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POLICY FORUM
OxyContin, the FDA, and Drug Control
Gary M. Reisfield, MD

"One percent of people will always be honest and never steal," the locksmith said. "Another one percent will always be dishonest and always try to pick your lock and steal your television. And the rest will be honest as long as the conditions are right—but if they are tempted enough, they'll be dishonest too. Locks won't protect you from the thieves, who can get in your house if they really want to. They will only protect you from the mostly honest people who might be tempted to try your door if it had no lock."
—*Dan Ariely*, The Honest Truth About Dishonesty: How We Lie to Everyone—Especially Ourselves

In 2010, 16,651 Americans died from prescription opioid overdoses [1]. For each death there were 15 drug-treatment center admissions, 26 prescription opioid-related emergency room visits, 115 people who met criteria for prescription opioid abuse or addiction, and 733 people who used these medications nonmedically (that is, for the feeling that the drug provided) [2].

Access to prescription opioids—and the morbidity and mortality associated with their abuse—are not limited to the patients for whom they are prescribed. Indeed, according to the National Survey on Drug Use and Health, of the more than 12 million Americans who used prescription opioids nonmedically in 2010, 54 percent of respondents had most recently obtained their opioids from a friend or relative for free, and 17 percent had bought or stolen them from a friend or relative. Of note, 85 percent of respondents who obtained their opioids from a friend or relative for free indicated that the opioid originated from one or more physicians' prescriptions [3].

Normally, the FDA grants brand-name drugs five years of market exclusivity before allowing generic versions to be sold. The United States Food and Drug Administration (FDA) made the unusual decision to withdraw its approval for generic versions of OxyContin after a new, abuse-resistant formulation, OxyContin OP, was patented and approved. Critics have argued that efforts to create abuse-resistant opioids and restrict access to easily abused formulations place the interests of public health or law enforcement over the financial or clinical interests of patients with chronic pain (for whom the cost of a branded abuse-resistant formulation may be a barrier to appropriate opioid therapy) [4]. From a clinical perspective, the border between patients' interests and public health is an invisible one. The FDA's decision

is a reasonable, incremental step toward making long-term opioid therapy safer for everyone.

The Role of Tamper-Resistant and Abuse-Deterrent Opioids

The epigraph to this article is an apt metaphor for why "locks," that is, abuse-deterrent features on potent, controlled-release opioids, have a potentially important role in mitigating the harms associated with this indispensible class of analgesics. Some of our patients who are prescribed opioids always use their medications as prescribed, always keep them stored in a safe place, and never give away, trade, or sell them. For these patients, locks on opioids are unnecessary. Some of our patients are addicted to opioids and will do whatever is necessary to get them. For these patients, locks on opioids will not deter them: they will attempt to subvert ("pick the lock" on) the abuse-deterrent features of the opioid; they will insist on receiving "unlocked" (non-abuse-deterrent) opioids; or they will seek out other sources of opioids that can be smoked, snorted, or injected.

The remainder of our patients comprise a vast and heterogeneous middle ground. Some abuse prescription opioids by a variety of means and out of a variety of motivations, including boredom, curiosity, impulsivity, or the desire to get high. Some well-intentioned patients give opioids to friends or family members. Many, because of unsafe households or neighborhoods, are at risk of having their medications stolen. A small percentage criminally diverts some or all of their opioids—for cash, sex, or other drugs. It is for all of these patients—and for their families and friends and others who gain access to their medications—that abuse-deterrent opioids can play a role in mitigating the harms associated with these drugs.

Physicians would like to believe that every patient for whom they prescribe opioids is a patient who has a medical need for opioid pain relief. But things are not nearly so simple. There are no laboratory tests or imaging studies that prove the presence of pain. Nor are there such tests or studies to diagnose abuse or addiction. It is nearly impossible to detect the 84-year-old patient who sells part of his opioid prescription to a neighborhood drug dealer in order to pay his utility bill, or the 78-year-old patient whose grandson makes an interesting find in her medicine cabinet. Complicating the picture further, chronic pain, substance use disorders, and diversion can, and often do, coexist in the same patient.

Knowledgeable and conscientious physicians screen for substance use disorders and assess for risk factors associated with the future development of opioid-related problems. They tailor their pain treatments to the risk posed by each patient. If they prescribe opioid therapy, they monitor for problems by speaking with their patients about the effects of these medications on their pain and on their lives, by querying state prescription drug monitoring databases for evidence of "doctor shopping," and by performing random drug testing.

