

Discarded syringes for injecting heroin litter the street in Philadelphia, Pennsylvania.

PUBLIC HEALTH

# The natural history of an epidemic

Understanding how the opioid epidemic arose in the United States could help to predict how it might spread to other countries.

# **BY SARAH DEWEERDT**

In 2015, something happened in the United States that hadn't occurred there in the past 100 years: life expectancy entered a period of sustained decline. According to the World Bank Group, the country's average life expectancy fell from 78.8 years in 2014 to 78.7 years in 2015, and then to 78.5 years in 2016 and 2017.

In most high-income countries, life expectancy has been increasing, gradually but steadily, for decades. The last time that life expectancy in the United States showed a similar decline was in 1915–18, as a result of military deaths in the First World War and the 1918 influenza pandemic.

This time, the culprit has been a surge of drug overdoses and suicides, both linked to the use of opioid drugs. The death rate from drug overdoses more than tripled between 1999 and 2017, and that from opioid overdoses increased almost sixfold during the same period.

More people in the United States died from overdoses involving opioids in 2017 than from HIV- or AIDS-related illnesses at the peak of the AIDS epidemic. "Most people living have never seen anything this bad," says Keith Humphreys, a psychiatrist at Stanford University in California and a former White House drug-policy adviser.

This crisis is often referred to as the opioid epidemic and, just like an infectiousdisease epidemic, it has a distinct natural history. In the United States, the country most severely affected, it arose through a confluence of well-intentioned efforts to improve pain management by doctors and aggressive — even fraudulent — marketing by pharmaceutical manufacturers. Characteristics of the US health-care system, regulatory regime, culture and socio-economic trends all contributed to what is now a full-blown crisis. The epidemic has evolved over time, becoming more deadly — and other countries could be vulnerable to its spread.

## **PRE-EXISTING CONDITIONS**

Opioid addiction is not a new phenomenon in the United States, but in the past, it did not have such a marked impact on the nation as a whole. The groundwork for the crisis was laid in the 1980s, when pain increasingly became recognized as a problem that required adequate treatment. US states began to pass intractable pain treatment acts, which removed the threat of prosecution for physicians who treated their patients' pain aggressively with controlled



substances. And, in 1995, the American Pain Society, a physicians' organization in Chicago, Illinois, launched a campaign that framed pain as a 'fifth vital sign' that should be monitored and managed as a matter of course, in the same way as heart rate and blood pressure.

Before the present epidemic, opioids were prescribed mainly for short-term uses such as pain relief after surgery or for people with advanced cancer or other terminal conditions. But in the United States, the idea that opioids might be safer and less addictive than was previously thought began to take root. A letter to the editor in the New England Journal of Medicine in 1980 reported that of 11,882 hospitalized people who were prescribed opioids, only four became addicted<sup>1</sup>, but the short letter provided no evidence to back up these claims. A widely cited 1986 study, involving only 38 people, advocated using opioids to treat chronic pain unrelated to cancer<sup>2</sup>. The prevailing view is that these studies were over-interpreted. But at the time, they contributed to the perception that opioids were addictive only when used recreationally - and not when used to treat pain.

Prescriptions for opioids increased gradually throughout the 1980s and early 1990s. But it wasn't until the mid-1990s, when pharmaceutical companies introduced new opioid-based products — and, in particular, OxyContin, a sustained-release formulation of a decades-old medication called oxycodone, manufactured by Purdue Pharma in Stamford, Connecticut — that such prescriptions surged and the use of opioids to treat chronic pain became widespread.

Purdue Pharma and other companies promoted their opioid products heavily. They lobbied lawmakers, sponsored continuing medical-education courses, funded professional and patient organizations and sent representatives to visit individual doctors. During all of these activities, they emphasized the safety, efficacy and low potential for addiction of prescription opioids.

In fact, opioids are not particularly effective for treating chronic pain; with long-term use, people can develop tolerance to the drugs and even become more sensitive to pain. And the claim that OxyContin was less addictive than other opioid painkillers was untrue — Purdue Pharma knew that it was addictive, as it admitted in a 2007 lawsuit that resulted in a US\$635 million fine for the company. But doctors and patients were unaware of that at the time.

### SYSTEM VULNERABILITY

Doctors didn't question what they were told by pharmaceutical representatives and on continuing medical education courses about prescription opioids, in part because of a lack of experience, says Stephen Bernard, a palliativecare specialist at the University of North Carolina at Chapel Hill. "Physicians don't get a lot of good training in pain management," he says.

