June 2014

Wolters Kluwer Law & Business White Paper

The Risk of Opioid Abuse, Addiction, and Overdose in Treatment of Chronic Pain—Should States Limit Access to FDA-Approved Opioids?

Inside

By Patricia K. Ruiz, JD and Michelle L. Oxman, JD, LLM
Health Law Writer Analysts

The use of chronic opioid therapy (COT) for the treatment of chronic pain began slowly in the early 1990s and accelerated from there, according to a report by Jane C. Ballantyne published in the Journal of Medical Toxicology. By 1995, a noticeable increase in drug overdose death emerged, and when the coding of opioid analgesics changed in 1999 to separate them from heroin, opioids were found to be largely to blame for the trend. By 2009, 100,000 deaths were attributed to opioid analgesics—15,500 were recorded in 2009 alone. This number accounted for deaths of those who gained possession of prescription drugs through diversion (the drugs are diverted to individuals without prescriptions), as well as those who were using opioids to treat their pain.

The effectiveness of opioids in treating certain kinds of pain is constantly at odds with the risk of addiction and overdose-related death. While many patients receiving opioid treatment for chronic pain attest to the relief provided by opioid medications, others argue that such treatment has not been proven to be safe or effective. Ultimately, it is the responsibility of the physician to identify high risk individuals and behaviors and understand how to choose appropriate drugs and doses for treating pain in patients.

In October 2013, controversy erupted when the FDA approved Zohydro®, an opioid pain reliever containing 10 to 50 milligrams of pure hydrocodone. This dose is up to 10 times the dose contained in previously existing hydrocodone-based drugs, all of which also contain acetaminophen, ibuprofen, or another nonopioid pain reliever. Zohydro is designed for extended release over several hours, but it is easily crushed, allowing a user to effectively convert it to an immediate release drug with a much higher potency. Opponents of approval argued that abuse, addiction, and deaths from overdose were certain to increase dramatically. At the very least, they contended, the FDA should not have approved the drug until it was submitted in a tamper-proof, i.e., abuse-deterring, form.

The FDA's experts, the Advisory Committee on Anesthetics and Analgesics, overwhelmingly recommended disapproval of the drug by a vote of 11-2. The FDA usually follows the Advisory Committee's recommendations, but, in this instance, it did not.

In addition to the concerns about the potential for addiction and overdose, there are several reasons that state officials and medical professionals lacked confidence in the FDA's determination to approve the drug. First, it is unusual for an advisory committee to recommend against a drug. Second, there were questions about whether the agency's decision might have been affected by the access that pharmaceutical companies had to FDA staff.

Wolters Kluwer
Law & Business

Prescription Opioid Drugs

While the term "opioid" applies to illegal drugs like heroin, prescription medications used to treat pain—such as morphine, codeine, methadone, oxycodone, hydrocodone, fentanyl, hydromorphone, and nuprenorphine—also fall under the category of opioids. Opioid analgesics bind to certain receptors in the brain, spinal cord, and gastrointestinal tract, minimizing the body's perception of pain, according to the Substance Abuse and Mental Health Services Administration (SAMHSA) Opioid Overdose Toolkit, a resource for community members, first responders to possible opioid overdose, and prescribers of opioids. Opioid receptors in the brain—or "reward centers"—also are triggered by the drug, affecting systems in the body that regulate mood, breathing, and blood pressure.

Effects of the drug can include drowsiness, mental confusion, nausea, constipation, and, depending on the amount taken, depressed respiration, according to a National Institute on Drug Abuse (NIDA) research report. Users of opioid medications experience a euphoric response and, according to the research report, "[t]hose who abuse opioids may seek to intensify their experience by taking the drug in other ways than prescribed," such as combining the medications with other drugs or alcohol. These actions can put users at risk for medical complications and overdose.

