, the FDA issued 3 guidance documents, each focusing on one of the key aspects of risk management: conducting premarketing risk assessment, developing and implementing risk minimization actions plans, and performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments. To advance an improved approach to risk management on the part of industry, the FDA, in 2005, issued updated guidances representing the current position of the FDA on the role of the pharmaceutical industry in managing prescription drug risks.[46]

From the FDA's perspective, risk management on the part of the pharmaceutical industry should be an ongoing process throughout a drug's life cycle. This process should encompass assessments of a drug's benefit/risk balance as well as the development and implementation of tools to minimize a drug's risks while maintaining its benefits. In addition, the process should include an ongoing evaluation of the effectiveness of those tools. These guidelines can be viewed in detail at http://www.fda.gov/cder/guidance. The risk management plans implemented by the pharmaceutical industry have typically included product surveillance of drug abuse and diversion, both passive and active; patient and clinician education; and monitoring adverse event and national drug use databases.[47,48]

In addition, Congress, in the 2005 Appropriations Bill, prohibits the DEA from establishing a procurement quota after the approval of a new drug application or an abbreviated new drug application for a controlled substance, unless the DEA reviews and provides public comments on a company's labeling, promotion, risk management plans, and any other documents.[49]

Although the boundaries of where the responsibility of pharmaceutical companies end and those of other organizations begin is under active discussion, in general, the pharmaceutical industry is perceived to have additional product stewardship responsibilities related to opioid products, including the further education of patients and healthcare providers to increase awareness of potential abuse, notification of local law enforcement agencies and state medical boards when a signal for abuse or diversion is detected through postmarketing surveillance, tight control of the supply chain for products with the potential for abuse, and coordination with efforts by the FDA and DEA to dampen abuse and diversion.

IDENTIFYING OPIOID ABUSE AND DIVERSION

There are several information systems that track abuse, but a paucity that can identify sources of diversion. Premarketing drug studies have limited usefulness in detecting the magnitude of a drug's abuse and diversion potential because the patient sample is small and select.[47] Postmarketing surveillance databases and law enforcement surveys to determine street drug activity are, thus, essential in gauging the types and methods of drugs abused and the populations most likely to engage in abuse and diversion. Several surveillance systems have been implemented to assess the risk for abuse and diversion in different subpopulations, groups that may be associated with vastly different levels and types of risk.

Adolescents and Young Adults

Monitoring the Future

One of several approaches to monitoring drug abuse among youth—the Monitoring the Future (MTF) Project—focuses on assessing changes in the attitudes, beliefs, and behaviors of adolescents and young adults regarding licit and illicit drug use.[50] MTF is an annually conducted survey that presents the same set of questions to the same segments of the population—8th, 10th, and 12th graders; college students; and young adults (up to age 28)—and monitors how those responses change over time. Since 1975, MTF has surveyed approximately 50,000 students in 420 public and private secondary schools annually. The 2004 survey findings indicate that, among 12th graders, nonheroin narcotic use more than doubled from 1992 to 2000 before leveling off in recent years.[50] Youths and young adults remain populations at particular risk for opioid abuse and should be the target of more intensive drug-abuse prevention initiatives.

General Community

NSDUH

Conducted since 1971, the NSDUH—formerly the National Household Survey on Drug Abuse—remains the largest community-based drug use survey.[47] NSDUH surveys about 70,000 individuals at least 12 years of age to glean estimates of drug abuse at the national and state levels. Responding to a growing awareness of oxycodone abuse, NSDUH has recently added questions specific to its abuse. NSDUH findings in 2003 detected a significant elevation in the lifetime nonmedical use of pain relievers between 2002 and 2003, from 29.6 to 31.2 million individuals nationwide.[11] Opioid medications responsible for this increase included hydrocodone/acetaminophen,

