



Responding to the opioid crisis in North America and beyond: recommendations of the Stanford–Lancet Commission

Keith Humphreys, Chelsea L Shover, Christina M Andrews, Amy S B Bohnert, Margaret L Brandeau, Jonathan P Caulkins, Jonathan H Chen, Mariano-Florentino Cuéllar, Yasmin L Hurd, David N Juurlink, Howard K Koh, Erin E Krebs, Anna Lembke, Sean C Mackey, Lisa Larimore Ouellette, Brian Suffoletto, Christine Timko

Executive summary

The Stanford–Lancet Commission on the North American Opioid Crisis was formed in response to soaring opioid-related morbidity and mortality in the USA and Canada over the past 25 years. The Commission is supported by Stanford University and brings together diverse Stanford scholars and other leading experts across the USA and Canada, with the goals of understanding the opioid crisis, proposing solutions to the crisis domestically, and attempting to stop its spread internationally. Unlike some other *Lancet* Commissions, this one focuses on a long-entrenched problem that has already been well characterised, including in several reviews by the National Academies of Sciences, Engineering, and Medicine. This Commission therefore focused on developing a coherent, empirically grounded analysis of the causes of, and solutions, to the opioid crisis.

The North American crisis emerged when insufficient regulation of the pharmaceutical and health-care industries enabled a profit-driven quadrupling of opioid prescribing. This prescribing involved a departure from long-established practice norms that prevailed before the mid-1990s—particularly in the expanded prescribing of extremely potent opioids for a broad range of chronic, non-cancer pain conditions. Hundreds of thousands of individuals have fatally overdosed on prescription opioids, and millions more have become addicted to opioids or have been harmed in other ways, either as a result of their own opioid use or someone else's (eg, disability, family breakdown, crime, unemployment, bereavement). In response to the large pool of people who became addicted to prescription opioids, heroin markets expanded, which further increased morbidity and mortality. As heroin markets became saturated with illicit synthetic opioids, such as fentanyl, an already dire situation became a public health catastrophe, which has only worsened since the onset of the COVID-19 pandemic. Since 1999, more than 600 000 people have died from opioid overdoses in the USA and Canada, and the current rate of mortality in each country exceeds even that of the worst year of the HIV/AIDS epidemic.

The first wave of the opioid crisis began in the 1990s, when the long-acting opioid OxyContin and other high-potency opioids were prescribed to an extremely wide array of patients. The first wave inflicted the most harm on white and Indigenous people in both the USA and

Canada. An unusually high number of middle-class people and people living in selected rural areas (eg, Appalachia in the USA, the Yukon in Canada) were affected in this wave of the crisis compared with previous epidemics of opioid addiction and overdose. The second wave, as heroin markets became resurgent in response to demand from people addicted to prescription opioids, began around 2010 and led to rapidly rising mortality among African Americans in the USA, and more generally in urban areas in the USA and Canada. These demographic shifts persisted into the third wave of the crisis, which began around 2014 and was characterised by rising addiction and fatal overdoses linked with synthetic opioids such as fentanyl. In 2020, fatal opioid

Key messages

- The profit motives of actors inside and outside the health-care system will continue to generate harmful over-provision of addictive pharmaceuticals unless regulatory systems are fundamentally reformed.
- Opioids have a dual nature as both a benefit and a risk to health, function, and wellbeing. This dual nature should be taken into account in drug regulation, prescribing, and opioid stewardship.
- Integrated evidence-based systems for the care of substance use disorders should be developed and supported financially on a permanent basis.
- Policies are available that maximise the benefit and minimise the adverse effects of criminal justice system involvement with people who are addicted to opioids.
- Fostering healthier environments (eg, through programmes for the safe disposal of opioid pills, substance use prevention, and childhood enrichment) could yield long-term declines in the incidence of addiction.
- Innovations in biomedical research into pain relievers and medications for opioid use disorder treatment, supply control strategies, and the delivery of treatment for substance use disorder are urgently needed in response to the opioid crisis.
- High-income nations have a responsibility to prevent their opioid manufacturers from fomenting opioid overprescribing in other countries, and all nations should consider how to strengthen regulatory systems to prevent domestically driven opioid crises.

Published Online
February 2, 2022
[https://doi.org/10.1016/S0140-6736\(21\)02252-2](https://doi.org/10.1016/S0140-6736(21)02252-2)

Department of Psychiatry and Behavioral Sciences (Prof K Humphreys PhD, Prof A Lembke MD, Prof C Timko PhD), **Stanford Center for Biomedical Informatics Research** (J H Chen MD), **Division of Hospital Medicine** (J H Chen), **and Department of Emergency Medicine** (B Suffoletto MD), **Stanford University School of Medicine, Stanford, CA, USA**; **Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA** (Prof K Humphreys, Prof C Timko); **Division of General Internal Medicine and Health Services Research, University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA, USA** (C L Shover PhD); **Department of Health Services Policy and Management, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA** (C M Andrews PhD); **Department of Psychiatry and Department of Anesthesiology, University of Michigan Health System, Ann Arbor, MI, USA** (A S B Bohnert PhD); **Veterans Affairs Center for Clinical Management Research, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI, USA** (A S B Bohnert); **Department of Management Science and Engineering, Huang Engineering Center, Stanford University, Stanford, CA USA** (Prof M L Brandeau PhD); **Heinz College, Carnegie Mellon University, Pittsburgh, PA, USA** (Prof J P Caulkins PhD); **Stanford Law School, Stanford, CA, USA** (M-F Cuéllar JD, Prof L Larimore Ouellette PhD); **Addiction Institute, Icahn School of Medicine, New York, NY, USA** (Prof Y L Hurd PhD);

Sunnybrook Health Sciences Centre, Toronto, ON, Canada (Prof D N Juurlink MD); Department of Medicine, University of Toronto, Toronto, ON, Canada (Prof D N Juurlink); Department of Health Policy and Management, Harvard T H Chan School of Public Health, Boston, MA, USA (Prof H K Koh MD); Department of Medicine, University of Minnesota, Minneapolis, MN, USA (Prof E E Krebs MD); Center for Care Delivery and Outcomes Research, Veterans Affairs Minneapolis Health Care System, Minneapolis, MN, USA (Prof E E Krebs); and Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Palo Alto, CA, USA (Prof S C Mackey MD)

Correspondence to: Prof Keith Humphreys.

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305-5717, USA
knh@stanford.edu

overdoses reached record highs both in the USA (more than 70 000 deaths) and Canada (more than 6300 deaths). Each wave added to rather than replaced the previous waves, with addiction and overdoses persisting among individuals using any or all of prescription opioids, heroin, and synthetic opioids such as fentanyl.

In both the USA and Canada, fatal opioid overdoses are concentrated among men and young-to-middle-aged people. Mortality among African Americans in the USA has grown rapidly and is now on par with that among white, and American Indian and Alaska Native populations. People experiencing homelessness and those recently released from incarceration have been hit particularly hard throughout the crisis, and the frequency of overdose mortality is shockingly high in these populations. Overdoses involving both stimulants and opioids are common and seem to be increasing in both the USA and Canada. Many opioid overdoses also involve concurrent use of benzodiazepines.

The Commission's analysis of the crisis focused on seven domains: (1) the North American opioid crisis as a case study in multi-system regulatory failure, (2) opioids' dual nature as both a benefit and a risk to health, (3) building integrated, well supported, and enduring systems of care for people with substance use disorders, (4) maximising the benefits and minimising the adverse effects of the involvement of the criminal justice system with people who are addicted to opioids, (5) creating healthy environments that can yield long-term declines in the incidence of addiction, (6) stimulating greater innovation in the response to the opioid crisis, and (7) preventing the North American opioid crisis from spreading globally. In each area, the Commission recommended evidence-informed policies that are responsive to the identified challenges.

Domain 1: The Commission concludes that the initial wave of the opioid crisis arose as a result of weak laws and regulations, and poor implementation thereof. This included failures at the US Food and Drug Administration, which approved OxyContin with what was later shown to be a fraudulent description of the drug as less addictive than other prescription opioids. Further problems arose as a result of overly intimate relationships between opioid manufacturers and universities, professional societies, patient advocacy groups, and lawmakers, and aggressive product promotion to prescribers and (to a lesser extent) the general public. These problems were compounded by the limited tools that regulators have after approval to conduct drug harm surveillance and provide risk management education to prescribers. US laws make the government largely dependent on the pharmaceutical industry to manage these activities, which the industry does poorly. The Commission therefore recommends curtailing pharmaceutical product promotion, insulating medical education from pharmaceutical industry influence, closing the so-called revolving door between

regulators and industry, making post-approval drug monitoring and risk mitigation a function of government, and firewalling bodies with formal power over prescribing from industry influence. To lessen the often-overwhelming political clout of the industry, the Commission also recommends exposing advocacy groups funded by industry and restoring limits on corporate donations to political campaigns.

Domain 2: The Commission is cognisant that perceptions of opioids are polarised and simplistic, when in reality these drugs are in some cases of great benefit and in others very harmful. Regulators should hold this dual nature of opioids in mind rather than adopting either overly lax or overly restrictive prescribing policies, both of which have substantial potential for harm. The drug-approval process would be improved if consideration of the risk of a drug being misused and more long-term, pragmatic clinical trials on the risks and benefits of opioids were done. Improvement of pain management is crucial and could be facilitated in the USA by re-energising the National Pain Strategy, which was released in March, 2016, near the close of the Obama Administration. The medical profession should promote opioid stewardship both for its own value and to help restore trust in medicine among policy makers and the public, which the opioid crisis has damaged. Methods for fostering opioid stewardship include prescription drug monitoring programmes, prompts in electronic prescribing systems that nudge clinicians towards safer prescribing, and expanded access to opioid agonist therapy for addiction while still maintaining adequate controls.

Domain 3: The Commission notes the lack of accessible, high-quality, non-stigmatising, integrated health and social care services for people with opioid use disorder in the USA (and in Canada, to a lesser but still noteworthy extent). This situation could be improved by financing such care through the mechanisms that support the rest of the health-care system. The Commission recommends reforming public and private health-insurance systems to address this issue, including cutting off funding for care that is likely to be harmful. The Commission suggests that care systems should follow established models of chronic-disease management to promote many pathways to recovery from addiction. It also calls for long-running disputes between factions in the field to be set aside, and urges these factions to unify under the banner of public health. Finally, a major investment in workforce development is recommended—specifically increasing the number of addiction specialists and increasing the addiction-related knowledge and skills of general practitioners.

Domain 4: Although some advocates believe that the criminal justice system should not have any role in responding to addiction, some role is inevitable given the public safety harms of intoxicated conduct and the fact that many arrests of people who are addicted

involve non-drug crimes (eg, domestic violence). The Commission therefore focused on ways of maximising the good the justice system could do while minimising the damage it can inflict. The former includes provision of addiction treatment and other health services during incarceration; the latter includes foregoing incarceration for possession of illicit opioids for personal use, repealing collateral penalties for drug-related crimes, and repealing laws punishing opioid use during pregnancy.

Domain 5: Epidemics are never resolved solely through the provision of services to identified cases. Prevention of new cases is essential. One practical tactic to curtail the opioid epidemic in the USA is to adopt methods used in other countries to facilitate the disposal of the billions of excess opioid pills in households. Because most risk factors for developing drug problems are generic (eg, chaotic or unrewarding environments, social exclusion, violence and other trauma, child abuse and neglect, and individual risk factors such as difficulty managing emotions, coping with challenges, and exercising behavioural self-control), another important tactic is to support horizontal prevention programmes for young people that strengthen core capacities and reduce risk not only for drug use, but also for many other problems such as depression, anxiety, poor academic performance, and obesity. Restriction of youth-targeted advertising of addictive drugs (eg, alcohol, tobacco, cannabis, pharmaceuticals) is another valuable prevention effort that keeps the environment in mind. Finally, the Commission notes evidence that enriching supportive structures and rewards within the environment more broadly, particularly for children and adolescents in economically struggling, high-stress regions, could plausibly lower the incidence of addiction in the long term.

Domain 6: The Commission is dismayed to note the slow pace of innovation in society's response to drug problems across law enforcement, health care, data science, drug development, and technology. Some programmes and policies worthy of endorsement are variants of approaches that were recommended during previous drug crises. The Commission therefore recommends implementing public policies that correct for failures in patent law and market incentives, prioritising opioid molecule redesign and development of non-opioid medications, and weighing international data more heavily in medication approval decisions. It also suggests deploying innovative strategies to disrupt fentanyl transactions (eg, spoofing internet-based drug markets) and tasking a federal agency with out-of-the-box demonstration projects (eg, delivery of prevention and treatment programmes for substance use disorder in unconventional settings, development of a device for automated naloxone administration, application of machine-learning methods to predict response to pain and risk of addiction in patients for whom an opioid prescription is being considered).

Domain 7: Finally, the Commission warns that pharmaceutical companies based in the USA are actively expanding opioid prescribing worldwide, and are using fraudulent and corrupting tactics that have now been banned domestically. This highlights risks of a repeat of the tobacco experience, in which an addiction-promoting industry adapted to tighter regulation in wealthy countries by expanding its business in lower-income nations. The Commission urges regulators in the USA to stop pharmaceutical producers from exporting aggressive opioid-promotion practices abroad. To provide an alternative to partnering with for-profit multinational corporations, the Commission recommends that WHO and donor nations coordinate provision of free generic morphine for analgesia to hospitals and hospices in low-income nations.

Because the opioid crisis developed over decades, reversing it in the USA and Canada and preventing it from spreading abroad will not be easy. Even perfect attainment of all the recommendations here will not eliminate the opioid crisis. Tragically, many future deaths are inevitable at this point. But implementing the Commission's recommendations has substantial potential to save lives and reduce suffering in the USA and Canada, and around the world. The gains of such policies will be long lasting if they curtail the power of health-care systems to cause addiction and maximise their ability to treat it.