The drug Zohydro has recently come under fire for its hydrocodone-only formulation, which contains up to 10 times the dosage of other products and contains no abuse deterrents. Attorneys General have joined together in an effort to keep the drug off the market, and the FDA's Analgesic and Anesthetic Advisory Committee recommended against the approval of Zohydro. As we previously reported, the danger of addiction and overdose stem from the extended release formulation of the drug, which abusers can easily defeat by removing the powder from the capsule and ingesting it all at once. For patients receiving Zohydro for treatment of their chronic pain, the misunderstanding that the medication can be taken "as-needed for pain" can lead to death.

Levels of Abuse of Opioids and Other Prescription Painkillers

The most recent results of SAMHSA's National Survey on Drug Use and Health show that, in 2012, psychotherapeutics used nonmedically are the most commonly used illicit drugs among persons aged 12 and older, second only to marijuana, with 4.9 million reporting that they used prescription painkillers in the past month. Of the approximately 2.9 million individuals who reported using illicit drugs for the first time within the past 12 months, 17 percent reported having initiated with nonmedical use of prescription pain relievers.

According to the Centers for Disease Control and Prevention (CDC) Policy Impact report, nearly 75 percent of prescription drug overdoses are caused by opioid painkillers, and about 50 percent of prescription painkiller deaths involved at least one other drug, such as benzodiazepines (central nervous system depressants used as sedatives), cocaine, and heroin. A CDC infographic within the report shows that for every one prescription painkiller death, there are 10 treatment admissions for abuse, 32 emergency department visits for misuse or abuse, 130 people who abuse or are dependent, and 825 nonmedical users.

Opioid Abuse and Overdose

Prescription drug abuse comes in many forms, and not all fit the stereotype of a junkie looking to get high. According to NIDA, opioids and other prescription drugs are considered to be abused when "taken for reasons or in ways or amounts not intended by a doctor, or taken by someone other than the person for whom they are prescribed." "Taken as prescribed, opioids can be used to manage pain safety and effectively," the NIDA research report states. "Properly managed, short-term medical use of opioid analgesics rarely causes addiction." According to the CDC, however, a person abusing prescription opioids may become dependent and feel compelled to take larger doses to achieve the same pain-reducing effects, increasing the risk of addiction and fatal overdose.

Dependence and Addiction

Physical dependence is the result of normal adaptations to long-term exposer to a drug and is distinguishable from addiction, for which physical dependence can be a symptom. According to the research report, addiction "is distinguished by compulsive drug seeking and use despite sometimes devastating consequences." Physical dependence can sometimes result in tolerance to the medication, necessitating higher doses of the medication to achieve the same effect. Physicians of patients experiencing tolerance must evaluate whether the patient is developing an addiction or whether higher doses have become a medical necessity.

There have not been any placebo-controlled, long-term randomized clinical trials on the safety of opioids for chronic pain, as patients with a history of addiction or abusive behaviors are excluded from the start, according to Ballantyne. The best evidence may be epidemiologic studies of patients treated with COT, she said, and "[s]ix such studies published since 2010 have found significantly increased risk of over-dose associated with the use of opioids."

Sources of Drugs

An April 2014 research letter by CDC researchers published in the Journal of the American Medical Association (JAMA) Internal Medicine reported that, while most abusers of prescription opioid drugs receive the drugs for free from a friend or relative, the highest risk abusers—or those who use prescription opioids nonmedically, 200 times or more per year—are just as likely to obtain the drugs through a prescription from their own doctors.

A study titled "High-Risk Use by Patients Prescribed Opioids for Pain and Its Role in Overdoes Deaths," also published in JAMA Internal Medicine, noted a doubling in drug overdose deaths between 2003 and 2010, most of which involved prescription opioids than heroin and cocaine combined. The study also found a strong link between opioid analgesic-related overdose deaths and the prescription of high dosages of opioids, equivalent to more than 100 milligrams of morphine per day. Many of the deaths due to opioid overdose occurred in individuals who obtained the drugs from multiple prescribers and pharmacies.

