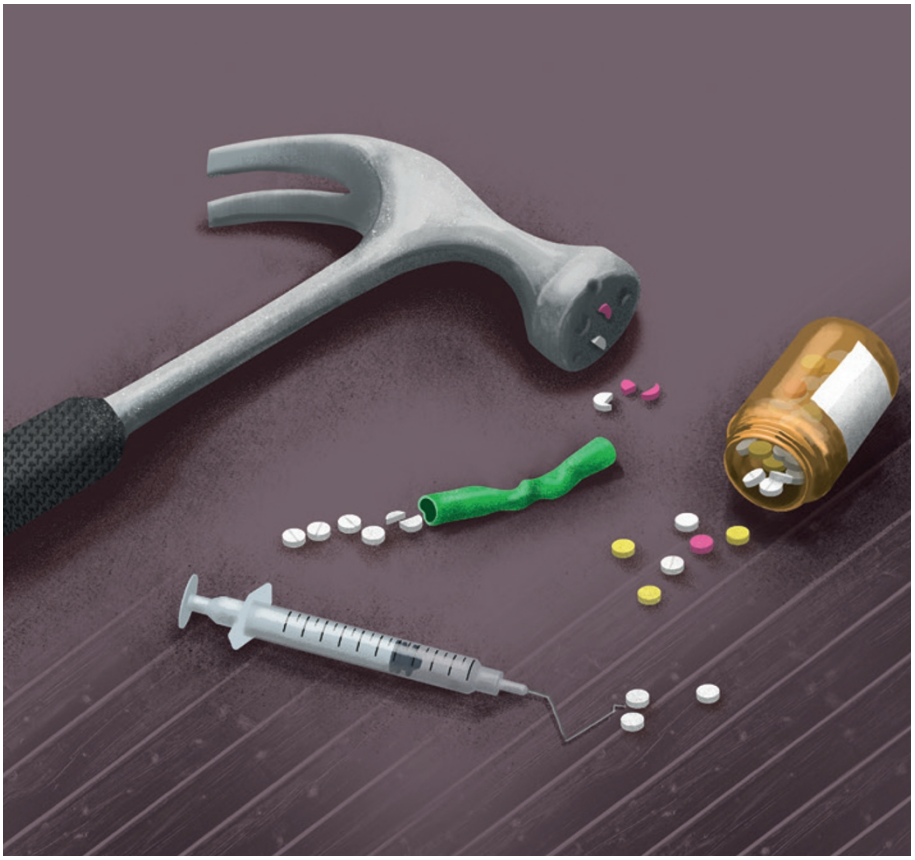

NIK SPENCER

TECHNOLOGY

# Barriers to misuse

*Ingenious pill formulations and the latest manufacturing technologies are helping to stem the tide of painkiller addiction.*

BY ELIE DOLGIN

Mary Marcuccio's life was turned upside down by drug misuse and addiction. Her son, now 26, started with alcohol and marijuana. Then came cocaine and hallucinogens. By 14, he was stealing prescription painkillers from friends' medicine cabinets, crushing and snorting the pills to achieve a quick and euphoric high. Within one year, he had graduated to injecting heroin.

This progression is "so stereotypical", says Marcuccio, founder of My Bottom Line, a Florida-based consulting business for families dealing with substance misuse. According to US survey data, 77% of heroin users say that, like Marcuccio's son (who remains addicted to heroin), they misused prescription opioids — derivatives of natural or synthetic forms of opium or morphine — before trying heroin.

But substance-misuse specialists think that this chain of addiction might be broken with the aid of the latest manufacturing processes to make powerful opioid pain medication more resistant to various forms of tampering. Such drug preparations could also save lives. The death toll from misusing prescription opioids has skyrocketed around the world in the past 20 years, with opioid-linked overdoses exceeding fatalities from road accidents or deaths from heroin and cocaine in countries including the United Kingdom, the United States and Australia. "It behooves us to make a greater effort at creating unabusable formularies," Marcuccio says.

Fortunately, the science and manufacturing of misuse-deterrence are advancing rapidly — and so is the political climate. In the United States — a country that consumes more than 80% of the global opioid supply — politicians are beginning to craft bills to incentivize the development of misuse-resistant formulations. "The idea is to transition the market," says Dan Cohen, chair of the Abuse Deterrent Coalition, a network of advocacy organizations, technology manufacturers and drug companies based in Washington DC. "There are now so many different abuse-deterrent formulations that are either in products or in development that there's enough variety out there for any product to be able to put abuse-deterrence in it."