The structure of the health-care system in the United States also contributed to the overprescription of opioids. Because many doctors are in private practice, they can benefit financially by increasing the volume of patients that they see, as well as by ensuring patient satisfaction, which can incentivize the overprescription of pain medication. Prescription opioids are also cheap in the short term. Patients' healthinsurance plans often covered pain medication but not pain-management approaches such as physical therapy. "The incentives were there for people to prescribe more and more, particularly when they had already been convinced it was the right thing to do - the compassionate thing to do," Humphreys says.

Canada shares some of these vulnerabilities. For example, like their counterparts in the United States, Canadian doctors are entrepreneurs who are paid by the unit. And they, too, were subjected to aggressive marketing by opioid manufacturers, alleges a Can\$1.1 billion (\$752 million) lawsuit filed in May at Ontario Superior Court of Justice in Guelph.

This might help to explain why Canada is also experiencing an opioid crisis, with 10,337 opioid-related deaths between January 2016 and September 2018.

Most European countries, however, have so far been insulated from the epidemic. Doctors in Europe are not motivated financially to make prescriptions. And whereas the US medical community eagerly embraced the small studies that suggested that people had a low risk of developing an addiction to opioids, European pain specialists viewed that work more sceptically, says Jan Van Zundert, an anaesthesiologist at East Limburg Hospital in Genk, Belgium. "During the last 20 years, I almost did not prescribe opioids for chronic non-cancer pain," Van Zundert says. That practice "is based on the fact that there is no literature supporting it", he adds.

Cultural differences between Europe and North America probably also contribute to the regions' differing fortunes with opioids. Large-scale surveys show that there is a similar prevalence of pain in France and Italy as there is in the United States<sup>3</sup>. But according to data from the United Nations, US doctors write five and a half times more prescriptions for opioids than do their counterparts in France, and eight times more than do physicians in Italy. Humphreys says that this might be because people in the United States expect to receive a prescription when they go to the doctor with a health concern. Meanwhile, direct advertising of pharmaceuticals to consumers (permitted only in the United States and New Zealand) encourages them to ask doctors for specific drugs.

### **EPIDEMICS ON EPIDEMICS**

Racial attitudes and socio-economic trends also helped the opioid epidemic to gain a foothold in the United States. Purdue Pharma focused the initial marketing of OxyContin on suburban and rural white communities. That strategy took advantage of the prevailing image of a drug addict as an African-American or Hispanic person who lived in the inner city to head off potential concerns about addiction, says Helena Hansen, an anthropologist and psychiatrist at NYU Langone Health in New York City. The company targeted doctors who were "serving patients that were not thought to be at risk for addiction", Hansen says. "There was a definite racial subtext to that."

The hardest-hit communities can be found in the US states of West Virginia, Ohio, Kentucky and New Hampshire. "They're communities where there is a problem of under-employment; there is a problem of concentration of poverty," says Magdalena Cerdá, an epidemiologist at NYU Langone Health. The term 'deaths of despair' has arisen to describe the suicides and opioid-overdose deaths of white people in parts of the United States that have been affected by de-industrialization and economic decline.

But Hansen points out that, in this respect, the natural history of the opioid crisis might not be as unique as commonly thought. She suggests that a heroin epidemic that ravaged inner-city communities of minority ethnic groups in the 1960s and 1970s involved similar causes — such communities were first to be affected by that era's economic decline. "We have a parallel process that happened in black and brown communities, even though it was framed quite differently," she says.

The opioid epidemic has had three phases: the first was dominated by prescription opioids, the second by heroin, and the third by cheaper — but more potent — synthetic opioids such as fentanyl. All of these forms of opioid



With the introduction of drugs such as OxyContin came a surge in opioid prescriptions for pain relief.

remain relevant to the current crisis. "Basically, we have three epidemics on top of each other," Humphreys says. "There are plenty of people using all three drugs. And there are plenty of people who start on one and die on another."

During the first phase, from the mid-1990s to about 2010, there was a steady increase in deaths from prescription-opioid overdoses. Patient-privacy laws and a lack of coordina-

tion between US states meant that users could amass numerous opioid prescriptions and then sell their excess pills. This was a departure from the supply chain of previous epidemics, says Jonathan Caulkins,

*"Every past* epidemic has been about an increase in the number of users."

a drug-policy researcher at Carnegie Mellon University in Pittsburgh, Pennsylvania. Rather than the supply being dominated by organized drug traffickers, users were responsible for the drugs entering the black market. This enabled the epidemic to spread quickly, he says. "As the use spread, the supply spread along with it."