Introduction

Over the past 25 years, the USA and Canada have experienced an increasingly devastating opioid crisis, which has cost those nations more lives than World War 1 and World War 2 combined.¹ Although COVID-19 has seized the attention of policy makers and the public, the epidemic of addiction and overdose that preceded it remains unabated, and seems to have been worsened by the consequences of COVID-19.² This deepening disaster led Stanford University School of Medicine and *The Lancet* to assemble a Commission on the North American opioid crisis. Here we present the findings and analysis of the Commission and the recommendations that follow from them.

A brief review of the evolution and status of the North American opioid crisis provides the context for the Commission's recommendations. One aspect of the crisis is not new: opioid addiction was prevalent for more than a century before the crisis began. Beginning in the late 19th century, advances in chemistry and capitalism have combined to dramatically expand population exposure to tobacco, stimulants (eg, cocaine, amphetamines), sedatives (eg, barbiturates, benzodiazepines), and opioids (eg, morphine, heroin), making addiction a much more prevalent public health problem in the USA, Canada, and many other societies. But nothing in the drug history of either the USA or Canada was remotely on the scale of the contemporary opioid crisis.

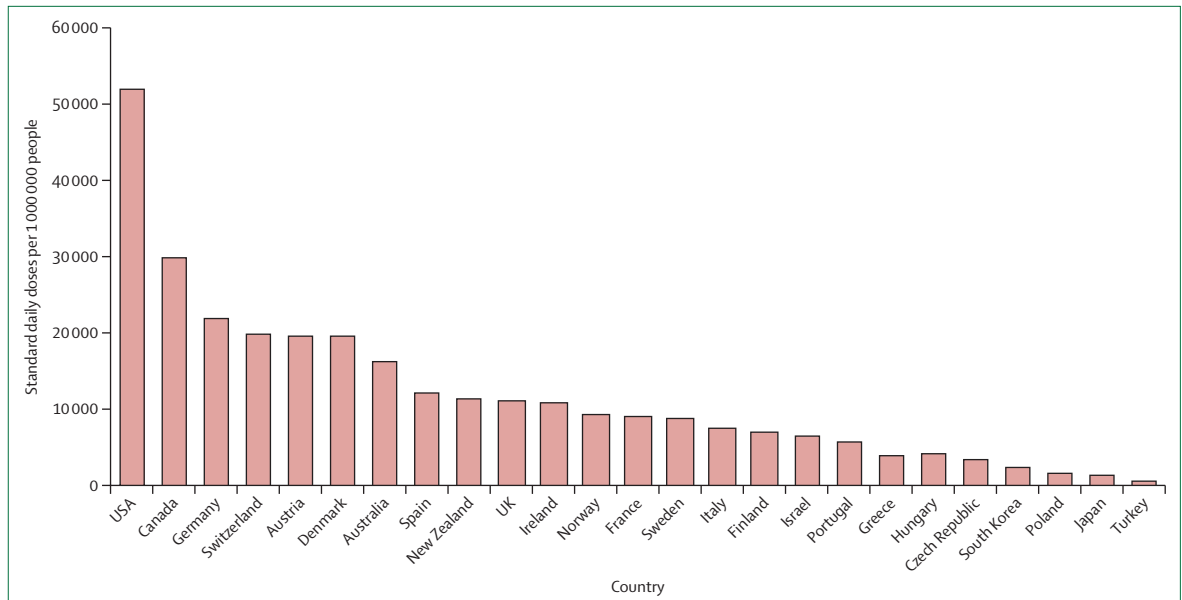


Figure 1: International per-person consumption of prescription opioids (2010–12)
 This period coincides with the peak of opioid prescribing in the USA and Canada.

The approval of Purdue Pharma’s long-acting opioid medication OxyContin in 1995 is as reasonable a point as any to date the beginning of the modern opioid crisis.³ OxyContin was fraudulently marketed as less addictive than other opioids and hence as more acceptable to use for a broad range of indications and at high doses. But when crushed to immediately release all their active ingredients, OxyContin and other long-acting opioids that followed are more potent than any formulation that had preceded them. The widespread availability of pharmaceutical opioids also has no historical parallel. Backed by the most aggressive marketing campaign in the history of the pharmaceutical industry, OxyContin became the best known of a number of opioid medications (both extended-release and immediate-release formulations) whose prescription rate exploded in the USA and Canada.⁴ Regulators failed to step in, for reasons ranging from industry co-optation to incompetence to a sincere but mistaken belief that they were ushering in a new era of improved patient care.⁵

Departing from decades of medical practice in which opioids were used mainly for cancer, surgery, and palliative care, US and Canadian regulators, physicians, and dentists expanded opioid prescribing to a broad range of non-cancer pain conditions, from lower back pain to headaches to sprained ankles.^{6–9} Per-person opioid prescribing in morphine milligram equivalents roughly quadrupled between 1999 and 2011.¹⁰ In 2012, medical practitioners in the Canadian and US health-care systems wrote 275 million opioid prescriptions—roughly equivalent to one prescription for each adult in those two nations.^{10,11} This level of opioid exposure has no historical antecedents worldwide.^{12,13} The UN gathers data converting different types of opioids into a standard

daily dose, which allows comparison across countries. These data (figure 1) show that the population-adjusted standard daily dose in the USA and Canada substantially exceeded those in other high-income countries.¹⁴ This excess is particularly notable for the USA, because the comparator nations mostly have older populations and all have universal health care, both of which would be expected to increase prescribing.

The political and cultural environment at the time the crisis emerged was not conducive to an early response; indeed, complacency allowed it to worsen. To attain respectability, trust, and influence throughout the world, opioid manufacturers strategically donated a small share of their profits to prominent institutions, including hospitals, medical and dental schools, universities, museums, art galleries, and sporting events.^{4,5,15} These donations secured goodwill and increased the credibility of the industry’s message that it was a selfless healer, pushing back against cruel anti-opioid prejudices. Also, in the wake of the aggressive response to the USA’s crack cocaine epidemic, a backlash against any form of drug-supply control was ascendant, and some prominent cultural commentators characterised any concerns about opioid overprescribing as a war-on-drugs-style crackdown,¹⁶ reinforcing the messages of the corporations that were profiting from the epidemic.

Some patients in pain might have benefited from increased opioid prescribing, but the overall effect was catastrophic. The health-related consequences were prescription opioid-linked morbidity (eg, addiction, depression, hormonal dysregulation) and mortality (eg, from overdoses and accidents), which rose roughly in parallel with increased prescribing (figure 2). The deleterious effects transcended health to include

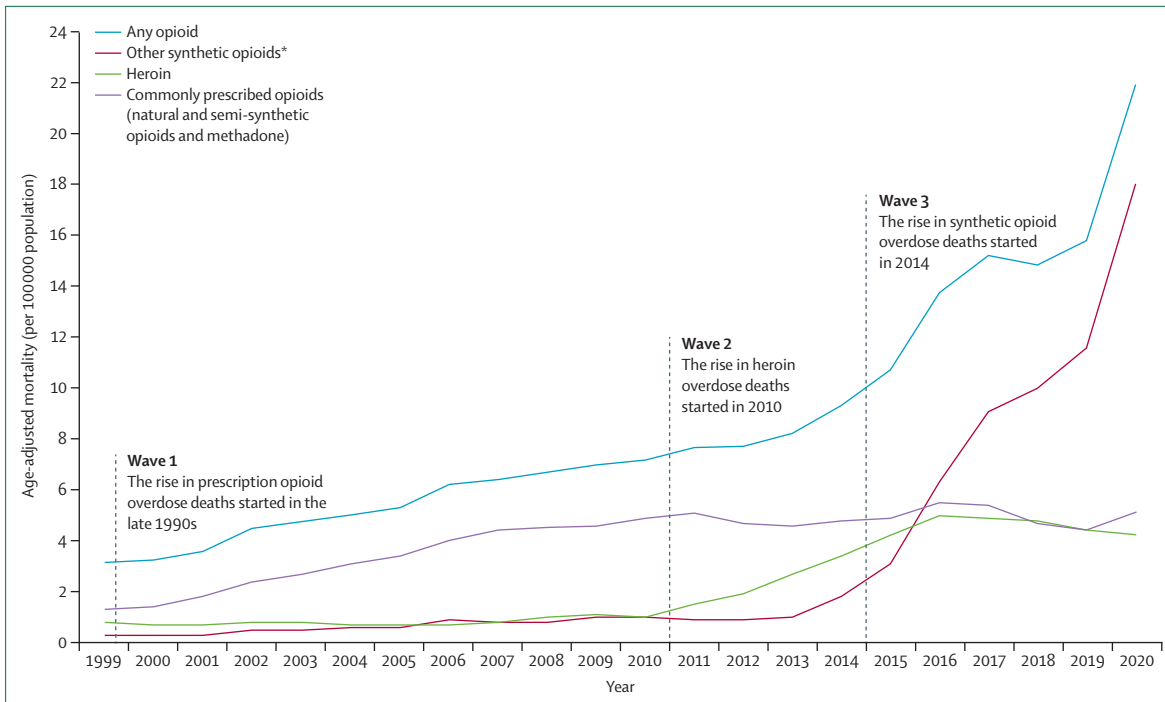


Figure 2: The three waves of the epidemic of opioid overdose deaths in the USA

Data are from the US Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research.¹⁷ *Tramadol or fentanyl prescribed or illicitly manufactured.

For the **Wide-Ranging Online Data for Epidemiologic Research** see <https://wonder.cdc.gov/>

increased unemployment, disability, crime, school dropout by children who used opioids (or whose parents used opioids), and family disintegration.¹⁸ The US Centers for Disease Control and Prevention (CDC) estimated the annual cost of the epidemic at a trillion dollars in 2017, equivalent to a staggering 5% of US gross domestic product.¹⁸ Despite Canada and the USA differing on many dimensions that might be assumed to limit the spread of drug-related morbidity and mortality (eg, the availability of universalised health care, levels of inequality, and availability of addiction-focused health services), the frequency of opioid overdose deaths is similar in the worst hotspots in the two countries.¹⁹ The opioid crisis has shown that, in the absence of adequate supply control over addictive drugs, damage to human health and wellbeing is unavoidable, an issue that we will return to later in the Commission's report as part of our discussion of the prospect that the crisis could spread beyond the USA and Canada.

The first wave of the contemporary opioid crisis involved prescription opioids and started in the mid-to-late 1990s, and occurred at a time when illicit markets in heroin were isolated and stable in much of Canada and the USA. The second wave, which began around 2010, was fuelled by the first, and was instigated by drug traffickers realising that individuals addicted to prescription opioids were a fertile potential market for heroin.²⁰ As traffickers expanded heroin markets, including in small cities and towns where they had never operated before,²¹ many people addicted to

prescription opioids were drawn in by the comparatively low price of heroin.¹ An analysis of pooled national data from 2002 to 2011—a period before any substantial controls on prescribing were introduced—calculated that 79·5% of Americans who initiated heroin use started with prescription opioids.²² Once efforts began to stop the rise in prescriptions and to reduce the diversion of prescriptions to individuals other than the intended recipient, some people addicted to prescription opioids began shifting to heroin more rapidly than they otherwise might have.^{23,24}

The third wave of the opioid crisis began around 2014, as illicit drug producers began adding extraordinarily powerful synthetic opioids, such as fentanyl, to counterfeit pharmaceutical pills, heroin, and stimulants.^{25,26} This wave brought unprecedented lethality in addition to—rather than instead of—the previous waves, both of which continue today. Large numbers of US and Canadian people are still becoming addicted to prescription opioids each year, and most of those who die from heroin and fentanyl overdoses are previous or current users of prescription opioids.^{27,28}

The waves of the opioid crisis did not crash with equal force on all shores of life. In the USA, the first wave had a greater adverse effect on white Americans than African Americans, partly because white Americans are more likely to have health insurance—and thereby ready access to prescription opioids—than Black Americans.²⁹ Racist beliefs that African Americans have unusually high

Panel 1: Voices of individuals and families facing opioid addiction

"I've got terrible pain, but I'm also addicted to painkillers, and right now my addiction is worse than my pain."

Patient in recovery from alcohol use disorder for 10 years who became addicted to prescribed morphine⁴⁴

"I started seeing a lot of pills around 15 years old and I told myself I was never going to do them. But kids were selling Oxys at school for \$3 a pill. By the time I was 19, I was looking in every medicine cabinet and bathroom."

Jonathan Whitt, Minford, OH⁴⁵

"Those people you keep hearing about on television who they find passed out in parking lots? That was me ... I wasn't homeless or in trouble. I was just bankrupt inside. I was empty. There wasn't another use left in me."

Nina Zakas, Charleston, WV⁴⁶

"I don't want Nick to be only a statistic or thought of as a throwaway person who didn't matter. People always said how positive, polite, and well mannered he was. But I don't want people to think that that should be the criteria for not dying of a fentanyl overdose."

Patricia O'Connor (Nick's mother), Vancouver, BC⁴⁷

"After the surgeries, when I got back home ... at that point I was lost. I was in a different world, on deep, deep, deep medications, different types. And then I started finding myself calling more, and then at some point your mind turns to the only thing that really makes any difference [which] is to get pain medication. It was kind of an irrational thing, that this is supposed to help me get up and move around, but it's keeping me down and destroying me."

Patient addicted to prescribed meperidine⁴⁸

tolerance for pain or are particularly prone to divert medication might also have reduced opioid prescribing in African Americans compared with white people.^{30,31}

In both the USA and Canada, Indigenous peoples had extremely high overdose rates during the first wave of the epidemic.^{32,33} In the USA, Native lands were the only areas in which the volume of opioid prescriptions rivaled the very high rates reported in Appalachia.³⁴ High rates of prescribing to Canadian First Peoples have also been reported and the community has experienced substantial opioid-related harm,³² both of which can be partially traced to so-called fly-in physicians on short-term contracts. Such physicians administer much of the health care for many of Canada's Indigenous communities, and often favour quicker pharmaceutical fixes over more time-consuming pain treatments (eg, physiotherapy).³⁵

Many middle-class, employed people have prescription opioid use disorder (OUD), but the problem is more prevalent among unemployed people and people in low-income families.³⁶ People experiencing homelessness and unstably housed people are at high risk of overdose, though few jurisdictions collect data on housing status as part of routine surveillance.³⁷⁻⁴⁰ People who have recently been released from incarceration are at very high risk of overdose.^{40,41} Unlike previous opioid epidemics in the USA and Canada, some of the regions with the highest mortality in the contemporary epidemic have been predominantly rural (eg, West Virginia and Maine in the USA, the Yukon in Canada). Other rural areas had lower than average mortality. National US survey data gathered in 2015 showed that the prevalence of prescription OUD gradually became similar across rural, suburban, and urban areas.³⁶

The second and third waves hit urban areas and some minority populations harder than did the first wave.⁴² In the USA, the rate of death from overdose is growing fastest in African Americans.⁴³ Some of these deaths are among stimulant users and long-term heroin users, who were probably unaware that the drugs they consumed were laced with fentanyl analogues.