Limited Effectiveness in Treatment of Chronic Pain

Approximately 90 percent of patients who receive treatment at pain centers are prescribed opioids, according to a review of literature published in the journal Pain Physician titled "Effectiveness of Long-Term Opioid Therapy for Chronic Non-Cancer Pain," by Laxmaiah Manchikanti and other researchers. Despite the high prescription rates, there is "sparse evidence on long-term opioid effectiveness in chronic pain patients due to the short-term timeframe of clinical trials, insufficiently comprehensive outcome assessments, and incomplete identification and quantification of adverse drug reactions." While some believe that physicians should continue to prescribe opioid painkillers "because they are indispensable for the treatment of pain and suffering," the medical community also recognizes the many side effects of opioid use, including drug abuse and addiction.

The review noted that, in Denmark, where opioids are free-flowing, "the results showed worse pain, higher health care utilization and lower activity levels" in patients treated with opioid medications, compared to chronic pain patients not using opioids. "This provides prima facie evidence that when opioids are prescribed liberally, even if a small number of patients benefit, the overall population does not."

The highest risk abusers—or those who use prescription opioids nonmedically, 200 times or more per year—are just as likely to obtain the drugs through a prescription from their own doctors.

Short- and Long-Term Effectiveness

Manchikanti, *et al*, undertook an analysis of systematic reviews, randomized trials, observational studies, and guidelines regarding the analgesic efficacy of opioids for the treatment of chronic pain conditions. For a range of one to 16 weeks, the review of literature found that opioids were more effective than placebo for pain and functional outcomes in patients suffering from nociceptive or neuropathic pain or fibromyalgia. Short term efficacy for neuropathic and musculoskeletal pain was also good, but significant abuse, addiction, and aberrant behaviors also resulted. For an intermediate term of 8 to 70 days, the trials showed substantial efficacy over placebo.

While "long-term opioid therapy is associated with some degree of pain relief," Manchikanti, *et al,* found that the evidence regarding the effectiveness of long-term treatment with opioids—16 weeks or more—was unclear, as approximately 56 percent of patients in

randomized clinical trials (RTCs) drop out because of lack of efficacy or side effects. The researchers suggested that less vigorous forms of evidence are needed to evaluate such effectiveness, "since it is not feasible to conduct RCTs over prolonged periods."

Despite inadequate evidence of effectiveness, the trials showed that an increase in dosages used to overcome opioid tolerance resulted in no change of worsening of pain in some patients, with improvement of pain emerging when opioid treatment is discontinued. This "shows that the premise that tolerance can always be overcome by dose escalation is unrealistic," according to the researchers.

Responsible Prescribing

According to a guide by the Physicians for Responsible Opioid Prescribing (PROP), "[w]hile COT at lower doses may be a useful treatment for some patients, it should only be considered for carefully evaluated, closely monitored patients when a cautious, structured and selective approach is employed, and clear benefits for pain and function are documented."

Before Prescribing Opioids

According to PROP, long-term use of opioids should not be started by accident, but only after the patient has been evaluated carefully and the doctor has discussed risks, realistic expectations, and rules for safe use with the patient. It is imperative that physicians consider safer alternatives, such as primary disease management, cognitive-behavioral therapy, physical therapy, nonopioid analgesics, and exercise. PROP also stresses the importance of performing a medical evaluation, a psychiatric screening, and a urine drug screening before beginning a COT program, especially considering that patients are hesitant to disclose a history of drug abuse. Further, PROP discourages the prescription of extended-release opioids, such as Zohydro, for acute pain or to patients who have never taken opioids previously.

Continually Ensuring Safe Use

PROP recommends that physicians explain to patients receiving their first opioid prescription that opioid treatment will only be used for a limited period of time, setting the expectation that the medication should be discontinued when the pain is no longer acute. It also discourages the routine authorization of refills, which "may cause patients to expect the prescription to continue indefinitely." During the course of treatment, the physician should perform random urine drug screens to determine if illicit drugs are being used or if the patients are not taking the medication as prescribed. Physicians should not assume that patients will use the opioids as prescribed, as patients may vary their dosages or combine the medication with drugs the physicians do not know about.