## THE NEW GUARD

Some of the latest tablet formulations are so hard that even a hammer-blow cannot pulverize them. Many pills form a gelatinous goo when dissolved that renders them difficult to inject. Others contain reversal agents that negate the high when the tablets are messed with. The idea is to create pain-relief medicines that are less prone to misuse yet work when taken as directed.

The technologies in place today are not ironclad, though. A quick perusal of online message boards and videos reveals numerous tips on how to circumvent the defences of even the most reinforced tablets. What is more, not all prescription opioids on the market are misuse-resistant. "We're still in abuse-deterrent formulations 1.0," says Richard Dart, director of the Rocky Mountain Poison and Drug Center in Denver, Colorado. But, he adds with a touch of hyperbole, "there are a zillion abuse-deterrent formulations coming".

Manufacturers have been worried about prescription-drug misuse for decades. When the first controlled-release formulation of the opioid oxycodone hit the US market 20 years ago, the drug's manufacturer, Purdue Pharma of Stamford, Connecticut, touted the twice-a-day medicine as a less-addictive alternative to the faster-acting painkillers that provide a big opioid hit all at once. In reality, however, Purdue's longer-lasting pill, sold under the trade name OxyContin, had the opposite effect.

Drug users easily defeated OxyContin's time-release mechanism by crushing or chewing it. Just one OxyContin could contain more oxycodone than a dozen instant-release pills but no extra ingredients such as paracetamol that make people sick if taken at high doses. OxyContin quickly became the number one addiction problem in many parts of the world, particularly in the United States and Australia. The drug was so popular among the rural poor of Appalachia in West Virginia and Kentucky that it earned the street name 'hillbilly heroin'.

Purdue set to work to guard against some of the worst forms of misuse. In 2010, the company introduced a misuse-averting version of OxyContin that contains a polymer made of long-chain molecules. This makes the new tablet more difficult to crush — although it is not rock hard. "It behaves more like plastic," explains Richard Mannion, executive director of pharmaceutics and analytical development at Purdue. "So, it will deform if subjected to force, but it doesn't break into a powder easily." The revised formulation is thus much harder to snort. Plus, Mannion says, when combined with water, the polymer forms a gummy substance that makes it very difficult to draw into a syringe (although misuse is still possible).

PURDUE PHARMA LP

**The original OxyContin pill could be crushed (left) and snorted; and (right) the new tamper-resistant form.**

The new version of OxyContin has proved to reduce the incidence of therapeutic misuse. A study[1] of more than 140,000 people treated at rehabilitation centres across the United States found that misuse by injection, snorting or smoking declined by two-thirds in the two years after the reformulation. In light of these results, in 2013, Purdue won the right from the US Food and Drug Administration (FDA) to describe the misuse-deterrent benefits of OxyContin on the drug's label and to make marketing claims accordingly. The FDA said at the time that any future generic versions of OxyContin would have to incorporate equivalent misuse-deterrent protection. (In April 2015, the FDA released a guidance document outlining the types of study needed to establish misuse-deterrence, but the report stopped short of addressing generic opioid products.)

Other painkillers that now have FDA-approved misuse-deterrent labelling include Embeda, an extended-release morphine from New York-based pharmaceutical firm Pfizer, and Targiniq, another long-acting preparation of oxycodone from Purdue. Both contain antagonist agents — offsetting ingredients that remain largely inactive when the drugs are taken as directed, but that will annul the opioid's effects if the drugs are snorted or injected.

"These new technologies are showing some positive results," notes Robert Jamison, a pain psychologist at the Brigham and Women's Hospital Pain Management Center in Chestnut Hill, Massachusetts. In Australia, for example, OxyContin users accounted for more than 60% of the visits to the Medically Supervised Injecting Centre in Sydney. After the tamper-resistant version of OxyContin hit the Australian market in April 2014, a team led by Louisa Degenhardt, a drug-addiction researcher at the University of New South Wales in Sydney, found[2] that the number dropped to 5%. In the United States, levels of opioid misuse have decreased from their peak in 2010, when the new formulation of OxyContin arrived on the market. Rates of opioid dispensing and overdoses have dropped appreciably, too.