No group was immune from any of the three waves of the opioid crisis, even though each wave affected different communities differently. The combined effect has harmed almost every subpopulation in the USA or Canada, with enormous human cost (panel 1). In the USA, the 2020 mortality rate for opioid toxicity is nearly 22 per 100 000 population, whereas in Canada the rate is nearly 17 per 100 000. Both of these rates exceed the mortality rate at the peak of the HIV/AIDS epidemic in these countries.⁴⁹⁻⁵¹

Current status of the opioid crisis in the USA and Canada

In the USA and Canada, 2020 was the worst year on record for fatal opioid overdoses in terms of both total number of deaths and percentage increase compared with the previous year. Opioid toxicity deaths in Canada increased by 72%, from 3668 in 2019 to 6306 in 2020.⁵² Total deaths from opioid toxicity in Canada numbered 21111 between Jan 1, 2016, and Dec 31, 2020, with a further 3515 reported in the first six months of 2021.⁵² US data from 2020 show that the incidence of fatal opioid overdoses rose by 37% (from 51133 in 2019, to 70168 in 2020), bringing the total number of such deaths since 1999 to more than 583 000.¹⁷ Moreover, the CDC's provisional data analysis estimates that for the 12 months ending May 30, 2021, 75 387 deaths from opioid toxicity occurred,⁵³ suggesting the problem continues to worsen. Although the 2020 spikes might be partly attributable to the effects of the COVID-19 pandemic, a rising trajectory of deaths was evident in the USA throughout 2019, and in both countries during the first quarter of 2020, before the pandemic had properly taken hold in either country.⁵⁴⁻⁵⁷

The COVID-19 pandemic has affected virtually every aspect of life and society, and substance use disorder and overdoses are no exception. Before the pandemic, fentanyl and other synthetic opioids had already begun spreading throughout the entire USA (previously they had been rare in illicit drug markets west of the Mississippi River, but common in western Canada).⁵⁴ Disruptions to drug supplies as a result of shelter-in-place restrictions could have further favoured synthetic opioids, which are cheaper by weight compared with lower-potency drugs and are largely distributed by post.^{57,58} A study⁵⁹ of five of the 33 regions that the US Drug Enforcement Administration has designated as significant centres of illicit drug production, manufacturing, importation, or distribution (known officially as High Intensity Drug Trafficking Areas) showed that between March and September, 2020, the number (but not aggregate weight) of seizures of fentanyl and methamphetamine increased significantly compared with the same period in 2019. By contrast, there was no significant change in the count or weight of heroin or cocaine seizures.⁵⁹ During the COVID-19 pandemic, treatment policy for OUD also changed in several ways, including an expansion of telehealth in the USA and Canada, greater provision of take-home methadone in the USA, and the suspension and eventual removal of the additional training requirement to prescribe buprenorphine for OUD treatment to up to 30 patients in the USA.^{60–62} (As of December, 2021, US prescribers are required to complete additional training and register with the federal government to qualify to prescribe buprenorphine for OUD to more than 30 patients at a time.⁶⁰) The implementation of these measures varied greatly in ways that are still being assessed, but evidence from some states suggests that the number of people receiving medications for OUD increased after regulations were relaxed.^{63–65} Changes to incarceration policy and practices could also have affected both the frequency of overdose and treatment for OUD, as some jails and prisons reduced populations or adapted corrections-based treatment for OUD in response to the pandemic.^{66–68} Importantly, the social effects of living through a pandemic—including isolation, unemployment, lack of familiar daily structures, and well-founded worries about life in uncertain times—have probably contributed to rising overdoses and worse outcomes for people living with OUD.⁶⁹

This epidemiological overview draws on the most recently available national mortality data from the USA (ie, CDC Wide-ranging Online Data for Epidemiologic Research)¹⁷ and Canada (ie, the Public Health Agency of Canada's Special Advisory Committee on the Epidemic of Opioid Overdoses);⁵² it also incorporates data from various subnational jurisdictions that have reported more recent data than national governments.⁵³ Fatal overdoses constitute only one dimension of the opioid crisis, but such overdose data are more recent and of

higher quality than data for other areas (eg, prevalence of heroin use and OUD). Furthermore, overdose deaths are arguably a proxy for other harms. Therefore, we did basic analyses on the 2020 national data in the USA and Canada to establish the landscape of opioid overdose mortality in terms of geographical, demographic, and social factors. These were the most recently available data common to both countries as of December 2021, when we updated our analyses.

Although much of the data from the USA and Canada can be directly compared, the CDC and Public Health Agency of Canada classify opioid toxicity deaths differently in two important ways: origin and category. The most recent Public Health Agency of Canada report distinguishes between pharmaceutical and non-pharmaceutical opioids and separately categorises drugs as fentanyl, fentanyl analogues, or non-fentanyl opioids. The CDC does not classify by pharmaceutical origin and uses the categories heroin, natural and semi-synthetic opioids (which includes most prescription opioids such as oxycodone, hydrocodone, and codeine), methadone, other synthetic narcotics (which includes fentanyl, fentanyl analogues and precursor chemicals, tramadol, meperidine, and novel psychoactive substances like isotonitazene or U-47700⁷⁰), and opium. The CDC data do not distinguish pharmaceutical from illicitly manufactured fentanyl, although the former accounts for only a very small proportion of deaths in both countries.²⁶ To facilitate approximate comparisons between the two countries with pharmaceutical opioids, we combined natural and semi-synthetic opioids and methadone in the CDC data.

The Canadian statistics described here are based on data that included apparent toxicity deaths involving opioids available as of Nov 12, 2021, with some province-level reporting differences.⁵² Most provinces reported all completed death investigations, whether the manner of death was ruled accident, suicide, or undetermined; some provinces report deaths when investigation is ongoing, Alberta had incomplete reporting for suicides, and Prince Edward Island did not report suicides or undetermined deaths. In 2020, only partial year data for Manitoba were available. In 2020 and 2021, Quebec reported all illicit drug toxicity deaths in one category (n=547 in 2020, n=212 for January–June, 2021) rather than separating opioids from other substances as it had in 2019 (n=203 opioid toxicity deaths). In total, it is not clear to what degree these combined reporting differences would lead to overestimation or underestimation of the national total. Statistics on sex of decedents was available only for apparent accidental opioid toxicity deaths.

For our analyses of CDC data, we used the Multiple Cause of Death File. For longitudinal analyses, we included deaths occurring between Jan 1, 1999, and Dec 31, 2020,¹⁷ that were coded with International Classification of Diseases (10th edition; ICD-10) codes for at least one of the following as a cause of death: accidental poisoning (X40–X44), intentional self-poisoning (X60–64),

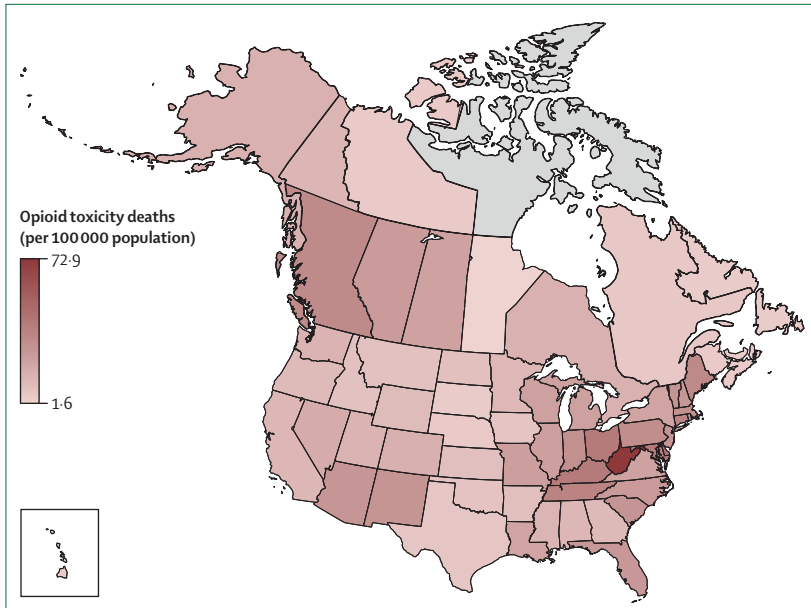


Figure 3: Age-adjusted opioid toxicity deaths (per 100 000 population) in the USA and Canada, 2020
 Canadian data from Public Health Agency of Canada. US data from the Centers for Disease Control and Prevention Wide-Ranging Online Database for Epidemiologic Research. Values for Quebec include all illicit drug toxicity deaths—separate statistics for opioids were not available. Values for Nunavut were unavailable due to small counts.

assault by drugs (X85), or poisoning of undetermined intent (Y10–14), and at least one of the ICD-10 codes for opioid involvement (T40·0–T40·4 and T40·6). For demographic analyses, we used the same criteria to examine deaths occurring between Jan 1, 2020, and Dec 31, 2020. In the US total, we included 70 168 fatal opioid toxicity deaths, many of which involving several categories of opioids or other substances. Deaths were associated with use of other synthetic narcotics in 57 350 cases (82%), natural and semi-synthetic opioids in 14 005 (20%) cases, heroin in 13 388 (19%) of cases, methadone in 3704 (5%) of cases, unspecified narcotics in 1739 cases (2%), and opium in four (<1%) cases. Detailed US mortality data that specified the drugs involved were downloaded from public online datasets (Connecticut; Cook County, IL; Dallas-Fort Worth, TX),^{71–73} or provided to the Commission via public records requests (Milwaukee County, WI; Jefferson County, AL; Los Angeles County, CA). Because of the way the online data extraction is set up, it was only possible to examine polysubstance involvement in the CDC dataset coded with an underlying cause (rather than any contributing cause) of X40–44, X60–64, X85, and Y10–14. For this polysubstance analysis only, we therefore included 68 380 deaths in 2020, indicating that overdose was the underlying cause of 97% of the deaths for which it was a contributing cause.¹⁷ To examine polysubstance involvement we used ICD-10 codes for cocaine (T40·5); psychostimulants with abuse potential, a category that is nearly entirely composed of methamphetamine (T43·6, Y49·7); alcohol (T51, X45, X65, Y15); and benzodiazepines (T42·4, Y47·1).

The December, 2021, report from Public Health Agency of Canada’s Special Advisory Committee on the Epidemic of Opioid Overdose documented 6306 opioid overdose deaths in 2020. During this period, 81% of deaths involved fentanyl, 11% involved fentanyl analogues, and 31% involved non-fentanyl opioids (percentages total more than 100 because, as in the USA, many deaths in Canada involved substances from two or more categories). For some statistics, this report provided only percentages; when available, numbers are included here. Overall, 76% of fatal overdoses involved only non-pharmaceutical opioids, 13% involved only pharmaceutical opioids, and 7% involved both. In 3% of cases, it was not possible to establish if the opioids involved were pharmaceutical or non-pharmaceutical.⁵²

In both the USA and Canada, the mortality varied substantially between states and provinces (figure 3). The highest rates in Canada were in the western provinces of British Columbia and Alberta. The highest rates in the USA were in Appalachia, the mid-Atlantic region, and the northeastern seaboard. Canada’s 2020 age-adjusted rate was 16·8 opioid overdose deaths per 100 000 population, a 70% increase on the 2019 rate of 9·9 deaths per 100 000 population. In the first 6 months of 2021, Canada’s opioid overdose rate has continued to increase, reaching 19·3 deaths per 100 000 population.⁵² The USA’s age-adjusted rate in 2020 was 21·8 per 100 000 population, a 38% increase on the 2019 rate of 15·8 per 100 000 population.

In the USA and Canada, most fatal opioid overdoses occur in men.^{52,53} In 2020, 49 682 (71%) of the 70 168 fatal opioid overdoses in the USA occurred among men, who had a population-adjusted and age-adjusted rate of death 2·5 times that of women. In 2020, men in Canada died from accidental opioid overdose at a population-adjusted (not adjusted for age) rate 3·2 times that in women, with men accounting for 75% of opioid overdose deaths during this period.⁵² In Canada, the largest sex disparity was in British Columbia, where men died from accidental opioid toxicity at a rate 4·8 times higher than that in women during this period. New Brunswick had the smallest sex disparity: the accidental opioid toxicity mortality rate among men was only 1·3 times that among women. In the USA, the 2020 rate ratio for age-adjusted opioid overdose mortality among men versus women was greatest in Rhode Island (3·3), California (3·2), New Jersey (3·1), and Connecticut (3·1), and least in Arkansas (1·3), Idaho (1·3), Utah (1·4), and Nebraska (1·4).

