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FT BIG READ. PHARMACEUTICALS

Prescribing pain

The abuse of painkillers in the US has reached epidemic proportions amid claims that over-zealous prescribing is to blame. Now the industry is under pressure to make the drugs tamper-proof.

By David Crow

When Brandon had his appendix removed at the age of 26, his doctor gave him a supply of opioid-based painkillers to help with the discomfort. Within a week, he no longer needed them, but by then he had discovered a hankering for the high he got from taking the drugs.

"Mostly I would use them on nights where I wouldn't go out to the bar — just stay at home, take a bunch of pills and draw or play video games in my room." Three months later, the drugs from the doctor ran out, "so I proceeded to just find them here and there from friends".

And so Brandon joined the ranks of the many millions of people who have found euphoria in drugs derived from the opium poppy, a flower first cultivated in 3400BC in lower Mesopotamia by the Sumerians, who referred to it as the "joy plant".

He also became one of the more than 2m Americans who abuse prescription opioid-based painkillers such as OxyContin, a popular form of the drug oxycodone, and Opana, a type of oxymorphone. His family soon found out about his pill-popping, but it was rarely discussed. It became, he says, an "unspoken truth".

The US drugs watchdog recently declared opioid abuse in America to be a national epidemic, claiming an average of 45 lives through overdose each day. Eighty per cent of heroin addicts say they first became addicted to opioid prescription painkillers, both of which are cleaved from the "joy plant".

Pain wars

Dealing with the crisis has become the subject of a fierce debate in the American medical establishment. On one side are those doctors who believe their profession has spent decades overprescribing opioids, helping patients pursue zero pain while unwittingly pushing many of them to addiction. In supporting their case for sharp curbs on prescriptions, this group points to statistics showing that US opioid distribution on a measure known as "morphine equivalent milligrams" soared from 25.3 per person per year in 1980 to 550.7 by 2012.

"It can be traced to a period of overprescribing of opioid analgesics by providers and physicians," argues Adrienne Abbate, who runs a charity to tackle opioid abuse in New York. "Pharmaceutical companies aggressively marketed to physicians, and made it seem as if it would be a safe and non-addictive form of pain treatment."

Others in the medical establishment, including some pain specialists and most drug makers, say the solution is not necessarily fewer drugs but better ones — a new generation of opioids with physical or chemical features to drive down improper consumption.

In May, the US Food and Drug Administration issued a set of guidelines to encourage the pharma industry to develop tamper-resistant painkillers. Those who develop pills with novel technologies are rewarded with a drug label that allows them to market their products as "abuse-deterrent".

To qualify, these drugs need physical qualities intended to make them more difficult to use recreationally, such as hard shells designed to withstand crushing and snorting, or gumming agents that make it more difficult to dissolve a pill in water before injecting it. More advanced approaches include planting a chemical designed to counter the effect of the opioid inside the pill, which is released if the drug is tampered with — the equivalent of a car immobiliser that is activated when the vehicle is stolen.

There are just four opioid-based painkillers on the US market classed as abuse-deterrent, but there are scores more in development.

The potential size of the commercial opportunity is huge, especially if the FDA blocks painkillers that do not have anti-abuse features, or if Congress goes a step further by removing products without tamper protection from the market — a move some in the industry are lobbying for.

Ronny Gal, an analyst at Bernstein Research, is predicting an "intellectual property bonanza" for companies working in this field. He estimates that switching the 18m US prescriptions that are filled with generic drugs to new abuse-deterrent alternatives would generate roughly $4.4bn in additional revenue for the industry each year.

Some argue that tamper-proof painkillers are just another money-making wheeze for big pharma, which gets to take old drugs — many of which have lost patent protection or are about to — and charge higher prices.

"It is hard to swallow the idea that those companies who made so much money from drugs that did more harm than help should now get an additional reward for developing new versions just before the patents run out," says Dr David Juurlink, a professor of drug safety at the University of Toronto.