These public-health benefits come with an economic bonus. According to calculations from Noam Kirson and his colleagues at Analysis Group, a consulting firm in Boston, Massachusetts, the reformulated OxyContin has reduced misuse-related medical expenses and indirect societal costs by more than US$1 billion per year in the United States[3]. "These are substantial savings," Kirson says.

## OLD HABITS DIE HARD

Despite the gains, the misuse-deterrence field still has a long way to go. Drug users who have been thwarted by one technology can switch to another prescription medicine that lacks anti-tampering defences. That is what happened in rural Appalachia following the introduction of reformulated OxyContin. Opioid misusers simply started snorting and injecting the less potent immediate-release preparations of oxycodone, most of which lack misuse-deterrence characteristics. "It's kind of a whack-a-mole situation," says Jennifer Havens, an epidemiologist at the University of Kentucky Center for Drug and Alcohol Research in Lexington.

Plus, even with the latest physical defences it is still possible to get high by swallowing lots of OxyContin or Embeda pills at once. Preventing oral misuse requires a different approach — which a company called Signature Therapeutics, based in Palo Alto, California, is pursuing.

> *"It behooves us to make a greater effort at creating unabusable formularies."*

Signature Therapeutics' technology uses prodrugs, which are inactive until they undergo the appropriate chemical conversion in the body. When these pills are taken by mouth as directed, a digestive enzyme in the gut called trypsin releases part of the prodrug, initiating the process of opioid drug release. But because trypsin is not found elsewhere in the body, the prodrug remains inert when injected, snorted or smoked. Signature Therapeutics has already tested its painkilling hydromorphone prodrug in a phase I trial of healthy volunteers; the company plans to begin evaluating its oxycodone prodrug in human studies later this year.

Prodrugs alone do not prevent excessive pill-popping, but scientists at Signature Therapeutics have another trick up their sleeves. If the prodrugs look promising in the clinic, the company will add a second compound that blocks trypsin activity. This might seem counterintuitive, but it is all about threshold levels. The amount of trypsin inhibitor found in one or two pills will not interfere with the prodrug modification, but a handful of pills collectively contain enough inhibitor to shut down the conversion process. With this approach, Signature Therapeutics can create either extended-release or immediate-release opioids. Bill Schmidt, chief medical officer at the company, says that the potential of these drugs is "maximum therapeutic benefit with very low abuse liability".

New formulations such as these could ultimately prove to be almost addiction-proof, but they are not cheap. And their benefits might not be fully realized unless authorities require drug companies to include them. "The problem with abuse-deterrence right now is the lack of incentives," Cohen says.

Lawmakers in the US House of Representatives previously proposed legislation that would have barred the approval of any new pharmaceuticals that did not use formulas resistant to tampering. That bill died in committee, but, according to Cohen, revised legislation should be introduced again "soon". Individual US states have also begun to pass laws that compel pharmacists exclusively to dispense, and insurers to cover, misuse-deterrent versions of opioids unless instructed otherwise by a physician.

Ultimately, the success of long-term efforts to rein in opioid addiction could depend on the regulations surrounding generic painkillers. In December 2014, Australia allowed the sale of a generic long-acting oxycodone without misuse-deterrence characteristics. Degenhardt, who is monitoring the drug-misuse data, worries that many of the gains of OxyContin's reformulation will now be lost. By contrast, US authorities have already said that they will not approve such a product.

All of these efforts should help to bring down the number of overdose deaths and also prevent experimentation with prescription pills. In her study population in rural Appalachia, Havens has met so many young people like Marcuccio's son — for whom easily misused opioids were the gateway to addiction — that she has reached a simple, but absolute, conclusion: "The only way that abuse-deterrent formulations are going to work is if they're all abuse-deterring," she says. "It can't just be piecemeal. It's got to be all or nothing."

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1. Butler, S. F. *et al. J. Pain* **14,** 351–358 (2013).
2. Degenhardt, L. *et al. Drug Alcohol Depend.* http://dx.doi.org/10.1016/j.drugalcdep.2015.02.038 (2015).
3. Kirson, N. Y. *et al. Pain Med.* **15,** 1450–1454 (2014).