Types of opioids involved in fatal overdose also differ by sex. In 2020, opioid-related deaths among women were more likely to involve a prescription opioid than those among men in both the USA (6694 [33%] of 20 486 deaths among women vs 10 392 [21%] of 49 682 among men) and Canada (31% vs 17%).⁵² Nearly 80% of fatal fentanyl overdoses in Canada in 2020 occurred among men, as did 80% of fatal overdoses involving fentanyl analogues; similarly, 10 027 (75%) of the

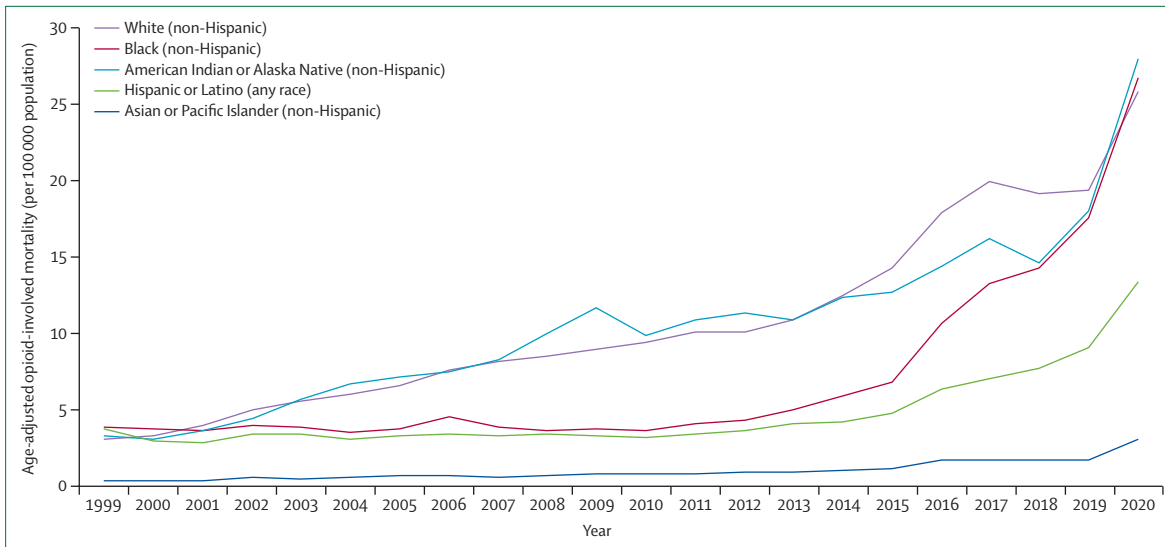


Figure 4: US age-adjusted opioid-involved mortality (per 100 000 population), 1999–2019

Data are from the US Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research.¹⁷

13 388 people who died from heroin overdoses, and 41 851 (73%) of the 57 350 people who died from synthetic narcotic overdoses, in the USA in 2020 were men.

From 1999 to 2019, the age-adjusted rates of fatal opioid overdose in the US were highest among non-Hispanic American Indian and Alaska Native people and non-Hispanic white people. Since 2011, the mortality rate has grown fastest among non-Hispanic Black or African Americans, surpassing non-Hispanic white populations in 2020 (figure 4).⁴³ In the USA in 2020, the age-adjusted rates of fatal opioid overdose was highest among Non-Hispanic American Indians or Alaska Natives (28.0 per 100 000 population) and non-Hispanic Black or African Americans (26.8 per 100 000), surpassing that of non-Hispanic whites (25.8 per 100 000). Overdose mortality rose steeply in Hispanic or Latino people of any race, from 4.7 per 100 000 in 2015 to 13.3 per 100 000 in 2020.

Substantial racial disparities emerge at the state level. In only eight of the 37 states and District of Columbia with sufficient race and ethnicity data available to calculate mortality rate ratios between non-Hispanic white people and non-Hispanic Black or African American people are the age-adjusted opioid toxicity mortality rates for the two populations within 10% of each other. Compared with white non-Hispanic people, the age-adjusted opioid overdose mortality rate for Black non-Hispanic people was 50–100% higher in six states, whereas in five Midwestern states (Illinois, Iowa, Minnesota, Missouri, and Wisconsin) and the District of Columbia it was more than double that in non-Hispanic white populations. Four southern states (Florida, Georgia, Mississippi, and South Carolina) had age-adjusted opioid overdose mortality rates in white non-Hispanic populations that were more than double those in non-Hispanic Black or

African American populations. Only ten states had counts of fatal overdose among non-Hispanic American Indian and Alaska Natives large enough to calculate age-adjusted mortality at the state level. In eight of these states, age-adjusted opioid overdose mortality among non-Hispanic American Indians or Alaska Natives was higher than that of non-Hispanic white people, and in six states it was higher than that of non-Hispanic Black people. The state with the most substantial racial disparities in 2020 was Minnesota, where American Indians or Alaska Natives had an age-adjusted opioid overdose mortality rate of 115.1 per 100 000 population, more than ten times that of non-Hispanic white people (10.7 per 100 000 population) and more than three times that of non-Hispanic Black or African American people (36.3 per 100 000 population). Opioid toxicity mortality rates were generally lower in Hispanic people (13.3 per 100 000 nationally) than in the non-Hispanic population. However, the age-adjusted opioid overdose mortality rate was higher among Hispanic people of any race than among non-Hispanic people of any race in four states: New Mexico (32.4 per 100 000 vs 23.9 per 100 000), Colorado (20.4 per 100 000 vs 15.6 per 100 000), Massachusetts (35.9 per 100 000 vs 29.9 per 100 000), and Pennsylvania (36.1 per 100 000 vs 32.5 per 100 000).

Most opioid toxicity deaths occurred among people aged 20–59 years in the most recently available data for both the USA (61 279 [87%]) and Canada (89% of apparent accidental opioid toxicity deaths).^{52,53} Fatal overdoses involving synthetic narcotics were most common among individuals aged 30–39 years, with 30% of opioid toxicity deaths occurring in this age group in both the USA and Canada.^{52,53} In Canada, deaths involving non-fentanyl opioids skewed older, with 39% of non-fentanyl opioid deaths occurring in people aged 50 or older.⁵²

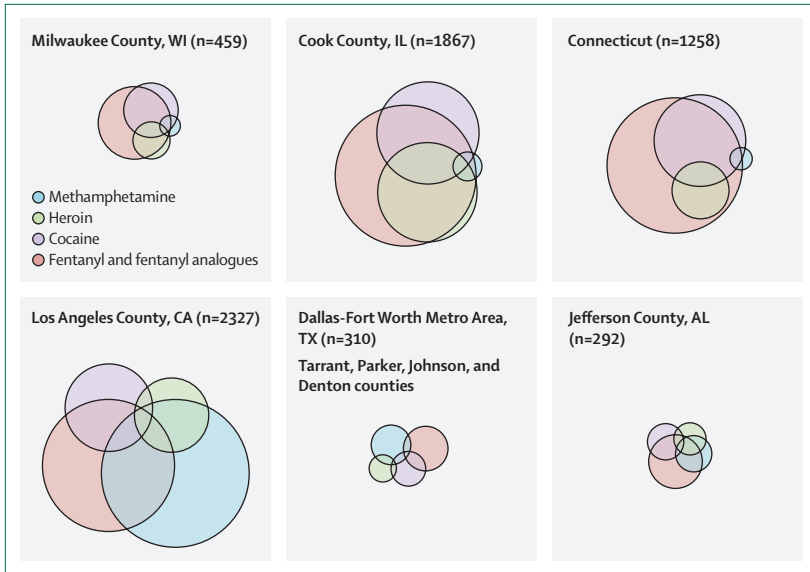


Figure 5: Proportional drug combinations involved in fatal overdoses in US jurisdictions with detailed medical examiner data available, 2020

Based on death investigations that were completed at time of data request.⁷¹⁻⁷³ Official counts by jurisdictions may differ as all investigations are completed. These areas were chosen to provide a country-wide view.

Polysubstance use, particularly involving stimulants, is common in fatal overdoses in the USA and Canada but the substances used and the degree of polysubstance use varies substantially within and between the two countries. Mortality data do not distinguish between intentional and unintentional co-use of opioids and stimulants. That said, in Canada, 60% of accidental fatal opioid overdoses in 2020 also involved stimulants and 40% involved other psychoactive substances.⁵² In the USA in 2020, 27 996 (41%) of the 68 380 fatal opioid overdoses for which overdose was the underlying cause of death also involved stimulants (either methamphetamine or cocaine). Specifically, 15 338 (22%) involved cocaine, 14 777 (22%) involved methamphetamine, 11 116 (16%) involved alcohol, and 10 771 (16%) involved benzodiazepines. Overlap between stimulants and opioids varies substantially in the US jurisdictions that make individual-level mortality data available (figure 5).

Differences in the drugs involved in fatal overdose can be striking even between proximal geographical areas. In British Columbia in 2020, 91% of accidental fatal overdoses involved fentanyl, and the proportion was similar in the first half of 2021.⁷⁴ A few hours' drive south, across the USA–Canada border in King County, WA, fentanyl was implicated in 33% of overdose deaths in 2020.⁷⁵ In US jurisdictions with detailed medical examiner data (which become available in advance of CDC mortality data), substantial differences are apparent in the substances implicated in fatal overdoses.^{54,70} For example, in the eastern and mid-western USA (ie, Connecticut; Chicago, IL; Milwaukee, WI), nearly all fatal heroin overdoses also involve fentanyl,

and cocaine is the more common stimulant. Conversely, methamphetamine is more common in the southern and western jurisdictions with available data, and a substantial proportion of heroin deaths do not involve fentanyl.

The Stanford–Lancet Commission on the North American Opioid Crisis

The Commission was created in late 2019, when *Lancet* editors reached out to KH. Stanford University School of Medicine (Stanford, CA, USA) subsequently agreed to partner with *The Lancet* and to provide all funding for the Commission's work. Ten Stanford-affiliated individuals already working on some aspect of the opioid crisis were invited to join by KH, as were eight leading experts from around the USA and Canada. One expert, Tom Coderre, contributed to the early work of the Commission but then stepped down in 2021 to assume a policy-making role in the Biden Administration. Three additional distinguished scholars (Prof Anne Case, Princeton University, Princeton, NJ, USA; Prof Richard Frank, Harvard University, Cambridge, MA, USA; and Prof Shelly Greenfield, Harvard University, Cambridge, MA, USA) were asked to participate in the special role of adviser.

Commissioners were drawn from addiction medicine, biochemistry, emergency medicine, epidemiology, health economics, internal medicine, law, pain medicine, policy analysis, psychiatry, pharmacology, and public health. The Commission included clinicians, researchers, educators, public policy makers, and people with lived experience of addiction and chronic pain. All Commissioners were based in the USA or Canada, reflecting the fact that the opioid crisis is, at the time of writing, concentrated in these countries.

After an initial meeting of Stanford-based Commissioners in January, 2020, to begin charting the project's timeline and goals, all Commissioners, the three advisers, and *The Lancet's* Americas Editor convened for two days at Stanford University in February, 2020, for a series of discussions about various aspects of the crisis. Each discussion section was facilitated by a different Commissioner, and generated lists of key analytic themes, critical data, and potential policy actions. After this meeting, the three advisers provided initial feedback and then, to avoid groupthink, absented themselves from all deliberations for the ensuing ten months.

Unlike some other *Lancet* Commissions, this Commission focuses on a long-entrenched problem that has already been well characterised, including in several reviews⁷⁶⁻⁷⁸ by the National Academies of Sciences, Engineering, and Medicine (on which several Commissioners had served). The Commission therefore did not aim to provide another comprehensive literature review, but instead focused on developing a coherent, empirically grounded analysis of the causes of, and solutions to, the opioid crisis. Some epidemic modelling work was done to support this process, and has been described in detail elsewhere.⁷⁹

The Commission moved its deliberations online with the onset of the COVID-19 pandemic. Subgroups with special expertise investigated and debated individual issues over email before presenting their findings to the full Commission for further discussion. Any major substantive conclusion or recommendation that did not receive at least 90% support from Commissioners was modified until it achieved such support. If it did not receive at least 90% support even after modification, then it was dropped.

Although more limited in geographical scope than other *Lancet* Commissions, this Commission draws on evidence from beyond the USA and Canada to discuss ways to prevent the international spread of the opioid crisis. The term “North American” is a linguistic convenience referring to the continent where the two countries are based, and does not imply that every country (eg, Mexico^{80,81}) and territory (eg, Greenland) on the continent is experiencing an opioid crisis.

Panel 2: Abbreviated list of Commission recommendations

Domain 1: The US and Canadian opioid crisis as a case study in multi-system regulatory failure

Curbing industry influence on prescribers

- Curtail promotion of pharmaceutical products
- Insulate medical education from pharmaceutical industry influence

Curbing industry influence on regulators

- Close the so-called revolving door between the pharmaceutical industry and regulators
- Stop relying on the pharmaceutical industry to oversee post-approval monitoring and risk mitigation
- Firewall bodies with formal power to regulate opioid prescribing from industry influence

Curbing industry influence on the political process

- Expose fraudulent advocacy groups (so-called astroturf groups)
- Restore limits on corporate donations to political campaigns

Domain 2: Opioids’ dual nature as both a benefit and a risk to health

Recognition of the risks and benefits of opioids in the drug-approval process

- Consider risk of diversion and drug market interplay in approval review
- Conduct long-term, pragmatic trials of opioids’ risks and benefits

Care of chronic pain during an opioid crisis

- Implement national strategies for the prevention and management of pain
- Anticipate and address potential adverse effects of prescribing policy changes on patient subpopulations who might be harmed by them

Promote opioid stewardship in medicine

- Restore trust in medicine by leading safer prescribing initiatives
- Exploit electronic medical record systems to monitor and guide prescribing
- Expand opioid agonist therapy (with reasonable controls) to patients with OUD

Domain 3: Build integrated, well supported, and enduring systems for the care of substance use disorders

- Permanently mainstream addiction care within health and social care systems

- Expand public and private insurance to adequately finance care of substance use disorder
- Curtail provision of harmful treatments
- Invest in addiction training for both specialists and generalists

Domain 4: Maximise the benefit and minimise the adverse effects of the criminal justice system’s involvement with people addicted to opioids

- Offer addiction-related health services during and after incarceration
- Do not incarcerate people for simple possession or use of illicit opioids
- End collateral penalties for drug-related crimes
- End penalties for substance use during pregnancy

Domain 5: Create healthy environments that yield long-term declines in incidence of addiction

- Raise the quality of disposal programmes for excess opioids in the USA
- Integrate substance use prevention programmes with other prevention programmes targeting children (such as those aimed at depression, anxiety, obesity, and school dropout)
- Expand early childhood enrichment programmes for low-income families

Domain 6: Stimulate innovation in the response to addiction

- Implement public policies that correct for failures in patent law and market incentives
- Prioritise redesign of opioid molecules and development of non-opioid medications for pain and addiction
- Weigh international data more heavily in medication-approval decisions
- Deploy innovative strategies to disrupt fentanyl transactions
- Task a federal agency with conducting innovative demonstration projects of new approaches to the opioid crisis

Domain 7: Prevent opioid crises beyond the USA and Canada

- Prevent pharmaceutical companies in the USA from exporting fraudulent and corrupting opioid promotion practices
- Distribute free, generic morphine for analgesia to hospitals and hospices in low-income nations

The Commission members are scholars rather than elected officials with a democratic mandate, and thus our analysis and recommendations are informed by science rather than based on purely political and philosophical rationales. All Commission recommendations therefore had to be grounded in evidence of probable benefit to public health or public safety, or both.