As the scope of the prescription-opioid problem became clear, physicians' organizations retooled their prescription guidelines (see page S13), US state and federal agencies clamped down on the availability of such drugs, and Purdue Pharma reformulated Oxy-Contin to make it more difficult to crush and inhale. This did discourage abuse. But at the same time, for unclear reasons, the supply of heroin increased, and its price dropped sharply. Some opioid users switched to heroin because it was easier to obtain than prescription opioids. Switching also enabled those who still had access to OxyContin to sell more of the higher-value prescription opioids on the black market. According to a study led by Cerdá, people with a history of using prescription opioids are 13 times more likely to start using heroin than those with no history of prescription opioid misuse<sup>4</sup>. And data from the US National

Center for Health Statistics show that between 2010 and 2016, deaths from heroin overdoses increased almost fivefold in the United States.

Around 2013, the contours of the epidemic shifted for a third time. Heroin dealers who wanted to increase profits began to mix their products with fillers and fentanyl.

Because fentanyl is more potent than heroin, it is also more deadly. According to the US Centers for Disease Control and Prevention, between 2013 and 2016, overdose deaths from fentanyl and similar molecules increased by 88% per year. "Every past epidemic has been about an increase in the number of users," says Caulkins. "This is a massive increase in death."

Other characteristics of the epidemic are also shifting. For example, there has been a surge in overdoses in black people. Many overdose deaths also now involve other substances as well as opioids.

# **FUTURE SHOCKS**

In the face of a backlash in the United States and Canada, opioid manufacturers are increasing their activities elsewhere. An investigation in 2016 by the Los Angeles Times (see go.nature. com/2z10a0r) revealed that Mundipharma International, the global counterpart of Purdue Pharma, which is based in Cambridge, UK, had been using similar tactics, such as aggressive marketing and claims of non-addictiveness, to promote OxyContin in numerous other countries, including Australia, Brazil, China, Colombia, Egypt, Mexico, the Philippines, Singapore, South Korea and Spain.

Van Zundert thinks that most countries in Europe will avoid an opioid crisis. "Since the opioid epidemic in the United States, of course everybody in Europe is very alert for it," he says. Doctors in the region are more likely to use milder opioids, such as tramadol, that are thought to pose a lower risk of overdose. And Mundipharma has curtailed the marketing of opioids in Belgium, Van Zundert says.

Yet opioid-related deaths are rising in

countries other than the United States and Canada, including England, Wales, Ireland, Norway and Sweden, according to a 2019 report by the Organisation for Economic Co-operation and Development (go.nature.com/2ydwag4). None of these countries is facing problems on the scale of North America. But, says Humphreys, there is no guarantee that such trends won't evolve into an opioid epidemic. "All we know is that they don't have one now."

The opioid crisis could also spread to lowerand middle-income countries, where opioids are rarely prescribed for pain associated with surgery, cancer or the end of life. Such countries therefore have a genuine need for improved pain treatments in the same way as did the United States in the lead-up to its epidemic.

With tight health-care budgets, these countries could be vulnerable to regulatory capture, a phenomenon in which governments come to serve the interests of the agents that they are meant to regulate, Humphreys says. For example, if a deep-pocketed pharmaceutical company offers to build a much-needed hospital, the government might be inclined to draft regulations that would loosen the supply of opioids in the country.

And as hard as the authorities in the United States are working to address the opioid crisis (S17), the country could still be vulnerable to epidemics of other types of prescription drug. Some researchers are concerned that benzodiazepines, a widely used class of sedative, are being overprescribed. Excess pills are often shared with family members or friends — in a similar way to what happened early on in the opioid crisis. But benzodiazepines are addictive and can be dangerous when mixed with other drugs. In fact, about 23% of US opioid overdose deaths in 2015 also involved benzodiazepines.

Certain aspects of the drug regulatory system in the United States leave the country exposed to such problems, says Caulkins. For example, the US Food and Drug Administration (FDA) is charged with evaluating the safety and effectiveness of drugs when used as directed. This prevented them from focusing on the potential for opioid misuse, and could have the same effect for other types of drug. "The system just wasn't designed to think about that," he says.

The FDA also evaluates drugs one at a time, rather than as families of semi-interchangeable molecules such as opioids. This has made it difficult to respond to the ever-increasing diversity of synthetic opioids. "They substitute for each other to a degree," says Caulkins, "so you can't really think about it chemical by chemical. There's a whole ecosystem out there."

# Sarah DeWeerdt is a science journalist in Seattle, Washington.

- 1. Porter, J. & Jick, H. N. Engl. J. Med. 302, 123 (1980). 2. Portenoy, R. K. & Foley, K. M. Pain 25, 171–186
- (1986). . Tsang, A. et al. J. Pain **9**, 883–891 (2008). 3.
- 4.
- Cerdá, M., Santaella, J., Marshall, B. D., Kim, J. H. & Martins, S. S. *J. Pediatr.* **167**, 605–612 (2015).