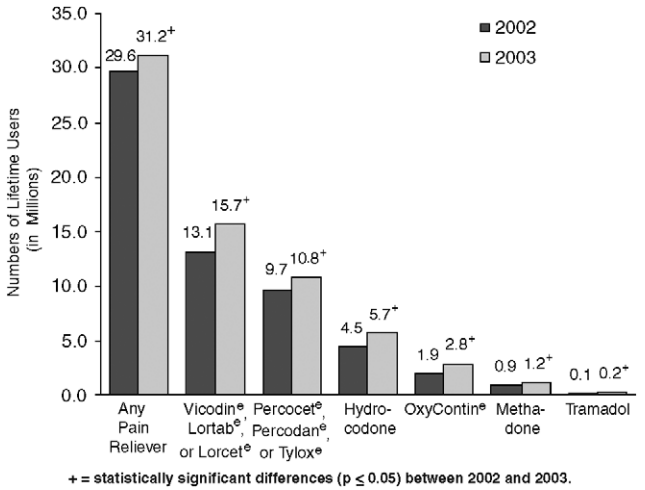

FIGURE 1. Numbers (in millions) of lifetime nonmedical users of selected pain relievers among persons aged 12 or older: 2002 and 2003 (NSDUH, 2004).[11]

oxycodone/acetaminophen, oxycodone, and tramadol, among others (Fig. 1). The 2004 NSDUH survey shows that, between 2003 and 2004, the number of lifetime users increased from 31.2 to 31.8 million individuals nationwide.[51] Although some product-specific information can be gleaned from NSDUH data, statistical power to distinguish product-specific abuse rates is possible only for lifetime use figures, which is obviously limited by the substantial influence of earlier behaviors.

DAWN

Begun in 1972, the DAWN, operated by SAMHSA, is an active public health surveillance system that monitors drug-related visits to hospital EDs and drug-related deaths investigated by medical examiners and coroners. DAWN uses a national probability sample of hospitals and a statistical weighting methodology to estimate the number of ED visits related to drug misuse and abuse and the drugs involved in these visits for the entire United States and for selected metropolitan areas. DAWN reports of drug-related deaths are based on data from participating medical examiners in selected metropolitan areas and states. DAWN has always focused on morbidity and mortality consequences of drug abuse; it does not produce direct measures of drug abuse prevalence.[13] Medical examiner participation, which is voluntary, includes jurisdictions from about 35 metropolitan areas and 6 states.[52]

In 2003, DAWN was redesigned, and a number of improvements were introduced to improve the accuracy and usefulness of the information. Still, the new DAWN system has limitations. DAWN has a very limited ability to measure emergent prescription drug abuse problems in rural areas. Only the medical examiner component of DAWN can address this at all. In addition, the case categorization scheme in the new DAWN has been confusing to clinicians and researchers comfortable with DAWN's legacy method. Efforts directed at clarifying the precise substances involved have met with some success; however, the accuracy of product-specific data remains uncertain.

Based on DAWN historical trend data from 1997 to 2002, the number of mentions increased dramatically for opioid analgesics such as fentanyl (642%), hydrocodone (118%), and oxycodone (347%).[12] Because of the many changes to DAWN, no comparisons of historical trends with estimates from the new DAWN are possible.

Adverse Event Reporting System

The FDA's Adverse Event Reporting System (AERS), a passive computerized surveillance system estimated to capture 1% to 38% of serious adverse drug reactions, is influenced by factors such as a drug's length of time on the market and media attention. The AERS database accepts reports from manufacturers, as required by regulation. In addition, healthcare professionals and consumers can submit reports voluntarily—via paper, phone, or the Internet—to the FDA's MedWatch program.[53] Reports in AERS are evaluated by clinical reviewers in the FDA's Center for Drug Evaluation and Research and in the Center for Biologics Evaluation and Research to monitor drug safety on an ongoing basis. Yet, AERS was designed to capture newly recognized, unlabeled adverse events and not common adverse events from appropriate use, prescription errors, or overprescribing of older drugs—factors that likely contribute to the greatest public health burden. Because this system likely underestimates the prevalence of drug adverse events, its use in detecting abuse patterns is problematic. In response to these serious limitations, the FDA plans to update the system to an easy-to-use, Web-based reporting system, which will be known as AERS II.[47,54,55] Nevertheless, it is unlikely that AERS will provide useful surveillance or accurate estimates of prescription drug abuse.

Drug Evaluation Network System

The Drug Evaluation Network System (DENS) was an ongoing, multisite, electronic data collection and reporting system that provided standardized, automated, and timely data on patients entering addiction treatment programs. DENS received the majority of its funding from the White House ONDCP. Federal funding for DENS ended in 2004; nevertheless, DENS continues to collect data from participating programs when possible,[56] and investigators can still obtain access to the DENS database at www.densonline.org.