The Commission took a population public health perspective, emphasising general principles and policies for responding to the crisis. It therefore did not attempt to delineate clinical issues such as how to manage the care of individual types of patients with OUD or what precise human service elements each individual health-care organisation should offer to such patients.

The Commission's model of the opioid crisis estimates that, in the absence of any intervention, 1220 000 fatal opioid overdoses will occur in the USA between 2020 and 2029.⁷⁹ The Commission therefore proposes bold responses (panel 2) that the USA and Canada can adopt to better meet this enormous public health issue. The remainder of this report analyses the challenges created or illuminated by the opioid crisis in seven key domains and presents recommendations that are responsive to each.

Domain 1: The US and Canadian opioid crisis as a case study in multi-system regulatory failure

"The opioid crisis is, among other things, a parable about the awesome capability of private industry to subvert public institutions"

Patrick Radden Keefe, Empire of Pain⁸²

The opioid crisis resembles previous drug crises (eg, the rise of heroin addiction in North American cities in the 1960s and 1970s) in some respects but differs in others. Most particularly, the origins of the opioid crisis reflect substantial failures within the corporate sector, regulatory and legislative bodies, the medical profession, and health-care systems. Because the epidemic of opioid addiction and overdose emerged from, and is still to some extent being fuelled by, legally prescribed opioids, policy responses need to be uniquely tailored to that reality. Drawing attention to regulatory failures is also essential to help the USA and Canada to avoid similar mistakes with other prescription drugs, and to inform other nations about how to avoid opioid crises of their own.

Perhaps the most important fact to remember about the opioid crisis is that, for some people, it brought not suffering but enormous wealth. OxyContin alone is estimated to have generated revenues of over US\$35 billion for Purdue Pharma and its owners, the Sackler family.⁸³ John Kapoor's shares in the pharmaceutical company he founded, Insys Therapeutics, were worth US\$650 million before he was imprisoned for having his sales representatives bribe doctors to prescribe a fentanyl spray and training other staff to defraud insurers who asked for justification for the prescriptions.⁸⁴ Johnson & Johnson, Endo, Teva, and

other opioid manufacturers also reaped substantial revenue from soaring prescription rates. Many pharmaceutical distributors also profited handsomely while knowingly making astonishingly large shipments of pills, which they were required to report to regulators but did not.^{85,86} And profit-seeking was not entirely external to the health-care system: some hospitals, clinics, pharmacies, professional societies, and individual health-care professionals also enriched themselves.^{4,44,86}

Public health professionals have long recognised that manufacturers, distributors, and retailers of explicitly recreational addictive drugs (eg, alcohol, tobacco) have to be tightly regulated to prevent the maximisation of profit at the expense of public health and safety. The opioid crisis makes it clear that the same need for tight regulation holds within ostensibly well regulated medical systems. Risks are not limited to opioids: barbiturate overprescribing generated harm in the past,⁸⁷ excessive benzodiazepine^{88,89} and stimulant⁹⁰ prescribing is causing harm currently, and the future could bring new prescription drug crises. Assignment of blame, punishment, and restitution for the past is a matter under consideration in various courts of law. A key question for the future is how to regulate industries—including the health-care industry—to prevent the profit motive from fomenting oversupply and overprescribing of drugs with addictive potential.

Opioid manufacturers directed their efforts to expand the market for their products towards three main targets: prescribers, regulators, and policy makers. Here, we analyse each of these targets in turn.

Pharmaceutical industry influence on prescribers and medical education

In 2016, the pharmaceutical industry spent US\$20·3 billion marketing its products directly to prescribers in the USA.⁹¹ This marketing comprises in-person office visits, large and small gifts (eg, branded office supplies, meals and receptions at conferences, travel expenses), and direct financial payments for endorsing industry products in lectures and case conferences. The pharmaceutical industry engages in these practices because they are proven to increase prescribing of their products.^{92,93} OxyContin was the subject of the most lavishly funded promotional campaign in the history of medicine,^{4,94} which was highly successful at generating revenue for Purdue Pharma and helped to ignite an epidemic of addiction and overdose in the USA and Canada. Counties in the USA that were targeted with higher levels of physician-focused marketing had higher rates of opioid prescribing and overdose mortality one year later than did those less targeted by marketing.⁹⁵

Some opioid manufacturers also inserted promotion of their products into the electronic medical record systems that physicians use to prescribe medications. In January, 2020, a vendor of electronic prescription systems was fined US\$145 million by the US Government for

accepting kickbacks from Purdue Pharma in exchange for designing software that promoted the prescription of OxyContin to patients for whom the drug was not appropriate.^{96,97}

Promotion directly to patients is less of a concern for opioids than for other prescription drugs because direct-to-consumer advertising of controlled medication is generally illegal. Nonetheless, the role of direct-to-consumer advertising in opioid overprescribing is still worth mentioning. New Zealand and the USA are the only countries that allow direct-to-consumer marketing that makes therapeutic claims about pharmaceutical products.⁹⁸ From 1997 to 2016, the pharmaceutical industry in the USA increased spending on such advertising from US\$1.3 billion to US\$6 billion.⁹¹ By comparison, the entire 2016 budget for the US Food and Drug Administration (FDA) was US\$4.9 billion.⁹⁹

Opioid manufacturers have various ways of using direct-to-consumer advertising to promote opioids even while abiding by laws that forbid mention of them. These methods include indirect promotion, such as buying a US\$10 million television advertisement during the Super Bowl for a non-controlled drug that makes long-term opioid use more tolerable by reducing constipation.¹⁰⁰ The pharmaceutical industry also sponsors unbranded campaigns to change the public perception of illness and broadly expand the market for medications, which opioid manufacturers did as a way of normalising the use of opioids for non-cancer chronic pain.¹⁰¹ The bombardment of US citizens with pharmaceutical advertising increases prescribing even for medicines not mentioned in advertisements,¹⁰² perhaps because direct-to-consumer advertising changes public expectations about the responsibilities, role, and power of physicians. Making individuals who have medical disorders aware of effective pharmacotherapies is valuable, but direct-to-consumer advertising can also be a form of public health miseducation (panel 3). Among other problems, it can foster the false impression that, if pressured enough by patients,¹⁰⁷ physicians can and should provide medicines that eliminate every source of human suffering.

Prescription drug manufacturers also attempt to influence prescribing by influencing the education provided by universities, hospitals, and professional societies. Collaboration between universities and private companies can spur innovation, and every academic member of the Stanford–Lancet Commission works at an institution that has received outside donations to support scholarly and educational activities. These realities coexist with evidence that the educational process has been corrupted by opioid manufacturers in various ways throughout the opioid crisis.

For example, in explaining its 2019 decision to strip the Sackler name from its School of Graduate Biomedical Sciences, Center for Medical Education, and other entities to which the family had donated, Tufts University acknowledged how educational

Panel 3: Medical cannabis, consumer-targeted advertising, and the opioid crisis

In several countries, the cannabis industry began marketing the legalisation of cannabis as a solution to opioid overdoses after a study¹⁰³ showed that, between 1999 and 2010, states with medical cannabis programmes had lower than expected opioid overdose mortality. The association between these two population-level indicators was vulnerable to the ecological fallacy, whereby individual-level relationships might differ from the aggregate relationship. Furthermore, when seven additional years of data were added to the time series,¹⁰⁴ the pattern of results reversed: states with medical cannabis laws had higher than expected mortality from opioid overdoses between 1999 and 2017, even after the restrictiveness of cannabis laws was controlled for.

Nevertheless, the cannabis industry promoted the initial study findings on billboards and in advertising campaigns (figure 6). Additionally, several states added opioid use disorder as a qualifying condition for medical cannabis on the basis of the initial ecological correlation—a level of evidence that would be judged unacceptable in other areas of medicine.¹⁰⁵ Compared with states where opioid use disorder was not a qualifying condition, a greater proportion of medical cannabis dispensaries operating in states where opioid use disorder was a qualifying condition advertised cannabis as a replacement for medications for opioid use disorder approved by the US Food and Drug Administration.¹⁰⁶ These dangerous practices continue despite their being based on study findings that have not been replicated.



Figure 6: An example of the cannabis industry marketing claims related to opioid use disorder and overdose

This billboard was installed in Salisbury, MA. This photograph originally appeared in the *Daily News of Newburyport* (on June 12, 2017), and was taken by Bryan Eaton.

decisions at the institution were inappropriately shaped to serve Purdue Pharma's interests (eg, using corporate materials in teaching, blocking a book documenting the opioid crisis from being chosen as the common book that all incoming MD and MPH students would read and discuss). It also disclosed how Purdue Pharma made use of its Tufts connections, including at one

point having a Tufts faculty member appear in an advertisement for the company's products.^{108,109} Similar problems have been documented at other universities.¹¹⁰

The pharmaceutical industry also attempts to shape education in academic medical centres through on-campus representatives. Some evidence of the effects of these activities comes from assessments of academic medical centres that restrict such visits, which often—though not always—hand out fewer prescriptions for marketed drugs than do those without such restrictions.¹¹¹ For example, in a study¹¹² of 85 medical centres, restrictions on receiving gifts, limits on accepting paid speaking opportunities and consulting engagements, requirements to disclose industry ties, and bans on sales representatives were associated with an 8.8% decrease in the amount of opioids prescribed.

Professional societies, which are leading providers of education for both clinicians and the public, are another potential site of unacknowledged industry influence. In 2021, five leading pain specialists publicly resigned from the taskforce on the 2021 Global Year Against Back Pain,¹¹³ which was established by the International Association for the Study of Pain and the European Pain Federation, to protest undisclosed links between the taskforce and the opioid manufacturer Grünenthal. These resignations brought the education campaign into public disgrace even before it was launched.

Recommendations for reducing influence on prescribers and medical education

Curtail pharmaceutical product promotion

The simplest way to curtail prescriber-focused marketing is for lawmakers to ban it outright. Some individual states and health-care systems in the USA have such bans in place, but they are not national in scope.^{114,115} By contrast, in Germany, professional traditions and laws generally forbid the provision to physicians of gifts or benefits that could influence future prescribing decisions or could be considered a reward for past prescribing decisions.¹¹⁶ In 2018, Canada's health minister finally asked opioid manufacturers to voluntarily cease marketing to physicians, and in 2019 Health Canada announced its intent to put formalised rules in place to legally restrict the content of such promotion.¹¹⁷

The Commission recommends that the USA make similar national policy moves immediately. Because of the potential for direct-to-consumer advertising of pharmaceutical products to mislead patients, including to the point where patients pressure prescribers to make suboptimal care decisions,¹⁰⁷ the Commission also recommends that the USA join the rest of the world in banning all direct-to-consumer pharmaceutical advertising that makes therapeutic claims.

Because the US Supreme Court has ruled that corporations have the same speech rights as individuals, a ban on pharmaceutical advertising is unlikely in the near term. A less potent but still valuable interim

alternative is to remove the ability of pharmaceutical companies to deduct the costs of advertising from their income when filing tax returns. This policy, which has been proposed both by Republican and Democratic US senators and by President Joe Biden, would raise the cost of advertising relative to other investments the industry might make—research and development, for example.^{118,119}

Additionally, the Commission recommends that the pharmaceutical industry should be forbidden from involvement in the design and implementation of electronic prescribing systems. Such systems should be designed solely with improved patient care in mind and should not be exploited as a commercial platform.

Decouple industry donations to universities and professional associations from control over educational content

Any for-profit industry given the power to shape educational programming that could increase sales of its products is very likely to take advantage of such an opportunity. Universities and professional societies should therefore accept only educational funding that is donated into a common pool over which the pharmaceutical industry has no control of any kind. The nature and content of courses on prescribing should be established by scientists, clinicians, and educators free of industry ties. These principles have gathered increasing support across the medical profession over the past decade and have been incorporated into the US Council of Medical Specialty Societies' code for interactions with industry¹²⁰ and in the US Accreditation Council of Continuing Medical Education standards.¹²¹ These principles should also be supported by accreditors of medical, nursing, dental, and pharmacy schools. Concealment of pharmaceutical industry support of clinician education or public education, including conferences given by professional associations and patient advocacy organisations, is never acceptable.

Pharmaceutical industry influence on regulation of addictive drugs

OxyContin is a highly potent extended-release form of the opioid oxycodone that was approved for wide use by the FDA on the basis of the fraudulent premise that it was less addictive than other opioids—a mistake that stained the FDA's reputation. But the FDA was not the only pliant regulator. Between 1994 and 2015, the quota of oxycodone that the Drug Enforcement Administration permitted to be legally manufactured was raised more than 20 times, from 3850 kg in 1994 to a high of 153750 kg in 2013.⁸²

Drug approval is only one step in a process that is modifiable or even reversible if problems arise, but further regulatory failures prevented such corrections from happening for years in the opioid crisis. Had post-marketing studies of the many approved opioid medications been promptly done, the risks of addiction would have come to light more quickly. Had effective risk-assessment strategies been rolled out to prescribers,

opioids might have been prescribed more safely. And had the second line of regulators who come into play after a drug is approved (eg, medical boards, accreditation organisations) acted more quickly, lives might have been saved. Understanding the role of industry influence thus has to go beyond drug approval to what happens after approval, and must go beyond illegal activity to include conduct that is within the bounds of defective laws.

