Drugmaker Purdue Pharma forever changed the landscape of pain treatment in 1996 with the release of a pinky-nail-sized pill etched with the letters “OC.” These small-but-mighty pills contained a larger dose of oxycodone, a semisynthetic opioid, than any that had come before. But they were also packed with ingredients that would prevent that whole dose from releasing immediately. Instead, the pills set the oxycodone free over approximately 12 hours in a person’s gut, extending pain relief. Patients taking these pills, dubbed OxyContin, had a less than 1% chance of becoming addicted, Purdue claimed.

“What they didn’t count on was how quickly people learned to bypass the pills’ extended-release mechanism,” says Matthew Ellis, a psychiatric epidemiologist at Washington University in St. Louis. Chewing and then swallowing the pills gave users a high, and for an even bigger jolt, they crushed the pills into a powder and then snorted it or dissolved the pills and injected the resulting solution. These routes were a speedier way for oxycodone to get to the brain, putting people at an even higher risk of overdose and addiction.

Propelled by aggressive advertising—“Swing in the right direction with OxyContin,” read the cover of a promotional CD, given to doctors along with fishing hats and plush toys—sales soared from half a million to $1.1 billion in the first few years after the drug’s launch. By 2004, it had become a leading drug of abuse in the U.S. Three years later, several Purdue executives pleaded guilty to misbranding the drug as having a low risk of addiction, abuse, and withdrawal and, along with the company, were fined $634 million.

Extended-release opioids and the push to prescribe opioids for chronic pain were major drivers of the current epidemic, Ellis says.

To help curb the crisis, in the early 2000s Purdue Pharma and other drugmakers began formulating opioid pills that were harder to misuse. Coated or infused with proprietary polymers or pellets, these abuse-deterrent formulations are difficult to snort or inject. Some formulations contain ingredients that make pills hard to crush or dissolve, and others release gooey or euphoria-blocking substances when cracked open. People can still get high by swallowing more pills, but as with regular extended-release pills, the rush they get is less immediate.

Today, abuse-deterrent pills represent only about 2% of all opioid prescriptions, according to Purdue Pharma. All of these are extended-release formulations.

So far, five abuse-deterrent opioids are commercially available, and several more, having received U.S. Food & Drug Administration approval, are set to hit the market soon, including the first immediate-release version. As part of its response plan for the opioid crisis, FDA has committed to expanding access to abuse-deterrent formulations. Local governments are embracing them as well.

Legislation in Massachusetts, Maine, Maryland, Florida, and West Virginia makes the prescription of abuse-deterrent opioids over non-abuse-deterrent formulations mandatory whenever possible, and 20 more states hope to follow suit.

Yet sparse evidence exists to show tamper-resistant opioids discourage misuse. According to a recent report by the nonprofit Institute for Clinical & Economic Review (ICER), to date, only one abuse-deterrent opioid on the market has been extensively studied. That
pills fighting the overall opioid crisis ahead of individuals who benefit from these products.

FDA declined C&EN’s request to elaborate on the decision, referring instead to a 2013 press release that supports Purdue’s claim that the older version of the opioid was removed from the market because it was less safe.

Unforeseen effects

That hard shift to abuse-deterrent OxyContin on Aug. 9, 2010, gave researchers a clear starting point for studying whether tamper-resistant formulations could attenuate opioid misuse. According to the ICER report, in the three years after OxyContin’s reformulation, the total rate of opioid overdose decreased significantly, somewhere between 34 and 65%—a wide range because data on opioid overdose and misuse are difficult to track and come from a variety of sources.

Another study of abuse-deterrent formulations, led by Marc Larochelle, an internist and researcher at Boston Medical Center’s Grayken Center for Addiction, looked at whether rates of opioid prescriptions and overdoses were lower than would have been predicted if the drug had not been reformulated (JAMA Intern. Med. 2015, DOI: 10.1001/jamainternmed.2015.0914). Larochelle says evaluating the impact of OxyContin’s reformulation was particularly challenging because other efforts to address the opioid crisis—for example, better prescription monitoring and the shutting down of “pill mills,” operations where drugs were prescribed inappropriately for profit—were happening at the same time. The “biggest threat to the validity” of the study, he says, was the withdrawal from the market of the opioid propoxyphene shortly after OxyContin’s hard switch. Propoxyphene was used by more than 10 million people in the year before it was removed by FDA after data suggested that it caused serious cardiac toxicity.