Physicians should use careful evaluation to determine if patients are experiencing pain relief and improved function when considering continuing with COT, and physicians should end COT for patients who are not showing progress. Finally, PROP stresses that physicians should not abandon patients who show signs of a prescription drug problem and should offer guidance or a referral for the treatment of substance abuse.

Concerns About the Agency's Process Approving Zohydro

In October 2013, the *Washington Post* and the *Milwaukee Journal Sentinel* reported that manufacturers of pain medications paid for access to FDA officials. The original sponsors of Zohydro were among the manufacturers that paid tens of thousands of dollars for the privilege of attending private meetings attended by FDA staff to discuss government policy on the design of clinical trials of pain medications. Academics and staff of other federal agencies, such as the National Institutes of Health (NIH), also attended the conferences. The meetings were held by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT), which was organized by professors Robert Dworkin of the University of Rochester and Dennis Turk of the University of Washington medical schools, respectively

A public records request to the University of Washington resulted in the release of hundreds of emails between Dworkin, Turk, and others organizing IMMPACT, dating back as far as 2002. The *Washington Post* article quoted an email from Dworkin to Turk from July 2003, discussing drug company objections to the $20,000 fee:

"$20k is small change, and they can justify it easily if they want to be at the table. …[T]hey are getting a huge amount for very little money (impact on FDA thinking, exposure to FDA thinking, exposure to academic opinion leaders and their expertise, journal article authorship, etc.) and they know it."

The *Washington Post* article also reported that an official from the NIH was concerned that the private meetings at expensive hotels paid for by drug companies

created an appearance of "pay to play." He suggested that the meeting be held on the NIH campus and opened to the public. According to the Post, Dworkin responded, "It is difficult to imagine how an open meeting would develop consensus recommendations."

One policy change that resulted from the meetings was the FDA's decision to accept clinical trials using "enriched enrollment." Conventional clinical trials are double-blinded, *i.e.*, subjects are randomly assigned to the drug being tested or a control drug, usually a placebo, and neither the subject nor the investigator knows whether a particular patient is receiving the drug being tested or a placebo. In enriched enrollment, all subjects receive the drug, and the results of subjects who have unacceptable side effects, or who, for other reasons, do not comply consistently or stop taking the drug may not be retained or reported. Critics of this method believe that it makes the tested drug appear more effective and/or safer than it actually is and that it does not accurately represent the population of patients with the disease being treated. At least one study comparing enriched enrollment random withdrawal (EERW) studies to conventional studies found that the EERW underreported clinically relevant side effects, including nausea, vomiting, somnolence, dizziness, and itching.

Learning from OxyContin®

Past experience with OxyContin also was cause for concern. The sponsors represented the drug to the FDA and the public as presenting little risk of abuse. In fact, it was quite addictive, and abusers found ways to defeat the extended-release action and ingest or inject the entire dose as immediate release. Deadly overdoses resulted. Eventually, the sponsor, Purdue Pharma, withdrew the original formulation from the market. In April 2013, the FDA issued a determination that the original formulation of OxyContin was withdrawn from the market for reasons of safety or effectiveness. Because of that determination, the FDA will not consider abbreviated new drug applications (ANDAs). No generic version of original OxyContin will be permitted.