The pharmaceutical industry clearly often succeeds at regulatory capture—ie, getting corporate interest prioritised over the public interest. A common method of regulatory capture is luring experienced individuals out of the regulatory world with lucrative salaries. This revolving door between the pharmaceutical industry and pharmaceutical regulation not only deprives regulatory bodies of talent, but also communicates to holders of official offices and regulatory agency staff that their future earnings could be shaped by how well the decisions they make please the industries they oversee.¹²²

Former US Congressman Billy Tauzin, for example, led the crafting of Medicare legislation that substantially expanded the US Government's purchasing of pharmaceutical products while simultaneously forbidding the Government from bargaining for lower drug prices. The day after his term ended, Tauzin became a leading pharmaceutical industry lobbyist, earning more than ten times his congressional salary.¹²³

Most cases are less dramatic than Tauzin's. When drug distribution firms oversupplied opioids and violated laws requiring that they report such suspicious shipments, they were investigated by the US Drug Enforcement Administration. One of the tactics the pharmaceutical industry used to fight these charges was to hire away key Drug Enforcement Administration employees to work for their side.¹²⁴ Several federal prosecutors in the USA who had initially been openly critical of Purdue Pharma recanted when they were hired by the company.⁴ The FDA can be subject to similar pressures.¹²² The official who oversaw the FDA's approval of OxyContin subsequently began working for Purdue Pharma at a salary that federal prosecutors allege was triple his FDA pay.¹²⁵ Similar concerns have been raised across the FDA's portfolio.¹²⁶

Under US law, once a risky drug is approved, monitoring and educating prescribers about these risks is to a large extent at the manufacturer's discretion. To protect public health, any post-approval risks or harms of medicines should be monitored, and prescribers should be equipped to mitigate such risks and harms if they arise. The FDA is legally empowered to mandate that manufacturers conduct studies of post-approval risks, which leaves the agency dependent on voluntary industry compliance. Many such surveillance studies have not even been begun years after the drug in question has been approved, others have been completed late, and still others have not been done at all.^{127,128} Studies that have been done have often not analysed or published their

data,¹²⁹ or were designed in a way that made the detection of adverse effects very unlikely.¹³⁰ This is not surprising given that identifying problems with approved drugs is of benefit to the public but could reduce sales and profits for manufacturers.

Similarly, when the FDA has mandated that manufacturers create and evaluate risk-assessment and mitigation strategies to help physicians prescribe opioids more safely, compliance has been grudging, and there is no evidence that patients have benefitted.^{131,132} Target numbers for the training of physicians are often not met,^{131,133} and the training materials are often of questionable utility.^{134,135} Mandated evaluations have often not been done, and if they have been done, they are rarely methodologically rigorous.¹³¹ When these evaluations have provided data, the pharmaceutical industry has rarely implemented changes to risk-assessment and mitigation strategies in response to findings.¹³⁶

Theoretically, the FDA has the power to respond to such industry non-compliance by pulling a drug from the market, but it rarely exercises this power. National medical leaders have advanced different explanations for this. Marcia Angell, former editor of *The New England Journal of Medicine*, has suggested that the FDA is reluctant to pull drugs from the market because it sees its institutional purposes and incentives as aligned with increasing the number of drugs available.¹³⁷ Indeed, in recent decades, successive congresses and presidential administrations have made changes to the FDA's authorising legislation that were specifically intended to enable more rapid approval of drugs.^{127,138}

Drummond Rennie, former deputy editor of the *Journal of the American Medical Association*, argues that the FDA is wary of offending pharmaceutical manufacturers because user fees provide part of its budget, which causes the agency to view the pharmaceutical industry rather than the public as its client.¹²⁷ Whether or not he is correct, the FDA might make some decisions based on rational fears of the pharmaceutical industry's considerable influence in Congress, which we discuss elsewhere in this report. In any event, the FDA cannot be blamed for following a law that gives more control over post-approval surveillance and risk-assessment and mitigation strategies to the pharmaceutical industry than to the government.

Once a drug is approved, more regulators come into play, including governmental agencies (eg, state and provincial medical boards) and non-governmental organisations that are formally ceded regulatory powers by government (eg, accreditation bodies specifically recognised in legislation). Industry connections to such bodies can be extensive. In the USA, the Joint Commission accredits hospitals and other health-care organisations, and its accreditation is formally recognised in the law of many states. A US Government Accountability Office investigation found that the Joint Commission's pain management education programmes

were funded and coauthored by opioid manufacturers, and that the Joint Commission's partnership with Purdue Pharma "may have facilitated its [Purdue's] access to hospitals to promote OxyContin".¹³⁹ The Joint Commission also promulgated in its accreditation standards the concept that pain is the "fifth vital sign", putting pressure on health-care organisations to increase opioid prescribing.¹⁴⁰ The Joint Commission began de-emphasising the term in 2002, and later clarified that the fifth vital sign concept was intended to raise awareness of pain. It also acknowledged that positioning pain as the fifth vital sign had been misinterpreted to mean that pain should be assessed at every patient contact, a practice which fuelled additional opioid prescribing.¹⁴⁰ Clinical practice guidelines written by individuals with ties to opioid manufacturers have echoed inaccurate promotional messages, including two guidelines that have been retracted by WHO and led the organisation to strengthen its conflict of interest policies.¹⁴¹

Provincial and state medical boards also have power through adjudicating patient complaints against prescribers, guiding practice norms in the field, and advising legislators and regulators. Industry is also involved at this level. For example, the US Federation of State Medical Board's guidelines on opioid prescribing were developed with the aid of individuals with extensive industry ties, and in 2003 distribution of the guidelines was funded by Purdue Pharma.¹⁴²

Even if it were possible for medical regulators to have extensive industry ties without their professional judgements being affected in any way, public perception of potential corruption still matters. Any regulatory standard for opioid prescribing or pain care risks substantial loss of credibility if funded by companies that have been criminally convicted of knowingly misrepresenting the risks and benefits of opioids.¹⁴³

Recommendations for limiting influence on the regulation of addictive drugs

Close the revolving door of officials leaving regulatory bodies to work for the pharmaceutical industry

Transfers of knowledge and skills between the public and private sector are not necessarily harmful to the public good and indeed might sometimes be beneficial.¹⁴⁴ But when such transfers occur specifically to enable industry to sway regulators, there are consequences for public health, as well as increased public cynicism and political alienation. The public good would be served by extending the length of cooling-off periods in state and federal law that constrain lobbying on behalf of an industry that an elected or appointed official used to oversee (eg, one proposed piece of legislation mandated a two-year period).¹⁴⁵⁻¹⁴⁷ Positive incentives should also be considered—eg, civil servants working in regulatory agencies could be paid higher salaries, with added retention incentives for senior officials with particularly deep knowledge of regulatory processes.

Post-approval study of adverse drug effects and education on risk mitigation should be handled by the government

Gathering data for post-approval drug safety and how to mitigate identified risks are essential for reducing drug-related morbidity and providing high-quality health care. US law entrusts these activities, which are essential for public health, to a for-profit industry whose revenue would be threatened by prompt, competent, and transparent assessment of, and education about, the risks of approved medications. That so much of the industry's work in this area is slow, of low quality, or non-existent is not surprising. The Commission recommends a fundamental change in approach: direct governmental control over post-approval drug surveillance and the development, implementation, and evaluation of risk-assessment and mitigation strategies are needed.

To avoid conflicts of institutional interest, these activities should not be overseen by the FDA's Office of New Drugs, which generally views its charge as being to bring more drugs to market. The funding and authority to monitor and mitigate post-approval drug risks—including the power to pull an approved drug from the market, if warranted—could be given to drug safety officials within the FDA, or, as some have proposed, to an independent agency outside the FDA.¹²⁷

Bodies with legal or regulatory power to shape prescribing should not accept industry funding or include people with direct financial ties to the pharmaceutical industry

We have already discussed the need to insulate organisations that can influence prescription decisions (eg, medical schools) from the pharmaceutical industry. The need for firewalls is even stronger when an organisation has formal legal or regulatory power to shape prescribing. The Federation of State Medical Boards' eventual decision to stop accepting funding from the pharmaceutical and medical device industry was a positive step, and should be uniformly adopted by US state and Canadian provincial medical boards.

Prohibitions against pharmaceutical industry influences in this arena are justifiable entirely because of concerns about protecting patients. But such rules also protect prescribers who practise ethically and compassionately. Like patients, physicians have a right to expect that the rules under which they prescribe were set based on scientific evidence and intended solely to benefit patients, not to enrich corporations.

Finally, the Commission notes that the spate of multi-billion-dollar lawsuits surrounding the opioid crisis in the USA can also create conflicts of interest. We propose that restrictions on regulatory bodies should apply not only to material connections to the pharmaceutical industry, but also to law firms suing some element of the industry and to people hired as expert witnesses by those firms.

Pharmaceutical industry influence on politics

Election campaigns in the USA are expensive, and office holders are aware of the need to raise sufficient funds to compete in them. Corporations and their employees have always been major donors to political campaigns, but changes to campaign financing laws—most notably the US Supreme Court's 2010 decision in *Citizens United vs Federal Election Commission*¹⁴⁸—have removed almost all limits on corporate political campaign contributions. (Canada, by contrast, has maintained caps on donation amounts.) Discussion of the effects of this Supreme Court decision across all areas of corporate influence is beyond the Commission's scope and expertise. We instead make the more focused observation that, in the specific case of the pharmaceutical industry, the removal of donation limits plausibly worsened the opioid crisis and increases the risk of further crises involving prescribed drugs.

The power that lobbying and unconstrained political donations give the pharmaceutical industry is hard to overstate. During a 10-year period, groups attempting to place some limits on opioid prescribing (eg, activist groups comprising people who had lost loved ones to overdoses) spent US\$4 million on lobbying and campaign contributions in US state legislatures. Over the same period, the pharmaceutical industry spent US\$880 million to persuade state legislators to serve their business interests.¹⁴⁹ Even if one conservatively assumes that only a small proportion of that money was spent on opioids, and that political donations from law firms suing the opioid industry have also entered the political equation as a partly countering force, the opioid industry's lobbying power is still clearly enormous.

The financial power of the pharmaceutical industry at the federal level is equally undeniable. For example, when the US Drug Enforcement Administration caught opioid distribution companies breaking the law by not reporting massive, suspicious shipments of opioids to particular communities, the companies asked Congress to pass a law curtailing the organisation's power to conduct such investigations. The pharmaceutical industry contributed US\$1.5 million to the campaigns of 23 lawmakers who sponsored the new law, including US\$100 000 to Representative Tom Marino, who led the law's passage in the House of Representatives.¹²⁴ Soon afterwards, Donald Trump, the president at the time, nominated Marino to become the Director of the White House's Office of National Drug Control Policy.¹

In addition to influencing policy makers with donations, opioid manufacturers have also followed the lead of other industries (eg, tobacco, fossil fuels) by engaging in what is known as astroturfing—ie, the creation of putatively grassroots groups (or infiltration of legitimate groups) that are covertly funded by the pharmaceutical industry and promote the industry's messages. A notable example in Canada was a coalition of industry-funded alleged patient advocacy organisations arguing against a government effort to

reduce drug prices.¹⁵⁰ A prominent US example is the American Pain Foundation, which publicly presented itself as an independent voice for people with pain while echoing opioid manufacturers' messages about the ample benefits and minimal risks of opioids.¹⁵¹ When it emerged that 88% of the American Pain Foundation's annual budget was provided by opioid manufacturers and medical device makers, and that the organisation closely coordinated its public messaging with industry representatives, the American Pain Foundation was dissolved.^{152,153} Other non-profit organisations in the opioid arena (eg, Pain UK) have been criticised by regulators for failing to disclose links with opioid manufacturers.¹⁵⁴

Surveys of patient advocacy groups across all areas of health estimate that 67–83% receive funding from for-profit entities (eg, pharmaceutical or medical device companies).^{155,156} A study¹⁵⁵ of 104 US advocacy groups with annual revenues of at least US\$7.5 million reported that 88% publish lists of donors in annual reports or online, but only 2% explicitly state that all corporate donors are listed, and 43% do not report any information about the number or size of donations. Extensive, rising, and underreported financial support of patient advocacy groups by the pharmaceutical industry has also been documented in other countries.¹⁵⁷

Recommendations for countering political influence

The USA should restore caps on political donations by pharmaceutical companies

The incentives in the US system of campaign finance are well aligned with the interests of the pharmaceutical industry and poorly aligned with public health. Pleas from politicians for individual virtue and courage are welcome but insufficient. The composition of the US Supreme Court at the time of writing means that immediate reform in this area is unlikely. But, in the long term, reinstating restrictions on corporate donations to political campaigns would help prevent the regulatory capture that increases the risk of future epidemics of addiction.

Prevent the pharmaceutical industry from covertly funding advocacy organisations

Patient advocacy is part of a healthy democratic society, and grassroots organisations should be welcome to accept donations and to advocate. However, when such organisations are financed by a for-profit industry, they should not be allowed to publicly represent industry messages as if they were independently derived grassroots opinions. Drug packaging must be labelled to identify its active ingredient; the same principle should apply to drug-related advocacy.

In the USA, corporations enjoy rights to free speech similar to those of people, but they do not have a right to purchase deceptive speech. For example, the US Federal Trade Commission has sued companies for purchasing positive online reviews of their products from third

parties.¹⁵⁸ Scott¹⁵⁹ has suggested productive regulatory changes in the USA context. First, to protect consumers, the Uniform Deceptive Trade Practices Act should be modernised to define astroturfing as a deceptive business practice and to mandate disclosure of material connections between alleged grassroots groups that endorse a company's products and the company in question. Second, because astroturfing can also represent a form of fraud against investors (by conveying that a company's products are more popular with the public than they are in reality), the Securities and Exchange Commission should exercise its authority to require full disclosure in annual corporate filings of all funding of advocacy groups in which corporations engage.

Legislative bodies and advisory boards at all levels of government should discourage astroturfing in hearings by adopting a public disclosure norm. For example, immediately after witnesses are sworn in (and thereafter legally required to tell the truth), the committee chair could direct that each witness publicly state whether they or their organisation have any financial connections to the industry whose products and practices are the subject of the hearing.