A few notable trends emerged from Larochelle’s study. One was that the rate of OxyContin being dispensed fell by 39% two years after its reformulation. Because the team didn’t find much of a change in price or an increase in the prescription of other opioids, the group’s best guess is that the drop came from decreased demand from patients.

And while the team saw a 20% drop in the rate of prescription opioid drug overdose, the rate of heroin overdose during that period surged by 23%.

Other studies have also reported a rise in heroin overdoses after OxyContin was reformulated, but exactly how those two events are related is still up for debate, Larochelle says. It’s hard to trace heroin use, which was already increasing, back to any one thing, he explains. “You’ll hear people who say it’s settled one way or the other, but I don’t think it is.”

Whereas Larochelle’s study looked at how abuse-deterrent formulations affected opioid abuse, other analyses probed how new formulations changed the type of use.

Washington University’s Ellis wanted to understand how different reformulations might shift the behavior of people who take the drug. He and his colleagues surveyed two groups of people who reported misusing opioids before and after they were reformulated: a group of 117 people with experience with OxyContin, and a group of 35 people who had used Endo Pharmaceuticals’ Opana ER, an abuse-deterrent version of the oxycodone metabolite oxymorphone (Pain 2016, DOI: 10.1097/j.pain.0000000000000511). Both pills rely on the abuse-deterrent Intac technology.

Survey responses revealed that after OxyContin’s reformulation, its use by snorting, injecting, gagging the overall opioid crisis steep: Abuse-deterrent opioids cost about twice as much as conventional ones—on average $11.60 per daily dose versus the $5.82 a conventional opioid costs per day.

Given the costs and uncertain benefits, the question for policy-makers, drug companies, and health care providers waging a fight against a national epidemic is, Are abuse-deterrent opioids a good bet?

The “hard switch”

The first abuse-deterrent opioid hit the U.S. market in 2010. Once again, it was Purdue Pharma leading the way.

After 14 years and billions of dollars in sales, regular extended-release OxyContin was pulled from the shelves. Purdue Pharma cited safety issues and replaced the formulation with a new abuse-deterrent version of the same name. These pills turn marshmallowy if crushed and gooey if dissolved, making them hard to snort or inject. Their specific formulation, which features high-molecular-weight poly(ethylene oxide), uses proprietary Intac technology from the German company Grünenthal.

The timing of the switch—a few years before OxyContin’s original patent expired—was “suspicious,” says Ameet Sarpatwari, assistant director of the program of regulation, therapeutics, and law at Brigham & Women’s Hospital and Harvard Medical School. He recently published a study on the pharmaceutical industry’s role in the opioid epidemic.

By removing a product from the market before a generic equivalent can be introduced, companies can force people taking the original product to begin taking the new version, which also happens to have a longer patent life, Sarpatwari explains. Called a “hard switch,” this maneuver is a tactic that pharmaceutical companies use to prolong their reign in the marketplace. Reformulated, OxyContin’s patent now expires in 2030, according to Purdue Pharma.

To further solidify its market dominance, Purdue Pharma filed a citizen petition asking FDA to bar any generic formulations of the original OxyContin from the market for safety reasons. And the agency granted the request.

It was a surprising move by FDA, Sarpatwari says, because painkillers like oxycodone help some people manage chronic conditions. Making them more expensive by blocking generic versions can cut off access to those in need, he says. It’s the sort of decision, Sarpatwari adds, that
or smoking went down by 48%. Yet at the same time, oral misuse went up by 49%.

In contrast, Opana ER’s reformulation prompted a more nuanced shift: People reported a 54% decrease in snorting, an 86% decrease in smoking, but only a 14% decrease in injecting the drug. Oral misuse remained about the same. On the basis of information from follow-up interviews, the researchers suggest that making it harder to snort the drug pushes people toward injection.