Treatment Episode Data Set

The Treatment Episode Data Set, which began in 1989, represents one of the 3 components of SAMHSA's Drug and Alcohol Services Information System (DASIS). The core of DASIS, the Inventory of Substance Abuse Treatment Services, is a continuously updated, comprehensive listing of all known substance abuse treatment facilities. Another component of DASIS, the National Survey of Substance Abuse Treatment Services, is an annual survey of the location, characteristics, and use of

alcoholism and drug abuse treatment facilities. Combined, these DASIS components yield national-level and state-level information on the numbers and characteristics of individuals admitted to alcohol and drug treatment facilities and describe the facilities that deliver care to those individuals.[57] DASIS, however, does not include all substance abuse programs in participating states, and it does not always report the specific drugs that triggered the need for treatment, factors which limit its usefulness in monitoring opioid abuse.[47]

Key Informant Networks

The first drug-specific postmarketing surveillance system focused on tramadol.[48] The approval of tramadol, in 1995, as an unscheduled drug was contingent upon the development of a proactive surveillance program that would be overseen by an independent steering committee, all funded by the drug sponsor. A central aspect of this surveillance program was the systematic collection and evaluation of reports of suspected abuse—not only spontaneous reports, but also those obtained through a network of selected abuse specialists who would be surveyed periodically regarding the number of cases of tramadol abuse they had encountered. Collectively, this large national base of abuse specialists is labeled the Key Informant Network and is comprised of 110 NIDA grantees conducting comprehensive epidemiologic and treatment outcome studies in drug-abusing populations, and 145 other drug abuse experts, among them clinicians, treatment counselors, and methadone clinic directors. Based on these data sources, the level of the abuse was reported to be low, and most (97%) of the abuse cases attributed to tramadol involved known drug abusers and were isolated to the geographic regions where they reside.

Key informant networks offer potential advantages in terms of drug monitoring. They are, to date, the only model for proactive product-specific prescription opioid abuse surveillance, and, as a result, their use has been expanded in recent years to opioids other than tramadol. Also, the surveys sent to key informants could potentially be modified relatively easily to explore new trends in drug abuse, and responses can be relatively time-sensitive depending on the frequency of surveys. Challenges with interpretation of key informant data include the lack of a scientific sampling and unknown accuracy of key informants' retrospective recollection of abuse rates in their practices. As a consequence, scientifically valid product-specific abuse rates cannot be calculated. In addition, inherent biases may exist in the data because informants may fail to respond or responses may cluster in specific geographic regions.

Assessing At-Risk Populations

Pain Patients With a History of Abuse

Clinician screening to identify patients at risk for abuse, addiction, and diversion remains an indispensable step in opioid risk management on a patient level. Small-scale studies have provided at least preliminary insights into the predictors of aberrant drug-taking behavior.[58–60] Factors found to be associated with substance abuse include a past history of opioid or polysubstance abuse, a family history of substance abuse, a history of legal problems, lack of involvement in a recovery program, and poor family support. Patients with substance abuse disorders were also more likely to have participated in unsanctioned dose escalations, obtained opioid analgesics from multiple sources, and expressed the subjective impression that they had lost control of their prescribed medications. Further, high-risk patients displayed a significantly higher prevalence of mental health problems, motor vehicle accidents, cigarette smoking, and high-dose opioid use. Together, the findings of these studies suggest that patients destined to engage in opioid abuse and diversion may, indeed, display certain characteristics that can be identified in the clinical setting with the use of the appropriate tools.