The Advisory Committee Discussions

The Anesthetic and Analgesic Advisory Committee met to discuss Zohydro in December 2012. The transcript shows that the committee members were concerned not only about this drug but the treatment of all opioids. Although the members brought different perspectives to bear and perhaps ranked some priorities differently, they were in agreement on several points:

- Hydrocodone combination products (HCPs) were already abused more frequently than other prescription drugs.
- One reason that HCPs are abused so often was their status as Schedule III drugs rather than Schedule II. Schedule III status allows practitioners to prescribe and pharmacists to dispense a drug based on a telephone call and to authorize refills without an additional prescription.
- Because Zohydro as proposed was easy to crush and inhale or inject, people would abuse it, which would result in addiction, overdoses, and deaths.
- Although Zohydro would be a Class II drug because it consists solely of hydrocodone, there was a risk that consumers would think that it would be safer than other opioids because the HCPs were listed as Schedule III.
- All opioids should be subject to similar restrictions, such as abuse deterrence, restrictions on prescribing, and/or monitoring through the prescription drug monitoring programs.

Hydrocodone combination products (HCPs) were already abused more frequently than other prescription drugs.

Many of the participants expressed concern that the Risk Evaluation and Mitigation Strategy (REMS) for extended release or long-acting opioids that the FDA had recently adopted would not be adequate to protect consumers. The REMS for ER/LA opioids was only a few months old, and the educational materials had not been released yet, so there was no way to know whether it would be effective. They repeatedly referred to the need to change policy and practice in light of the experience with OxyContin.

The FDA's Risk Evaluation and Mitigation Strategy

On July 9, 2012, the FDA announced the adoption of a REMS for extended-release (ER) and long-acting (LA) opioids. The REMS requires manufacturers to offer prescribers continuing education (CE) on the risks of ER and LA opioids, how to assess the appropriateness of the drugs for particular patients and counsel patients for whom they are prescribed. The manufacturers must pay for the programs, but the subject matter and key concepts would be defined by the FDA and taught by accredited CE providers. The FDA made the blueprint available in April 2013. It also included a template for the Medication Guide to be distributed to consumers when the drug is dispensed.

The FDA described the prescriber education component as the key feature of the program. The agency's records indicate that there were 320,000 practitioners who prescribed ER and LA opioids in 2011. Manufacturers are expected to educate 25 percent of the practitioners, 80,000, within one year of the release of the blueprint, 50 percent within two years, and 60 percent within four years from the date that the blueprint became available. The REMS does not appear to address the entry of new prescribers into the professions, nor is there any stated expectation that more than 60 percent of prescribers undergo the training.

Prescribers are not required to undergo training, however. The FDA did not impose the requirement because it would have to duplicate the registration system that the Drug Enforcement Administration (DEA) already has in place.

Terms of FDA Approval

In the initial application for approval of Zohydro, Zogenix stated the proposed indication was for treatment of "moderate to severe chronic pain when a continuous, round-the-clock opioid analgesic is needed for an extended period of time." The indication finally approved was "for management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatment options are inadequate." The FDA required several post-market approval studies to address:

- Quantitative estimates of the risks of abuse, misuse, addiction, overdose, and death from long-term use of opioid analgesics. Including the ratio of risk to efficacy.
- Development and validation of measures of adverse events, *i.e.*, misuse, abuse, addiction, overdose and death, and of the clinical terminology for them.
- At least one clinical trial to assess the risk of hyperalgesia, or abnormal sensitivity to pain, in patients who use extended release opioids over a long period of time.
- Completion of a trial to assess the possible toxic effects of hydrocodone on genes
- Two-year studies of mice and rats to assess the cancer-causing potential of hydrocodone; upon completion of the data gathering in January 2014, Zogenix was given 18 months to submit its final report.

The FDA also required Zogenix to comply with the REMS for long-acting opioids, including preparation of a Zohydro-specific Medication Guide with detailed warnings for both practitioners and patients and the financial support for prescriber education required of the manufacturers of all LA/ER opioids under the REMS

At the meeting of the FDA Advisory Panel, Zogenix representatives told the FDA's Advisory Panel that the company would: (1) target its marketing to professionals who treat the small percentage of chronic pain patients for whom Zohydro was intended; and (2) structure its compensation of sales representatives with incentive payments for enrolling prescribers in the REMS education programs rather than sales volume. However, the FDA approval did not require Zogenix to keep either of these commitments.