In 2010, Purdue Pharma, a group that specialises in opioid-based painkillers, removed its drug OxyContin from the market and replaced it with a reformulated version that has a coating designed to make it harder to abuse. It became the first product to receive abuse-deterrent labelling from the FDA in 2013.

According to a study published in April in the Journal of the American Medical Association, the removal of the older OxyContin from the market had by 2012 led to a dramatic fall in the overall number of opioid prescriptions, which were 19 per cent lower than would otherwise have been expected.

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"It raised eyebrows, because it was basically an admission that lots of their prescriptions had been going to abusers," says Mr Gal.

However, there are already signs the physical deterrents can be circumvented. On an online message forum for drug abusers, one participant recently offered a guide to removing the outer layer on OxyContin.

Earlier this month, Purdue cancelled a follow-up meeting at the FDA where it had been scheduled to present post-marketing studies intended to show that the newer OxyContin was being abused less than its predecessor. It said it needed more time to conduct extra analysis.

Other companies are trying to develop more effective physical barriers. Egalet, the Danish biotech group, is using injection-moulding techniques to develop a tamper-resistant version of morphine sulphate that is hard to crush and cannot be sucked into a syringe. A different approach, being pursued by Pfizer and others, involves planting an "antagonist" into the centre of the pill which counteracts the effect of the opioid. If the drug is ingested as intended, the antagonist is not deployed, but it is released if the pill is chewed, crushed or dissolved.

Human guinea pigs

Brandon did not become addicted to opioids, but his recreational abuse led to an unusual career move. He told his friends he had started working as an independent contractor for a pharmaceutical group — not a lie exactly, but a bending of the truth: it would have been more honest to say he had become a human guinea pig for pharma companies wanting to test their abuse-deterrent opioids.

He first took part in so-called "human abuse liability" studies after a colleague returned to work from a month-long break sporting an expensive new watch. "He told me he had done a recreational drug study and the financial benefits of it. Quite frankly I didn't believe him, so I called up."

He was paid $3,100 for his first study — a three-month trial that involved working three days every other week. A second, 30-day study earned him $4,500. "It was at that point I put in my two weeks notice and continued to do the drug studies, essentially full time."

Along with other participants, Brandon was given a series of pills — a mixture of abuse-deterrent drugs, normal opioids and placebos — and told to abuse them, before reporting back on the effects. Sometimes he had to snort the crushed pills, his least favourite method, while on one occasion he swallowed 21 tablets, most of them placebos, in five minutes. Researchers carried out so-called pharmacokinetic assessments to measure the speed at which the drugs were absorbed into his body.

These studies are not just legal, they are actively encouraged by the FDA, which wants proof that abuse-deterrent opioids really do deter abuse.

Dr Lynn Webster, who runs the Lifetree clinic in Salt Lake City, Utah, where Brandon participated in trials says: "The number of studies we're doing has increased tremendously in the last two years because of the opioid crisis, the need for safer forms and the FDA incentives."

Lifetree has a database containing the details of several thousand eligible participants, mostly in their mid-20s. Those taking part must be recreational users but cannot be physically dependent or addicted. Prospective subjects are first given naloxone, which binds to opioid receptors in the brain and cuts off the effect of the drugs. Anyone who displays signs of withdrawal symptoms is not allowed on the trial.

However, some addiction doctors warn that this process is not without its dangers and that it is unlikely to prevent potential opioid addicts from enrolling in the studies.

"It's usually only in hindsight that you can tell when someone has crossed the line from abuse to dependence," says Dr William Jacobs, head of addiction medicine at Georgia Regents University. "A lot of people enrolling in these studies may be opiate addicts — you just might not know it yet."

Rise of heroin

Recruitment is mainly by word-of-mouth, but it is not hard to find willing candidates: "These are individuals who like to use drugs," says Dr Webster. "They're getting paid to do something they love." Confidentiality, and protection from law enforcement agencies, is guaranteed by the FDA and the National Institutes of Health.

However, even those involved in developing a new class of opioids, concede that the drugs are no panacea for America's painkiller addiction. Hard shells and antagonists might foil the casual recreational user, but they can be easily circumvented by drug dealers with a basic grasp of chemistry.