Physician tools for assessing opioid drug-seeking behaviors and addiction typically include the use of medical interviews, standardized addiction screens, and physical examinations.[61] Yet, all of these approaches rely, at least in part, on patient self-reports, which can be unreliable. Information external to the patient's self-report is an invaluable adjunct to the clinician when assessing the risk for opioid abuse and can be gleaned from a variety of external sources, including prescription drug monitoring, review of medical records, interviews with family members, and the assessment of serum or urine specimens.[40,62,63] Compared with serum testing, urinary drug testing is less expensive and noninvasive. In addition, urine is readily available and easily collected and handled by office and laboratory personnel, and urine testing can detect the presence of drugs in the body for greater periods of time than serum testing. In one retrospective study, 27% of patients with no behavioral signs suggestive of opioid abuse presented with positive urine screens, implying that monitoring only drug-seeking behaviors without urine screens could result in a substantial number of failures to identify problems.[62] Indeed, monitoring self-reported drug seeking behavior, alone, yields limited or, perhaps, misleading information; adding urine toxicology testing may bolster detection rates in the clinical setting.[62]

Generally, patient behaviors that should immediately raise a red flag for potential opioid abuse include a persistent pattern of continued use of the drug despite adverse consequence or harm, compulsive drug use, and the emergence of behaviors consistent with drug craving.[61] It should be pointed out, however, that behavior patterns suggestive of opioid abuse may, in fact, reflect other health issues, among them undertreatment of pain, the presence of cognitive or psychiatric disorders, self-medication of nonpain states, and diversion by persons other than the patient (Table 4).

The Screener and Opioid Assessment for People with Pain, developed with support from both NIDA and the pharmaceutical industry, is used in conjunction with

clinician judgments to help clinicians make decisions about which patients are likely to have greater or fewer problems with opioid pain medications. A 2004 study of the validity of the Screener and Opioid Assessment for People with Pain found that the tool seemed to reliably predict aberrant drug-related behaviors in persons with chronic pain and may be an effective risk-screening device for clinicians when prescribing opioids to their patients.[39]

Healthcare Professionals

Clinicians represent a special population in need of substance abuse prevention and treatment services.[64] Although a substance abuse prevalence of 10% to 15% among physicians is similar to that in the general population, it may be more difficult to detect because the impact on job performance is not usually immediate, and physicians may adjust their substance abuse behavior in ways that decrease the likelihood of detection.[65,66] When impairments in clinical skills become apparent, the problem is usually severe and has been long-standing.[66]

Alcohol remains the leading cause of abuse among clinicians, although accessibility of narcotics, benzodiazepines, and other prescription drugs has become a concern.[67] Tramadol postmarketing surveillance data reveal that clinicians, especially family practitioners, are more likely to abuse tramadol than the general population, suggesting that abuse patterns among healthcare providers differ from those in the community at large and, as a result, may require specialized monitoring approaches.[68]

Recognition that drug abuse among physicians is, indeed, a public health problem has led to the development of numerous physician health programs. Available in many states, ''Impaired Physician'' programs are now mature models usually available through medical societies.[64] One such program, the Washington Physicians Health Program, conducted a study on the risk of relapse among healthcare professionals using a ''major opioid'' and found a significantly increased risk for those with a coexisting psychiatric illness and a family history of substance abuse.[69]

TABLE 4. Differential Diagnosis of Behaviors Suggestive of Addiction

Inadequate pain management	• Stable condition with suboptimal analgesia • Progressive pathology • Opioid tolerance/opioid-induced hyperalgesia
Inability to comply with treatment	• Cognitive impairment • Psychiatric disorder
Self-medication of	• Mood disorder • Sleep disorder • Trauma flashbacks • Addictive disease (opioid maintenance therapy)
Diversion by patient or associates for	• Other disorders • Analgesic use by others • Drug abuse • Profit
Theft or diversion by others	

Adapted from *J Pain Symptom Manage*. 2003;26:655–667.

INTERVENTIONS FOR PRESCRIPTION OPIOID ABUSE AND DIVERSION

Educational Programs

The FDA is acutely aware of reports about the marked increases in prescription drug abuse, misuse, and diversion. The FDA and the DEA regularly meet to examine new ways to thwart prescription drug abuse and diversion. To prescribe controlled substances, physicians must be registered with the DEA. This registration is required to be renewed every 3 years, but currently there is no requirement for physicians to demonstrate knowledge or training to maintain their DEA registration. The DEA is required to issue a registration to any physician based on the authority of his or her state medical license unless the physician has been convicted of a drug-related felony, falsified the application, or been excluded from participating in Medicare programs. The licensing of a physician is delegated to state medical boards and is not a law enforcement area of expertise. The FDA supports a link between the renewal of DEA registration and up-to-date training and education in the appropriate prescribing of opioid analgesics. The DEA has published a *Practitioner's Manual*, currently under revision, that provides guidance and information on the requirements of the CSA and its implementing regulations.[70]