On the same day that it approved Zohydro, the FDA denied a petition by the Center for Lawful Access and Abuse Deterrence (CLAAD) and other advocacy organizations to deny approval of new drug applications (NDA) and abbreviated new drug applications (ANDAs) for opioid products in solid oral dosage forms unless they are backed by predictive or determinative data concerning their potential to reduce abuse, except when there is a shortage of drugs or an unmet public health need. The agency did not believe that abuse-deterrent features had been proven effective enough to justify requiring them.

Response of State Officials and Congress

As we reported on April 16, 2014, there was widespread alarm at the FDA's actions. In addition to the response of health care providers and people concerned with drug

abuse, in December 2013, 28 state Attorneys General signed a letter asking FDA Commissioner Margaret Hamburg to reconsider the approval. In April, the Attorneys General of Florida, Georgia, Illinois, Indiana, Kentucky, and Maine sent a joint letter to HHS Secretary Kathleen Sebelius asking her to "exercise leadership" to keep the drug off the market until abuse-deterrent technologies have been incorporated. The Ohio Board of Medicine also wrote to the White House Office of Drug Control Policy asking that access to Zohydro be restricted until an abuse-deterrent formulation was developed.

Senators Joe Manchin (D) of West Virginia and David Vitter (R) of Louisiana called for an investigation of the relationship between the FDA's approval of Zohydro and the private meetings between FDA staff and industry discussed above. They also wrote to the Dean of the University of Rochester School of Medicine and Dentistry asking for details of the meetings and the payments and transfers received. Legislation has been introduced in both the House of Representatives and the Senate to reverse the approval until an abuse-deterrent formulation has been approved.

States' Options to Restrict Access

Massachusetts

Governor Deval Patrick of Massachusetts went even further. On March 27, 2014, he declared a public health emergency and announced a complete ban on prescriptions and dispensation of hydrocodone-only opioids that lacked any abuse-deterrent features. The Department of Public Health issued an emergency order implementing the ban. Within days, Zogenix sued in federal court. On April 15, 2014, the court ruled that Governor Patrick's action was invalid under the Supremacy Clause of the United States Constitution, which states that the constitution and federal laws are the supreme law of the land. When federal law and state law conflict, the federal law preempts state law. Because Congress gave the FDA the power to approve drugs, the state had no power to ban FDA-approved drugs outright. The court stayed its order for seven days. Massachusetts will not appeal the ruling, according to David Kibbe from the Department of Public Health.

On April 22, 2014, the date that the stay expired, Governor Patrick's administration announced new restrictions on providers' activities with respect to hydrocodone-only extended release drugs. The Board of Medicine issued emergency rules requiring physicians who wish to prescribe extended-release hydrocodone without abuse-deterrent features to:

- Thoroughly assess the patient, including risk factors, history of substance abuse, current condition, and current medications;
- Check the online prescription drug monitoring program (PDMP) database;
- Discuss the risks and benefits of the medication with the patient;
- Have the patient sign a Pain Management Agreement (PMA) that addresses pill counts, safe storage and disposal, drug screening, and other matters related to the patient's diagnosis and treatment plan;
- Issue a Letter of Medical Necessity as required by the Board of Pharmacy, stating that other treatment options have failed and describing the patient's diagnosis, treatment plan, and PMA; and
- Document compliance with all these requirements in the patient's medical record.

28 state Attorneys General signed a letter asking FDA Commissioner Margaret Hamburg to reconsider the approval.