"We can't stop the industrial user with a lab in their basement," says Bob Radie, chief executive of Egalet.

Another problem is that the current technologies focus on tampering with the pill — crushing, chewing, dissolving. But more than 90 per cent of opioid abuse is oral. Most users just take more pills than they should.

There is also a risk that addicts who cannot access abusable opioids will switch to heroin instead, joining the steady tide of those who progress from painkillers to the "heavy stuff".

Earlier this month, the US Centers for Disease Control and Prevention said heroin use had increased by 63 per cent between 2002 and 2013 across the US, especially among women, people with private insurance and those on higher incomes. The strongest risk factor for heroin use was a prescription opioid-use disorder, the agency said, as it called for improvements in prescribing practices.

"Heroin use is increasing at an alarming rate in many parts of society, driven by both the prescription opioid epidemic and cheaper, more available heroin," said CDC director Dr Tom Frieden.

Some doctors say abuse-deterrent opioids run the risk of making the problem worse, arguing that they send a "business as usual" message to the medical establishment.

"The biggest problem with these formulations isn't simply that they cost more, or give the drug companies more patent protection, or even that they lead doctors to think they're safer," says Dr Juurlink. "But when you focus on these as the solution, you draw attention away from a policy that might actually work."

Brandon's name has been changed to protect his identity

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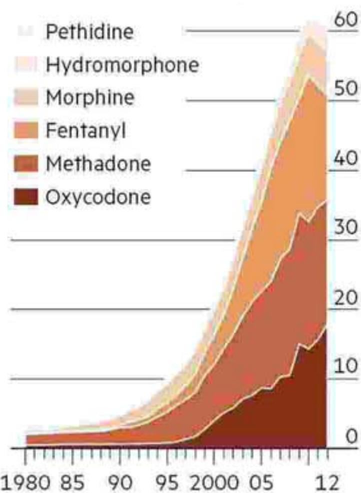
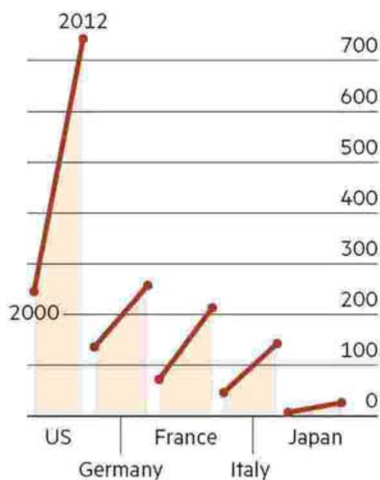
2m
Americans who regularly abuse prescription opioid-based painkillers

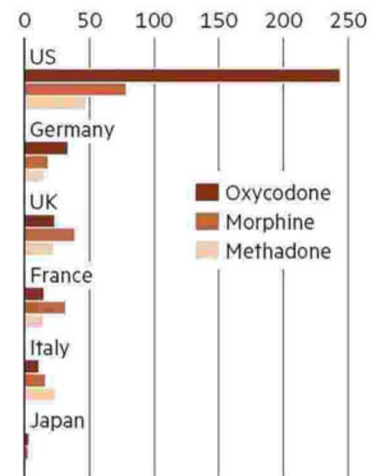
45
The number of daily fatal overdoses attributed to opioid-based painkillers

$4.4bn
Estimate of extra revenue generated by switching to abuse deterrent drugs

Opioid consumption







The source: Seed pod of opium poppy — SPL

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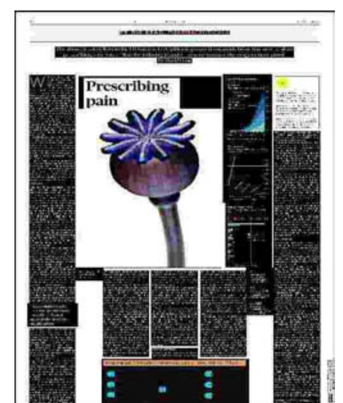
Tamper-proof: The lengths to which companies are going to prevent abuse



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