In January 2003, the FDA and SAMHSA launched a joint prescription drug abuse prevention education effort, with a primary goal of preventing and reducing the abuse of prescription drugs, especially opioid pain relievers by adolescents and young adults. This campaign includes brochures and posters, as well as print and televised educational advertising, emphasizing the dangers of prescription opioid analgesic abuse. In particular, the campaign underscores the potential lethal risks associated with the abuse of sustained-release opioid analgesics, chiefly oxycodone.[24] The effectiveness of this program remains uncertain; indeed, the method by which success of the program will be determined is unclear.

In addition, the pharmaceutical industry recognizes that opioid abuse and diversion has become a serious public health problem and, as a consequence, some pharmaceutical companies have developed programs to curb prescription medicine abuse. Such programs include education of clinicians, of patients, and of the general public. There are no published data measuring the effectiveness of such programs, however. Existing programs have been sponsored by individual companies and have been implemented with the goal of minimizing abuse of each company's specific products. Recent discussions have acknowledged prescription opioid abuse as an issue relevant to all such products and have begun to explore multisponsor initiatives.

Abuse-deterrent Formulations

To reduce the risks for extraction of opioids from prescription products for the purposes of abuse and diversion, many pharmaceutical manufacturers are moving forward with the development of abuse-deterrent formulations. The challenge, however, is to develop abuse-deterrent formulations that are meaningfully abuse-deterrent, maintain efficacy, do not create new safety issues for the intended population, avoid harming the potential abuser, and are economically viable.[71]

The pharmaceutical industry has employed several different technologies to develop abuse-deterrent formulations. One approach prevents the release of active opioid ingredients when tablets are crushed or attempts are made to extract the opioid chemically. Several pharmaceutical companies have entered into a drug development agreement to produce an abuse-deterrent formulation that encapsulates the opioid within microparticles that are either slowly soluble or not soluble in water, rendering extraction more difficult.[72]

A second approach uses prodrugs, which are drugs that are themselves inactive, but are converted into active opioid agents by saturable absorption or metabolic pathways. An analogous example is the process by which codeine is converted to morphine once ingested. This approach is expected to delay the euphoria that occurs when an abuser injects the opioid product and limit the exposure to active agent in the setting of an overdose in a manner that cannot be compromised by tampering with the product.[73]

A third approach incorporates an opioid antagonist in combination with an agonist in a single formulation. For instance, to reduce the intravenous abuse of oxycodone in OxyContin tablets, its manufacturer has proposed combining oxycodone with the opioid antagonist naloxone in a single product wherein naloxone would not be released if the tablets are ingested intact, but would be released if the product were tampered with for snorting or injection. Recently, the FDA has indicated that this formulation requires additional clinical studies to fully assess its safety and effectiveness.[74] Using analogous ideas, pentazocine hydrochloride with naloxone (Talwin, Winthrop Pharmaceuticals, New York, NY) was approved by the FDA in 1982. In the late 1970s and early 1980s, pentazocine had become a popular drug for intravenous abuse. To blunt this avenue for pentazocine abuse, low-dose naloxone was added to the tablet formulation. The new formulation is supposed to permit nearly full oral pentazocine analgesia with limited absorption of oral naloxone, but if dissolved and injected intravenously, the naloxone dose is fully bioavailable and blocks pentazocine's euphoric effects or produces a withdrawal syndrome. After the introduction of this new formulation, pentazocine intravenous abuse generally decreased,[75] but reports of abuse continue.[75–77]

Finally, 2 pharmaceutical companies working in alliance are developing a proprietary intranasal delivery system for buprenorphine.[78] This buprenorphine intranasal gel system remains in a liquid state until it comes in contact with mucous membranes. Once in the presence of sodium ions within mucous membranes, the liquid congeals, providing a practical limitation to the amount of drug that can be administered at one time and, theoretically, deterring abuse.

Regardless of the specific approach, a major challenge in the development of abuse-deterrent formulations is the paucity of methodological approaches to demonstrating scientifically that one formulation of an opioid product is less abusable than another. Scientific evidence will be required to support statements about relative abuse liability in the product label, which in turn is required for marketing and promotion. The development and validation of scientific methods for measuring abuse potential (and actual abuse) will be an important enabling factor in the development of abuse-deterrent products.