Journalists also have a role here, because mass media is one of the most common routes through which astroturf groups disseminate pro-industry messages. Journalists who consider quoting members of putatively grassroots advocacy organisations should adopt as standard practice asking whether the organisation is funded by the pharmaceutical industry and including that information in any reported coverage.

Domain 2: Opioids' dual nature as both a benefit and a risk to health

The second of the seven domains addressed by the Commission is opioids' dual nature—ie, opioids are both essential to modern medical practice and simultaneously potentially dangerous. Opioids' dual nature stems from the fact that they activate brain pathways that reduce pain, but also can slow breathing to the point of organ damage or death, and produce euphoria which can lead to addictive use. A further complexity is that opioid use can lead to OUD. However, the provision of opioid agonist therapies (eg, buprenorphine) often benefits people with the disorder.

Opioids can be prescribed in ways that have substantial negative effects, which has happened extensively in the USA and Canada, but they can also be prescribed with fewer adverse consequences (as in Germany, where prescribing is extensive but OUD and overdose are not).¹⁶⁰ Unrestrained opioid prescribing cannot reduce the population burden of pain (eg, through analgesic prescribing) or of opioid addiction and overdose (eg, through buprenorphine or methadone provision) without substantial collateral damage. At the same time, blanket downscaling of opioid prescribing can also do a lot of damage.

Many prescribers who contributed to the quadrupling of opioid prescribing in the USA and Canada sincerely believed that they were contributing to resolving the crisis of pain. Many equally well-meaning people today believe that throwing the switch the other way by massively reducing opioid prescribing, or flooding the addiction treatment system with opioid agonists such as buprenorphine and methadone, will resolve the opioid crisis. The human brain has an inbuilt propensity towards affectively simple judgements: people tend to categorise things as good or bad rather than good and bad.¹⁶¹ This human tendency towards black and white judgements is more pronounced when emotions run high,¹⁶² as is often the case when opioids are debated. Rising above those instincts to deal directly with the dual nature of opioids is essential for drug-approval decisions, the care of patients with pain, and opioid stewardship.

Recognising risks and benefits of opioids in the drug-approval process

During the opioid crisis, the health-care system supplied billions of dollars of dangerous, addictive drugs, which were diverted to illegal markets. In addition to doing damage directly, the massive expansion of prescription opioids also indirectly made illicit drug markets more deadly by creating an opportunity for heroin traffickers to expand their business.²⁰ Risks that a medicine might be diverted, and that it might exacerbate the damage of the illegal drugs markets, were historically not considered in the FDA's approval process. In 2018, the then-head of the FDA, Scott Gottlieb, ventured that the agency should assess approval applications for opioids in light of diversion risks and potential interplay with other drugs already available and in use in the health care system.¹⁶³

Some general risk factors for diversion are obvious, including the drug having recreational or performance-enhancing effects and being indicated for use in conditions that are hard to verify objectively. Other risk factors will require careful assessment on a case-by-case basis. The same points hold when anticipating interplay of the drug's supply with illegal markets, which will necessitate careful assessment of which illegal drugs might be a complement or substitute for the medication in question.

Another weakness in the approval process—which is not unique to opioids—is the reliance on short-term studies to assess safety and efficacy. To bring a product to market, pharmaceutical manufacturers have to meet the evidentiary standards of regulatory agencies (eg, the FDA, Health Canada, the European Medicines Agency). These standards include proof of efficacy, typically via a short-term trial (eg, of 12 weeks' duration). Manufacturers rarely extend the study longer, because doing so would raise costs and risk revealing longer-term adverse effects that could lessen their market

share. In the case of opioids, conducting short-term trials only can lead to underdetection of long-term physical dependence, OUD, and overdose, and reduced efficacy against pain over time.

Clinical trials of opioids for chronic non-cancer pain are only 5 weeks in length on average.¹⁶⁴ Such short-term trials tend to show better pain control with opioids than with placebo or non-opioid treatments, and few side-effects. However, to cite a well known exception, the SPACE trial¹⁶⁵ showed that, for back, knee, and hip pain, opioids produced more side-effects and were less efficacious at reducing pain intensity than non-opioid medications (eg, ibuprofen) over a 1-year period. The regulatory environment and the profit motives of the pharmaceutical industry create structural barriers to funding longer-term studies of opioids.

Additionally, across all areas of drug development, regulatory guidelines allow manufacturers to exclude broad swathes of the patient population from clinical trials but do not restrict drugs approved on the basis of such evidence from being prescribed to the patients who were excluded. If, for example, a manufacturer expects that a common comorbidity among patients with pain (eg, depression) raises the risk that a new opioid will result in addiction, they can exclude patients with depression from the trial, secure in the knowledge that they will still profit from sales to these patients after approval. Many studies of exclusion criteria across diseases have shown that clinical trials tend to exclude the most vulnerable individuals, including people with serious comorbidities, elderly people, and pregnant and lactating people.¹⁶⁶ Such individuals will receive the treatment within the health-care system anyway after it has been approved, an experience akin to receiving an experimental treatment—only without the usual informed consent or monitoring that would attend a scientific study.

Recommendations for recognising the risks and benefits of opioids in the drug-approval process

Drug-approval agencies should more heavily weigh concerns about diversion of drugs to illicit markets and the potential interplay of supply with other legal and illegal drugs

The Commission endorses Scott Gottlieb's call for drug-approval processes to encompass considerations beyond how a drug affects the individual to whom it is prescribed, such as potential for and impact of diversion, which has also been endorsed by other former high-ranking FDA officials.¹⁶⁷ We also recommended broadening Gottlieb's proposal in two ways. First, both intentional and unintentional diversion risk should be considered when national regulatory agencies contemplate the approval not only of opioids but of all substances with addictive potential (eg, stimulants, benzodiazepines). Second, regulatory agencies should weigh how introducing a new drug could interact not only with approved medicines, but also with drugs available in illegal markets. Regulatory agencies should be provided added funding

to conduct such assessments, which will require them to research illicit drug markets and to employ staff with the relevant expertise to analyse the data gathered.

In calling for greater consideration of risks that extend beyond the intended patient, the Commission does not suggest that such risks be the only consideration in drug approval. A desperately needed medicine should still be approved even if it is associated with a substantial risk of diversion. In such cases, regulators might advise that use of the drug be limited to within health-care facilities. Cocaine is an FDA-approved schedule II drug with almost no diversion because it is used for surgery and administered by clinicians only at medical sites, such as hospitals. Similarly, Germany has a population opioid prescribing rate close to Canada's, but no evident opioid crisis, because in Germany opioids are used mainly in supervised settings, whereas in Canada they are frequently prescribed to ambulatory patients.¹⁶⁰ Policy makers thus have options between approving unrestricted use and denying approval in cases when a drug has unique therapeutic value but also poses risks.

Governments should invest in long-term clinical trials of opioids and their effect on pain, function, and addiction in broadly representative patient samples

Over-reliance on short-term trials in specifically selected patient populations is built into the approval process, and means that drugs can be approved with no consideration of their potential longer-term harms. This issue can be rectified only via a sustained public commitment of resources to long-term trials or through changes to regulations to make drug approval contingent on longer-term trials. The Commission recommends expanded support for pragmatic trials of drugs that enrol all types of patients who are likely to receive the treatment in practice.¹⁶⁸ In addition to having a greater chance of detecting adverse effects because of their heterogeneous samples, such trials would also have more power to identify subgroups of patients who benefit particularly from treatments. These trials would not necessarily require public funding: manufacturers could be required to provide funding to non-industry investigators. Importantly, the findings of such longer-term trials should be consistently reviewed by drug-approval agencies so that they can make informed judgements about whether medications approved on the basis of short-term results should be restricted or pulled from the market because of their longer-term harms. The close monitoring of potential long-term effects of COVID-19 vaccines is a model worth applying to opioids.

Care of chronic pain during an opioid crisis

Chronic pain conditions are increasingly pervasive causes of functional impairment, reduced quality of life, and morbidity (eg, depression).¹⁶⁹ For example, low back pain is a leading cause of disability globally from adolescence

Panel 4: Patients and physicians on decisions about whether to prescribe opioids

“I constantly struggle on wanting desperately to believe the patients about their pain, but having that fear that it’s being diverted. Medications are being diverted or not used appropriately all the time. So, the subjectivity of it I find I struggle with all the time. And, again when I graduated residency it was [an] everyone is innocent until proven guilty-type thing. But I feel in our high-risk clinic almost it’s guilty until proven innocent, and that saddens me as a physician.”

Family physician, Ontario, Canada¹⁷⁸

“[Buprenorphine] can diffuse within the [addiction treatment departments], but to get it to diffuse beyond that, that’s the challenge. And that’s where it really will have its benefit ... Because, there are more people with the problem than can be handled [in addiction treatment settings] ... I think primary care clinicians need to take ownership and responsibility for helping their patients with addictions.”

Physician, USA¹⁷⁹

“They used to do every 2 weeks of getting my medication. Now it’s down to once a month or they [the physician] may say instead of a third of the pills [30 pills], we’re only going to give you 15. So, it [the opioid epidemic] has definitely affected me personally and I hate that.”

Patient with sickle cell anaemia, USA¹⁸⁰

“[The law] affects people like me [who are employed] because they won’t give [opioids] to you unless, you know, you go ... to the special clinic, the classes, to get them. Well, I knew that I couldn’t get [medications] until I went to the classes. I had to go to the classes in the winter. I had to hop out and catch the bus and go out west to go to the [pain] clinic to see the doctor.”

Patient with chronic pain, Indiana, USA¹⁸¹

“I don’t think people in chronic pain think about long term. We are basically, ‘How do I get through today?’ I just gotta get through today.”

Patient tapering opioids, Colorado, USA¹⁸²

through late life and ranks ninth in terms of overall disease burden.^{170,171} Low back pain was also one of the ten leading contributors to global decreases in disability-adjusted life years from 1990 to 2019.¹⁷¹ In the USA, 8% of adults reported experiencing “high-impact” chronic pain, which is defined as pain that limits life and work activities on most days, in the past 6 months.¹⁷² Although not a direct cause of death, pain can contribute indirectly to mortality by raising the risk of suicide and opioid overdose, for example. Pain is often poorly managed by health-care systems and is usually an orphan in public policy circles and research funding organisations. The lack of investment in basic and clinical science research could

contribute to the high costs of chronic pain. Lower back and neck pain account for more spending than any other condition in the USA’s health-care system, and much of this spending is on interventions of debatable effectiveness.^{173,174} Despite its impact, back pain was not tracked by the US National Institutes of Health as a research condition and disease-funding category until 2016,¹⁷⁵ and during that year only US\$23 million in research funding was devoted to the study of the condition.

Most prescribers, advocates, and health-care organisations were responding to a genuine problem when they increased opioid prescribing: patients in pain—sometimes excruciating, long-lasting pain. Debate continues about the proper role of opioids in acute and chronic pain management. Our intention here is not to review that debate, but rather to suggest that as long as pain is prevalent and poorly managed, overuse of opioids and attendant harms are more likely.¹⁷⁶

Debates about the proper level of opioid prescribing are sometimes bitter and unproductive because participants do not attend to the diversity of the patient population.¹⁷⁷ Patient subpopulations that are affected by prescribing policies include—but are not limited to—individuals not currently on opioids, individuals receiving short-term opioids for acute pain, patients with chronic pain who are taking opioid analgesics on a long-term basis, people addicted to opioids who are receiving medications for OUD, patients experiencing both OUD and chronic pain, individuals with untreated addictions, and various combinations thereof (panel 4).

Opioid prescribing policies should also recognise that, within and across cultures, there are substantial differences in perceptions of the proper role of doctors, the appropriate level of patient autonomy in care decisions, the meaning and tolerability of pain, the acceptability of risk, and the degree to which addiction is stigmatised, among many other factors (panel 5). These cultural forces merit attention not only because they affect patients’ expectations, but also because they influence the conduct and outlook of health-care professionals and policy makers.

One positive sign that the medical profession is dealing more effectively with the dual nature of opioids is the rise of opioid stewardship, which is defined by Canada’s Institute for Safe Medicine Practices as “coordinated interventions designed to improve, monitor, and evaluate the use of opioids in order to support and protect human health”.¹⁸⁶ Efforts to promote opioid stewardship explicitly recognise that opioids are essential for medical care and at the same time carry risks that must be carefully managed at the individual and system level. Sensible opioid stewardship programmes recognise that patients can be harmed by clinical decisions to prescribe or not to prescribe opioids. They also incorporate ameliorative strategies to protect patient subpopulations who face particular risks when health-care organisations alter prescribing policies.

Recommendations for the care of chronic pain in an opioid crisis

Nations should implement comprehensive strategies for pain prevention and management, of which opioid prescribing should be only one component

Patients with pain are more likely to receive better care if the care of pain is embraced as an urgent priority and organised in a rational fashion. The Commission therefore recommends that all nations develop a comprehensive pain strategy that embraces an interdisciplinary approach, is based on scientific evidence, addresses both prevention and treatment, and is insulated from the influence of the pharmaceutical and medical device industries.¹⁸⁷ Also crucial are a commitment to ensuring health equity across racial and ethnic groups, and a spirit of compassion towards—and willingness to listen to—people in pain and people experiencing addiction (and their families). The US National Pain Strategy (panel 6), upon which multiple members of the Commission worked, was released in March, 2016, near the end of the Obama Administration but was not funded or sufficiently implemented.¹⁷⁶ The Commission calls on the Biden Administration to revive the National Pain Strategy.

Policies restricting opioids should be sensitive to the needs of patients with pain

Responding to system-wide overprescribing by throwing the switch suddenly in the other direction by severely restricting opioid prescribing will have negative consequences for current and future patients with pain. Opioid stewardship initiatives and guidance documents in the USA and the UK emphasise that expanding the availability of effective non-opioid alternatives for pain increases the likelihood that decreased prescription of opioids will have a net beneficial rather than a net harmful effect on patients with pain.^{188,189} Relatedly, progressive tapering of doses in patients taking opioids should be an individually tailored activity, done carefully and slowly.¹⁸⁸ Prescribers should be specifically trained in this process, and should be compensated for this work. Canada's de-prescribing network is a promising effort to develop norms of practice in this area.¹⁹⁰ The US Department of Health and Human Services guideline¹⁹¹ deals well with the complexity of tapering opioid doses in clinical settings, including shared decision making to develop a collaborative approach with patients.