According to one person who used Opana ER, who was quoted in the paper: “I only snorted the old formula because it was very easy to shave down into a powder and snort. I also was not an IV user at that time. I only IV used the new [formula] because I could not turn the pill into powder but could prep it for IV use.”

After its reformulation, Opana ER was linked to an HIV and a hepatitis C outbreak in Indiana through needle sharing, and earlier this summer, FDA requested that Endo pull the drug from the market. Grünenthal declined to speak with C&EN for this story. C&EN did not receive a response from Endo by press time.

“The problem with abuse-deterrent formulations is that people assume it’s a fix-all when it’s not,” Ellis says.

Weighing the costs

As it stands, the biggest roadblock to determining the value of abuse-deterrent opioids is a lack of data. Having been available for seven years, OxyContin captures more than 90% of the abuse-deterrent market. None of the other commercial abuse-deterrent opioids has been around long enough to offer sufficient data. According to the ICER report, the first real-world studies for the abuse-deterrent opioids Hysingla ER from Purdue Pharma and Embeda from Pfizer won’t be complete until 2018 and 2019, respectively.

The 200-plus-page report did, however, rate abuse-deterrent OxyContin, concluding that the formulation is comparable to or better than existing non-abuse-deterrent opioids in terms of its pain relief and safety.

The researchers who crafted ICER’s report also ran a cost-benefit analysis to weigh abuse-deterrent opioids against their regular counterparts. On the one hand, abuse-deterrent opioids cost more than conventional opioids. On the other hand, conventional opioids are more susceptible to unhealthy use, leading to greater health care costs.

To treat a group of 100,000 people with abuse-deterrent opioids for five years, it would cost $533 million more than to treat a similar group with conventional opioids, the researchers calculated. With the addition of societal costs, such as incarceration and loss of productivity, that number shrank but still loomed large at $393 million.

Abuse-deterrent opioid prices should be lowered to match their potential benefits, says Dan Ollendorf, ICER’s chief scientific officer. The ICER report found that cutting current abuse-deterrent opioid prices by 41% would make them cost neutral; in other words, the additional cost of the drugs and the amount saved in treating misuse would even out. And at this reduced price, drugmakers would still make 18% more than selling regular opioids.

At least one company believes ICER’s analysis is “incomplete,” however. In the public comments included with the report, Daiichi Sankyo, which is preparing to launch RoxyBond, an immediate-release abuse-deterrent opioid, contends that the institute’s calculation failed to consider the impact of abuse-deterrent opioids on communities—namely, reduced potential of unhealthy use among friends and relatives of people who are prescribed those opioids. “Daiichi Sankyo stands behind the value of abuse-deterrent formulations of opioid medications as part of a comprehensive approach to addressing the opioid epidemic,” the firm says in its comment. Two additional manufacturers of abuse-deterrent products similarly expressed their support of these formulations to C&EN.

In a recent statement on reducing risky use of prescription drugs, Pharmaceutical Research & Manufacturers of America, an advocacy group representing 37 major pharmaceutical companies, calls abuse-deterrent opioids an important treatment option that can help prevent widespread misuse. More firms are joining this effort, with 15 abuse-deterrent opioids currently in late-stage clinical trials, according to Pharma Intelligence, a group that provides pharmaceutical research and analysis.

Yet given the unknowns around expensive abuse-deterrent opioids, Larochelle suggests that health care dollars might be better spent on options such as increased prescriber education, prescription-monitoring systems, legislation to restrict pill mills, and most important, programs for treating opioid addiction.

“Unfortunately, the problem is complex—where we push, you can see an expansion somewhere else,” Sarpatwari says. “We need to take a system-wide approach to fight the crisis.”

Tamper-resistant opioids

Five abuse-deterrent drugs have been approved by FDA but are not yet on the market.

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<tr>
<th>BRAND NAME</th>
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* Only immediate-release formulation approved. ER = extended release
Source: Institute for Clinical & Economic Reviewa Only