Patient Management

Effective patient management is the sine qua non of optimal pharmacologic treatment. Although the specter of opioid abuse, addiction, and diversion, as well as the threat of regulatory scrutiny, can impede the use of opioid analgesics, the clinician can strike a practical balance between opioid risk reduction and optimal pain treatment. The optimal management of pain with the use of opioid analgesics requires that the prescribing clinician coordinate pain treatment with well-considered steps toward identifying risk patient factors and aberrant behaviors. If, in the opinion of the clinician, a safe pattern of opioid use cannot be established for a given patient, nonopioid alternatives should be considered,[61] or patients should be referred to a center experienced in the management of pain and comorbid substance abuse. Indeed, with the proper monitoring, even patients with substance abuse problems can be successfully managed in such settings.[79] Such settings are also useful in managing the tapering off of opioid therapy in patients for whom the risk-benefit balance does not favor continued opioid management.[80] Unfortunately, few such centers exist.

The clinical method alone is inadequate to determine with 100% accuracy which patients are at risk for problematic prescription drug use and which patients are currently diverting or abusing their medications. An undiagnosed substance use disorder, where it exists, will frustrate the assessment and management of any chronic medical condition, including chronic pain. In this context, Gourlay and colleagues[63] have proposed using an infectious disease model to draw a parallel between the chronic pain management paradigm and the experience with problems related to identifying "at risk" patients. These investigators suggest that, for each patient, especially those who might be candidates for opioid therapy, universal precautions for the monitoring and prevention of prescription opioid abuse should apply as universal precautions apply in the infectious disease settings (eg, wearing gloves for all contact with the patient). These precautions include using assessment tools to determine the risk for addictive disorders, using informed consent and treatment agreements, assessing preintervention and

postintervention pain level and patient functioning, employing an appropriate trial of opioid therapy with or without adjuvant medications, and conducting ongoing monitoring of patients for the development of abuse-related problems and other complications of opioid therapy. A convenient mnemonic for patient follow-up is the 4 "A's" of pain medicine—analgesia (degree of pain relief), activities of daily living, adverse effects, and abuse issues.[81] Finally, because the patient's condition may change over time, the patient's pain diagnosis and the presence of comorbid conditions, including addictive disorders, should be periodically reviewed.[63,80]

Based on this information, patients may be triaged into (at least) 3 categories depending on their risk for opioid abuse.[63] The first group comprises most of the patients treated with opioid analgesics who seek relief for chronic, noncancer pain. Most of these patients will not display standard risk factors for opioid abuse or diversion. The second group may have a family history of alcohol or drug abuse or some other evidence suggesting an elevated risk of opioid abuse. Finally, the third group comprises a small percentage of patients who may be active drug abusers. Distinguishing among these patients will help determine the level of attention needed to assess the presence of opioid abuse, the risks associated with opioid therapy for pain, and the level of follow-up needed to diminish the risk of abuse and diversion. It is important to note that unlike many pharmacotherapies, the risks are determined not only by the drug and by the patient, but also by the treatment setting, because high risk patients may do poorly in one setting[58] but well in another.[79]

Prescription Monitoring

Prescription monitoring has emerged as a potentially important tool for addressing prescription drug diversion. Currently, 22 states have prescription monitoring programs, and 3 other states have legislation that will require such programs.[35] Prescription data are collected from dispensers, reviewed and analyzed by state agencies, and reports are provided to authorized end-users. Prescription monitoring programs also can encompass educational initiatives and other programs that foster early intervention and prevention of diversion, as well as investigation and enforcement of abuse. The principal goals of prescription monitoring programs include promoting the early detection of drug diversion; increasing the efficiency of law-enforcement investigations related to illicit drug use; and, through the early identification of invalid complaints, minimizing disruption to practitioners, pharmacists, and patients while, at the same time, protecting practitioner, pharmacist, and patient confidentiality. For many years, prescription monitoring programs have been used by the states to prevent prescription drug abuse, with each state government determining the goals and structure of the prescription monitoring program that best fits its needs.[82] However, there are only anecdotal and survey data supporting the efficacy of these programs, and there are concerns about the "chilling effect" that they may have on the prescribing of pain medications.