The Commissioner of Public Health, Cheryl Bartlett, issued an emergency order that requires all prescribers to check the PDMP database before issuing each prescription for extended-release hydrocodone without abuse-deterrent features. The emergency order requires the prescriber to use a validated tool to screen the patient for substance abuse as part of the risk assessment. According to the Commissioner's guidance, because state law limits prescriptions for Schedule II and Schedule III drugs to a 30-day supply, prescribers must check the PDMP data base every 30 days for patients on maintenance, *i.e.*, continuing, therapy with the drug. Only prescribers registered with the PDMP have access to the database, so the effect of the rule is that only prescribers registered with the PDMP may lawfully prescribe the drug. Nurse practitioners and physician assistants, who have prescribing authority in the state, are encouraged to register.

Vermont

In Vermont, most of the legal restrictions on hydrocodone are part of a comprehensive system regulating access to opioids and amphetamines. Act No. 75, enacted June 5, 2013, requires all prescribers and dispensers to participate in the state's prescription monitoring system, which records transactions concerning drugs in Schedule II, III or IV. Prescribers must check the database concerning an individual patient:

- The first time they prescribe an opioid under Schedule II, III, or IV to treat the individual's chronic pain;
- When starting a patient on a Schedule II, III or IV controlled substance "for nonpalliative long-term therapy of 90 days or more;"
- Before writing a replacement prescription; and
- At least once per year for patients in ongoing treatment.

In addition, the licensing boards that govern the prescribing professions must issue evidence-based guidelines for prescribing and determining whether prescribers should be required to check the data base on patients in other situations, such as the request for a prescription for relief of acute pain. Dispensers must notify the PMS at least every seven days of any Schedule II, III or IV drugs they dispense.

But Vermont also issued an emergency rule specific to extended-release hydrocodone without an abuse-deterrent formulation. The prescriber must perform a physical examination, use a recognized tool, such as the Screener and Opioid Assessment for Patients with Pain (SOAPP), to perform an assessment of the patient's risk of substance abuse, must require the patient to sign an agreement that addresses the rights, responsibilities, and risks of treatment with controlled substances, document that the particular medication is necessary to manage pain that cannot be controlled with other available treatments, and check the PDMP database. The prescription must be good for seven days and may not provide for more than a 30-day supply.

Other States

A Pennsylvania state representative has tried to take the same actions as Massachusetts through legislation. Initially, Rep. Gene DiGirolamo (R-18th) introduced a bill to declare Zohydro a Class I controlled substance. On May 6, 2014, he amended his proposed legislation to require prescribers who wish to prescribe Zohydro to: (1) perform a comprehensive assessment; (2) enter into a prescription drug monitoring agreement with the patient on terms similar to the Massachusetts and Vermont agreements; (3) query the Pennsylvania prescription accountability monitoring system; (4) document that the single-entity hydrocodone without an abuse-deterrent formulation is medically necessary for management of the patient's pain, and nothing else will manage the pain effectively; and (5) schedule regular follow-ups, all as a condition of maintaining a professional license.

Mark S. Armstrong, a member of Epstein Becker Green who represents providers, practitioners, managed care organizations, and other participants in the pharmaceutical industry, says that states cannot regulate opioids or other dangerous drugs directly, but they can regulate the actions of practitioners and providers. For example, they can require that prescriptions be in writing, limit the supply that may dispensed, or prohibit phone-in and fax prescriptions. They also can require prescribers and pharmacists to register with state prescription drug monitoring systems and to report to and check with those programs.

Are these efforts effective? "It's too early to tell," Armstrong says. "States may place reasonable restrictions on physicians" who prescribe controlled substances, but the use of this form of regulation to limit access to specific opioids is new. Only a few states require prescribers or dispensers to follow an assessment protocol or check a prescription drug monitoring database before prescribing drugs that are commonly abused.

Prescription Drug Monitoring Programs

Prescription drug monitoring programs (PDMP) involve the following: (1) reporting of dispensing of controlled substances; (2) identification of patients; and (3) identification of prescribers. They may be used to identify patients who "doctor shop" to obtain prescriptions from multiple providers and to identify practitioners with aberrant patterns of prescribing, which may indicate operation of a "pill mill."