Yet, each of these measures is imperfect. Every patient poses some finite degree of opioid-related risk. And every physician who prescribes opioid analgesics, no matter

how experienced, sometimes gets fooled. At the end of each office visit, the physician sends her patient out into the world with an opioid prescription and little knowledge of what will become of it. Thus, from a clinical perspective, the division between the welfare of the patient and the welfare of the public is nebulous.

OxyContin and the Role of the FDA in Mitigating the Abuse of Controlled-Release Opioids

Oxycodone—particularly in the original controlled-release formulation OxyContin—holds a place of ignominy in the current prescription opioid epidemic. First marketed in the US in 1996, it was the most abused prescription opioid in the country within a decade [5]. In Florida—the epicenter of the problem—prescription drug overdoses increased by 84 percent from 2003 to 2009. During this period, the greatest increase in death rate was observed for oxycodone (265 percent), followed distantly by methadone (79 percent), hydrocodone (35 percent), and morphine (26 percent) [6].

The original OxyContin was reformulated with abuse-deterrent properties in 2010 [7], and there is evidence that it has reduced the abuse of the drug. For example, according to the National Poison Data System, in the two years following its reformulation, poison center reports for OxyContin-related intentional events (i.e., abuse, suspected suicide, and misuse) and unintentional events (i.e. misuse, general, and therapeutic errors) each declined by 25 percent. In contrast, reports for each of these events increased for other single-entity oxycodone products [8]. On the basis of data such as this, the FDA approved abuse-deterrent labeling for the reformulated OxyContin—the only C-II opioid ever to receive such approval. The agency also determined that the risk-benefit ratio of the original OxyContin tilted in favor of risk, and announced that it would not accept applications for generic versions of the original OxyContin [7]. Thus, generic competitors to OxyContin are likely years away [9].

The suggestion that the FDA's decision, which is likely to keep the costs of controlled-release oxycodone high, will limit access to opioids for some patients who do not abuse the drug may be legitimate, but it is not compelling. We are awash in prescription opioids. Comprising less than 5 percent of the world's population, the US now consumes more than 99 percent of the world's hydrocodone, 82 percent of its oxycodone, 59 percent of its morphine, 53 percent of its methadone, 52 percent of its hydromorphone, and 48 percent of its fentanyl [10].

Moreover, OxyContin is only one of several controlled-release or long-acting opioids available on the US market. The group comprises buprenorphine (Butrans), fentanyl (Duragesic and generic), hydromorphone (Exalgo), morphine (Avinza, Kadian, MSContin, and generic), oxymorphone (Opana ER), and methadone (Dolophine and generic). The FDA has approved an eighth controlled-release opioid, hydrocodone (Zohydro ER), which will probably reach the market in the first half of 2014. Moreover, immediate-release oxycodone is available in combination with acetaminophen (e.g., Percocet, Tylox, and generic), aspirin (Percodan and generic),

and ibuprofen (Combunox and generic), and as a single entity (Roxicodone and generic).

The FDA has taken other steps to mitigate the harms associated with controlled-release opioids. First, they recently adopted the Risk Evaluation and Mitigation Strategy (REMS) for these medications [11], which requires drug companies to provide physicians with educational materials on the safe prescribing of these drugs. Second, they have mandated labeling changes to these opioids that address correct prescribing, risks, and alternatives [12]. Third, they now require drug companies to conduct longer-term and more comprehensive post-marketing studies to assess the long-term risks associated with the use of this class of medications [12].

Conclusions

The US is at once in the midst of a prescription opioid epidemic [13] and a chronic pain crisis [14]. The FDA plays a vital role in ensuring appropriate access to the most powerful analgesics while helping to mitigate the harms associated with their abuse.

The development of abuse-deterrent formulations of controlled-release opioids has been described by the FDA as an agency priority [7]. For pharmaceutical manufacturers, the process of designing and producing these opioid formulations can take years and involves enormous expense, all without any guarantee of success. Purdue Pharma, the manufacturer of OxyContin, seems to have produced a success, and the FDA's decision to not accept abbreviated new drug applications for generics based on the original OxyContin formula appears to have rewarded Purdue's effort. Perhaps the OxyContin decision will serve as an incentive for other opioid manufacturers to pursue abuse-deterrent features for their most powerful opioids.

Ideally, all controlled-release opioids would have abuse-deterrent features. It would not solve the problem of prescription opioid abuse, but it would be an incremental step toward the goal of providing safer long-term opioid therapy in an unsafe world.

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Gary M. Reisfield, MD, is an assistant professor and director of pain management services in the Department of Psychiatry at University of Florida College of Medicine in Gainesville. He practices pain medicine and addiction medicine, and his research interests include long-term opioid therapy, drug-related impairment, and drug testing.

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