Supply Chain Interventions

Supply chain integrity refers to the chain of custody involved in the movement of a drug from the manufacturer to the wholesaler and finally to the retail pharmacy or healthcare facility. The principal problems with the pharmaceutical supply chain in the United States include drug diversion, counterfeiting, shortages, imported drugs of dubious quality, and renegade Internet pharmacies.[83]

The integrity of the supply chain can be compromised at any one of multiple points. A risk of diversion by theft or fraud exists at every level of the chain of distribution of prescription opioids from pharmaceutical manufacturers through licensed wholesalers to licensed pharmacies or healthcare facilities for final distribution to patients who have legitimate prescriptions.[84] Sources of diversion include drug gang distribution, illegal acts by prescribers and pharmacists, doctor shopping, prescription forgery, armed robbery, thefts, and telephone fraud.[85]

Various types of information can be used to identify sources of drug diversion, including law enforcement intelligence, pharmacy theft data, and Medicaid and prescription monitoring programs.[35] For example, the DEA's Automation of Reports and Consolidated Orders System is a comprehensive drug reporting system that monitors the distribution of controlled substances from the manufacturing site through commercial distribution networks to the point of sale or distribution at the dispensing/retail level—retail pharmacies, hospitals, teaching institutions, and practitioners. (Data regarding controlled substances dispensed or administered to patients is not reported to ARCOS.) ARCOS tracks all Schedule I and II controlled substances and narcotic substances listed in Schedule III. This automated system collects, aggregates and summarizes these transactions and generates reports that federal and state authorities can use to identify suspicious orders and diversion of controlled substances.[86]

No reliable statistics exist on the extent of drug diversion.[85] Additionally, few data exist about the extent to which various sources outlined above contribute to overall diversion and abuse.[87] A recent study by Joranson and Gilson[88] found, by aggregating reports of supply chain losses from DEA data obtained through the Freedom of Information Act, that over a 4-year period from 2000 to 2003, nearly 28 million dosage units were diverted through pharmacy robberies. Regardless of the magnitude of diversion, the need exists to identify and use approaches to prevent "leaks" in the supply chain.

Traditional methods employed to monitor and track supply chain activities and transactions include federal administrative requirements related to the procurement and prescribing of Schedule II opioids and restrictions on prescribers related to prescribing narcotics for detoxification purposes. An example of these administrative requirements is DEA Form 222, an official form issued to registrants to be completed with each distribution of a

Schedule I or II controlled substance. The "customer" places an order for a Schedule I or II controlled subject on Form 222, which is preprinted with the customer's name and address. The drug order can be shipped only to that particular customer at the designated address. The customer keeps 1 copy of this triplicate form and sends 2 copies to the supplier, who, after filling the order, forwards the third copy to the nearest DEA office.[89] On April 1, 2005, the DEA published in the Federal Register a final rule permitting the use of digital signature technology to electronically order Schedule I or II controlled substances and maintain electronic records of these orders. This rule responds to industry requests to provide an electronic means to satisfy the legal requirements for a DEA Form 222 for Schedule I and II orders.[90]

Some states mandate other practices to help maintain the integrity of the supply chain, such as:

- Using Electronic Data Transfer, a system that requires dispensing information on a select group of controlled substances be sent to a centralized database accessible by the state board of medical examiners and law enforcement authorities.
- Prohibiting telephone prescriptions for certain scheduled drugs.
- Precluding patients from obtaining narcotics from more than one physician.
- Filling Schedule II opioids within 5 days of the date of prescription issue.[91]
- Limiting the number of dosage units that may be prescribed on a single prescription or over a period of time.
- Requiring prior authorization for certain medications, including scheduled agents, before they are dispensed.[18]
- Upscheduling of drugs.
- Using triplicate or other types of multiple copy prescription forms for select controlled substances.[85]

In addition to the aforementioned methods used to monitor and track supply chain activities and transactions, other approaches can be used to help maintain the integrity of the supply chain, including:

- The DEA's Pharmacy Theft Prevention Program, a collaborative effort involving the pharmaceutical industry, regulatory agencies, and law enforcement. This initiative aims to deter pharmacy thefts through outreach, education, and the organization of networks and alert systems.
- R_xPATROL (Prescription Pattern Analysis Tracking Robberies and Other Losses), an information clearinghouse funded by a pharmaceutical company, designed to prevent pharmacy theft. This program allows pharmacy staff to submit theft information via the Internet, which is reviewed and analyzed by R_xPATROL staff and then forwarded to law enforcement agencies. Based on reported information, R_xPATROL develops profiles of pharmacies vulnerable to theft and strategies for preventing such occurrences.[18]
- DEA's excessive order monitoring system, a program requiring manufacturers and distributors to develop and implement a procedure to disclose to the DEA suspicious orders of controlled substances. Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.

Technology and increased state enforcement activities can also be used to help maintain the integrity of the supply chain, including:

- Radio Frequency Identification (RFID), a technology that uses electronic tags on product packaging to enable manufacturers and distributors to better track drugs as they progress through the supply chain. RFID creates an electronic pedigree, or record of the chain of custody, from the point of manufacturing to the point of dispensing. RFID can allow illicit drug transactions to be rapidly identified. One pharmaceutical manufacturer is reportedly using this technology on packages of one specific dose of an opioid analgesic.[92]
- The Medicaid Abuse Drug Audit System, a computer software program that can be used by the states to review Medicaid prescriptions of controlled substances to track unusual prescribing. The Department of HHS offers Medicaid Abuse Drug Audit System to the states free of charge.[18]
- The Verified-Accredited Wholesale Distributors (VAWD) program, which accredits wholesale distributors of prescription medications and medical devices and helps protect the public from the threat of counterfeit drugs affecting the United States' drug supply. Developed by the National Association of Boards of Pharmacy with the support of the FDA, VAWD is based on the National Association of Boards of Pharmacy's Model Rules for the Licensure of Wholesale Distributors. VAWD accreditation will provide assurances that the distributors will operate legitimately, is validly licensed, and is employing security and best practices for safely distributing and preventing diversion of prescription drugs from manufacturers to pharmacies and other institutions.[93]

Strictly speaking, what happens to an opioid prescription after it is dispensed to a seemingly appropriate patient for a legitimate medical need does not fall under the umbrella of supply chain management. Tools are available to help physicians appropriately prescribe medications and prevent prescription diversion. One such tool is the emPOWER software system, which allows physicians to access their Medicaid patients' prescription history, state prescribing guidelines and interactive screening tools.[18] The bottom line is that prescribers and pharmacists must do everything they possibly can to ensure that the "appropriate" patient receives a prescription for a medically necessary opioid by taking into consideration their knowledge of the patient, his or her medical history, and family, social and occupational environments.

FUTURE DIRECTIONS

Optimal pain treatment necessarily involves the appropriate use of opioid analgesics and the prevention and management of opioid abuse and diversion. In recent

years, considerable progress has been made toward achieving a balance between the benefits and risks of opioid analgesic therapy; yet, much remains to be done. As the appropriate use of opioid therapy has laudably increased, the parallel increased risk for opioid abuse and diversion has been an unwelcome companion that raises regulatory scrutiny and physician and patient fears. Because of the multiplicity of stakeholders at the national, state, and professional society levels with a vested interest in opioid use and abuse, the tenor and direction of future policy and direction remains obscured. Yet, even absent a coherent national strategy or a single organizational entity to oversee national and state opioid drug policy, certain beneficial trends have emerged in recent years: the development of educational initiatives to increase awareness of evidence-based treatment guidelines for chronic pain; FDA initiatives to provide clear and practicable guidelines to the industry for the development of opioid risk management programs; inchoate, but promising, abuse-deterrent opioid delivery systems; efforts on the part of state medical boards to remove unwarranted restrictions on the appropriate use of opioid analgesics; increased vigilance on the part of prescribers to identify and manage patients at risk for opioid abuse; and the beginnings of efforts to develop validated tools to measure abuse liability of specific prescription opioid products and actual levels of abuse. Although these initiatives emanate from a variety of key stakeholders, they represent a growing recognition of the therapeutic importance of opioid analgesia in selected patients and the attendant risks of these medications, critical steps toward a balanced approach to the effective management of chronic pain that should continue into the future.

Disclaimer

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