They vary widely on several key features:

- whether prescribers or dispensers must enroll;
- whether reporting is mandatory;
- how often reports are made or collected;
- whether a prescriber or dispenser must check the data base before writing a prescription or dispensing the drug;

- whether the prescriber, dispenser, or other entity with access may use a delegate to access or report information; and
- which agencies or entities have access to the information.

According to the National Alliance for Model State Drug Laws (NAMDL), as of March 2014, 49 states and the District of Columbia (DC) had passed legislation to create a PDMP; Missouri had yet to do so. The programs were not yet operational in New Hampshire and DC.

In order to use their PDMPs effectively to detect or deter diversion of opioids from medical to nonmedical uses and prevent patients from becoming addicts or victims of overdose, states would have to require reporting every time the specified drugs are dispensed and require checking before a practitioner writes a prescription. In addition, the data must be timely and complete enough to make checking the database worthwhile.

Nineteen states require at least some practitioners to access the PMDP database at least in certain instances, but, according to the NAMDL, 17 states explicitly do not require prescribers to check the database. Physicians tend to resist efforts to require them to check the database. Some argue that doing so adds administrative burden and cost that will prompt physicians not to prescribe opioids for patients who need them.

The vast majority of states (31) require dispensers to report within seven days. As of July 1, 2014, eight states will require reporting within 24 hours, and one, Oklahoma, requires reporting in "real time."

Proponents of greater state control over access to opioids contend that PDMP databases should be available to practitioners in other states, particularly in areas where a major metropolitan area comprises more than one state. However, there are few, if any, such arrangements.

Use of Professional Standards to Regulate Prescriptions and Dispensation of Drugs

The other major tool available to states is the regulation of prescribers, pharmacists, and facilities. State Boards of Medicine may set standards for the examination and assessment of patients before a physician writes a prescription for opioids. One example is the detailed sequence of steps that Vermont has imposed on physicians who prescribe extended-release, single entity hydrocodone without an abuse-deterrent formulation, discussed above. States also may require adherence to a published policy, either through legislation, regulation, or professional standard setting. Such policies may require the physician to try other methods of pain control before prescribing opioids, limit the supply that emergency rooms may order or prescribe, or require specific written agreements from patients that call for drug testing, pill counts, or other controls.

In order to use their PDMPs effectively to detect or deter diversion of opioids from medical to nonmedical uses and prevent patients from becoming addicts or victims of overdose, states would have to require reporting every time the specified drugs are dispensed and require checking before a practitioner writes a prescription.

Several states specifically regulate pain management clinics in addition to regulating prescribers and pharmacists. Regulations include restrictions on and qualifications for the ownership and operation of the clinic, hours at which professional staff must be present, and requirements for locked storage of controlled substances. State laws may prohibit the operation of pharmacies or substance abuse treatment centers on the same premises as the pain clinic. Physicians and employees may be required to undergo continuing professional training on substance abuse and/or pain management.

Conclusion

Opioid analgesics can provide much-needed relief for acute pain and, despite a lack of supporting evidence,

patients and physicians alike continue to attest to the effectiveness of opioids in treating chronic noncancer pain. Because of the rising number of deaths associated with opioid abuse and overdose, physicians play a large role in weighing the risk faced by patients who turn to opioids for pain relief—and for physicians who do choose to treat their patients with opioids, careful evaluation and ongoing vigilance is the key.

Once the FDA has approved a drug, state attempts to ban it outright will fail, no matter how well reasoned. But the problem of opioid addiction, overdose, and death extends beyond any one drug. States can use their power to regulate health professionals and health care facilities to require adherence to reasonable standards. There is ample support for the existence of standards that would require prescribers to perform a careful assessment of the particular patient and to check a prescription drug monitoring database upon meeting a new patient who requests pain relief, beginning a new course of treatment, or the expiration of a specified time period, to be sure that the patient has not been "doctor shopping." These methods will address the problems presented by opioids or controlled substances in general.