Promoting opioid stewardship in medicine

Proper opioid stewardship balances the benefits and risks of prescribing opioids in the care of patients. One underappreciated ingredient in stewardship is trust. From the earliest days of the opioid crisis, some individual physicians (eg, Art Van Zee)[†] raised concerns about the conduct of opioid manufacturers and the mounting death toll. Other physicians, professional associations, and health-care organisations joined the ranks calling for change in the ensuing decades. Yet

Panel 5: Opioid prescribing in Francophone regions

France and other Francophone regions have distinct patterns of opioid prescribing for reasons that are not well understood. The Swiss cantons in which high-potency opioids are the most heavily prescribed tend to be German-speaking, whereas those where lower-potency opioids predominate are in the Francophone region.¹⁸³ Among Canadian provinces, Quebec has the lowest rate of high-dose oxycodone prescribing; neighbouring Ontario exceeds its rate by a factor of almost eight.¹⁸⁴ Despite the proportions of the population reporting pain being broadly similar, US opioid prescribing rates in 2012–13 were more than five times those in France.¹⁸⁵

Advertisers have always appreciated the role of culture in driving product use, which is why they attempt to brand addictive products as culturally essential—eg, the Marlboro cowboy or Newcastle Brown Ale. Policy makers need to be equally aware that responding to the opioid crisis might require efforts to shift cultural attitudes in ways that support compassionate care of pain and addiction and towards judicious opioid prescribing (eg, media campaigns, public education).

other individual physicians and physician-dominated organisations impeded efforts to rein in the industry's misconduct. The motives behind this resistance varied, but the stance was harmful to the public. Most practising physicians were not on the front lines of what became a major conflict within the medical profession, but were still affected by it, and at times they made well intentioned prescribing decisions that they later came to regret.

Overprescribing and efforts to resist a return to judicious prescribing damaged public health and public trust. Health professionals being sent to prison for running so-called pill mills,¹⁹² defrauding Medicaid,²¹ and accepting illegal kickbacks from opioid manufacturers damaged the standing of medicine with the public.¹⁹³ Physicians who promoted opioids while being covertly paid by opioid manufacturers betrayed the trust not only of their patients, but of their colleagues and students too. Even the many well intentioned but harmful opioid prescribing decisions made by ethical prescribers over the past 25 years might have damaged the public's trust in their doctors. US people's confidence in medical leaders has been falling for more than 40 years,¹⁹⁴ and the opioid crisis has done nothing to reverse that trend.

Policy makers have also lost confidence in medicine, as evidenced by many governors and state legislators restricting the length of new opioid prescriptions to a month, a week, or even less.¹⁹⁵ Some physicians regard such laws with horror, both because of the intrusion on their autonomy and because these rules could harm patients, and while the former is certainly true, the

Panel 6: Priority areas and objectives in the US National Pain Strategy¹⁷⁶

Population research

- Objective 1: Estimate the prevalence of chronic pain and high-impact chronic pain in the general population and in primary care settings, both overall and in anatomically defined pain conditions and various population groups
- Objective 2: Refine and use standardised electronic health-care data methods to establish the extent to which people with common pain conditions, including people from vulnerable groups, receive various treatments and services, the costs of these services, and the extent of use of treatments that best evidence suggests are underused, overused, effective, or ineffective
- Objective 3: Develop a system of metrics for tracking changes in pain prevalence, effects, treatments, and costs over time that will enable assessment of progress and the effectiveness of interventions at the population health level (such as public education or changes in public policy, payment, and care), as well as identification of emerging needs

Prevention and care

- Objective 1: Characterise the benefits and costs of prevention and treatment approaches
- Objective 2: Develop nation-wide programmes for self-management of pain
- Objective 3: Develop standardised, consistent, and comprehensive pain assessments and outcome measures across the continuum of pain

Disparities

- Objective 1: Reduce implicit, conscious, and unconscious bias and their effects on pain treatment by improving understanding of the effects of bias and supporting strategies to overcome it
- Objective 2: Improve access to high-quality pain services for vulnerable population groups
- Objective 3: Facilitate communication between patients and health professionals

- Objective 4: Improve the quality and quantity of data available to assess the effect of pain on high-risk population groups, including data for group members' access to high-quality pain care and the costs of disparities in pain care

Service delivery and reimbursement

- Objective 1: Define and assess integrated, multimodal, and interdisciplinary care for people with acute pain, chronic pain, and end-of-life pain
- Objective 2: Enhance the evidence base for pain care, and integrate it into clinical practice through defined incentives and reimbursement strategies to ensure that the delivery of treatments is based on the highest level of evidence, is population-based, and represents real-world experience
- Objective 3: Tailor reimbursement to promote and incentivise high-quality, coordinated pain care through an integrated biopsychosocial approach that is cost-effective, comprehensive, and improves outcomes for people with pain

Professional education and training

- Objective 1: Develop, review, promulgate, and regularly update core competencies for pain care education, licensure, and certification at the undergraduate and graduate levels
- Objective 2: Develop a pain education portal that contains a comprehensive array of standardised materials to enhance available curricular and competency tools

Public education and communication

- Objective 1: Develop and implement a national public awareness and information campaign about the effects and seriousness of chronic pain, to counter stigma and correct common misperceptions
- Objective 2: Develop and implement a national educational campaign that encourages safe medication use, especially safe opioid use, among patients with pain

latter is still being assessed.¹⁹⁶ Regardless, the passage of these laws should be understood as a reflection of a loss of faith in medicine's ability to self-regulate. Even if such restrictive prescribing laws prove harmful to patients, they might persist or be expanded if policy makers and the public do not trust physicians to practise safely without tight supervision. These restrictions might feel unfair to physicians who have always prescribed carefully, and perhaps they are, but policy makers, like the public, sometimes make global judgements that are insensitive to nuance.

Trust is a precious commodity between patients and doctors, between the public and the medical profession, and between policy makers and health-care system leaders. The COVID-19 pandemic, during which many health professionals have acted heroically, increased trust in physicians in the USA.¹⁹⁷ An excellent way to

rebuild similar trust around prescription opioids is for every medical provider and health-care organisation to become actively engaged in the implementation of a culture of safer prescribing through the many strategies described in this report, irrespective of whether they are under external pressure to do so.¹⁹⁸ To cite an example, the US Veterans Health Administration employed 300 pharmacists to proactively provide evidence-based, in-person education about prescription drugs to medical staff. Individual and centre-level opioid prescribing was monitored, and clinicians and managers were equipped with computerised tools and skills to monitor patients' history of prescription drug use and risk profile.¹⁹⁹ Substantial resource investments were simultaneously made to increase capacity to manage pain without opioids. Over a five-year period, during which more than 2 million patients with incident chronic pain

were treated, the proportions receiving physiotherapy or occupational therapy and specialty pain clinic care increased by 10–20%.²⁰⁰ Prescriptions for most non-opioid medications also became more common for pain,²⁰⁰ and the number of patients receiving the risky combination of opioids and benzodiazepines fell by 47%. Contrary to fears that safer prescribing initiatives necessitate obliging long-term patients to taper opioids, more than 90% of the reduction in long-term prescription opioid use resulted from reducing the number of new long-term patients.²⁰¹

Electronic medical records and associated prescribing systems offer two avenues for improved opioid stewardship. The first is prescription drug monitoring programmes (PDMPs), which track prescriptions across health-care providers and pharmacies in both the USA and Canada.^{202,203} A key purpose of PDMPs is to prevent risky drug combinations (eg, to alert a primary care physician considering an opioid prescription that the patient is already taking a benzodiazepine prescribed by a psychiatrist). PDMPs also help to identify patients who covertly receive more prescriptions from more prescribers than could be justifiable for health reasons. This group of patients is small but noteworthy: a national US study²⁰⁴ showed that, in 2008, 0.7% of patients (around 135 000 individuals) received an average of 32 opioid prescriptions from ten prescribers, which accounted for 4% by weight (11 100 kg) of all opioid dispensing. Such individuals could be addicted to opioids or could be faking a serious pain condition to obtain drugs for supply to illegal markets. Proactive investigation of anomalous prescribing data (eg, to detect so-called pill mills) is another function of PDMPs. PDMPs with some law-enforcement involvement appear more likely to reduce fatal opioid overdoses than those without.²⁰⁵

PDMPs are only as good as the information upon which they are based, and their value is undermined if they are hard to use or if prescribers and pharmacists receive no training in how to use them, do not use them consistently, or do not enrol to use them at all. In the past 5 years, high-quality PDMPs with legally required enrolment and checking have reduced opioid-related harms more effectively than voluntary PMDP systems.²⁰⁶ The design and monitoring of PDMP data should have input from experienced medical professionals, who could, for example, advise on situations in which statistically unusual levels of opioid prescribing are appropriate (eg, palliative care).

Prescribing nudges are another opioid stewardship strategy enabled by electronic medical records. Nudge is a term from behavioural economics and refers to non-coercive ways of influencing decisions—for example by changing which choice is the default option. In a study²⁰⁷ of 2910 patients undergoing surgery, changing the default number of post-surgical opioid pills given from 30 to 12 reduced the median number of opioid pills prescribed after surgery by one third (from 30 to 20) without any indication of harm to patients. Findings of

this sort have been independently replicated.²⁰⁸ Nudges do not undermine physician autonomy because prescribers retain power to easily change the number of pills provided.

Just as for pain, the dual nature of opioids must also be recognised in addiction medicine. Opioid agonist therapy, particularly methadone maintenance, is probably the most extensively and rigorously assessed treatment in the addiction field.²⁰⁹ Across a range of patients, settings, and countries, clinical trials and observational studies have shown that methadone and other opioid agonist therapies are a cost-effective way to reduce morbidity and mortality in patients with OUD, criminal behaviour, and infectious disease transmission in the community.^{210–12} These medications, along with approved antagonist medications (eg, extended-release naltrexone), thus clearly have benefit for many patients with OUD.⁷⁸

Yet for several reasons, unconstrained use of opioid agonist therapy for OUD will not solve the opioid crisis. First, many patients with OUD do not want to be on opioid agonist therapy.²¹³ Second, many patients on such therapy have poor outcomes, including rapid dropout,²¹⁴ fatal overdose, and increased consumption of other drugs (eg, cocaine,²¹⁵ alcohol²¹⁶). Third, international experience (eg, in Denmark²¹⁷ and the UK²¹⁸) shows that when controls on methadone maintenance are loosened too much, the increase in population deaths from methadone overdose cancels out the drop in heroin deaths associated with increased access to methadone maintenance. Finally, the UK system, which has gone far in the direction of loosening controls on methadone, provides patients receiving opioid agonist therapy with only a few hours per year of evidence-based psychosocial services on average.²¹⁹

Recommendations for promoting opioid stewardship in medicine

To rebuild trust in medicine while helping patients, prescribers, health-care organisations, and professional associations should implement safer opioid prescribing initiatives

Programmes like the US Veterans Health Administration Opioid Safety Initiative should be actively adopted by prescribing clinicians. The primary reason to implement systematic opioid safety programmes is that doing so would benefit patients. Such programmes could also help to restore trust in the medical profession if physicians actively, willingly, and universally implement such efforts themselves rather than waiting for an outside regulator to impose controls (which may or may not be sensible). Many prescribers have already made steps in this direction, but these efforts should be expanded throughout the health-care system.

Opioid stewardship initiatives should embrace mandatory PDMPs and prescribing nudges

The Commission recommends universal mandatory enrolment in PDMPs in the US and Canadian health-care systems, with additional requirements to check the

system when starting patients on controlled drugs, such as opioids. Prescribers should be compensated for the costs of participation in PMDPs and, to make the process easier, technical improvements in PDMPs should be a high priority—eg, integration into widely used electronic medical record systems. For electronic prescribing, the ideal system would automatically do the PDMP check, alert the prescriber and pharmacist of any suspected doctor shopping or potentially dangerous drug interactions, and then upload the patient data to the PDMP database if and when the prescription is approved. PDMPs should also share data across states and provinces (eg, as per the US Veterans Health Administration PMDP).²²⁰ Further, PDMPs should include dispensing from methadone maintenance clinics and medical cannabis dispensaries to create a more complete list of controlled substances.

Nudges within electronic prescribing systems also merit expansion. Implementation of nudges at scale within electronic prescribing systems is a low-cost, minimally intrusive method of promoting judicious prescribing.

Availability of treatments for OUD should be expanded, but addiction care providers should recognise that maximising prescribing of opioid agonists with minimal constraints will not resolve the addiction crisis

The Commission recommends that opioid agonist therapy should be offered to every patient with OUD unless medically contraindicated (eg, because of comorbidities or potential drug–drug interactions), including patients who do not wish to participate in psychosocial services, because research does not clearly establish that such services are necessary for patients to benefit from opioid agonist therapy.^{214,221,222} Formal regulatory expansion of access to opioid agonist therapy should be considered. The COVID-19 pandemic has led US federal regulators to relax some requirements in place for medications for OUD. As a result, more methadone take-home doses can be given, and requirements that initial buprenorphine dosing be observed in person have been waived. Such loosening of requirements is necessary in a public health emergency. When the worst of COVID-19 has passed, governments should assess whether the balance of benefits and risks supports keeping these emergency measures to make care more accessible.^{223,224}

At the same time, evidence clearly shows the folly of assuming that population health inherently improves when health-care systems provide as many opioids as possible with as few possible regulatory constraints as possible. Policies that should attract scepticism include the dispensing of hydromorphone from vending machines and prescribing a range of potent opioids and other drugs (eg, benzodiazepines, stimulants) to individuals with OUD in hopes of creating a safe addictive-drug supply and eliminating the supervision of methadone patients—ie, converting the system to

unmonitored, long-term prescriptions on a take-home basis.²²⁵ Although expressed from a public health viewpoint, these messages echo the opioid manufacturers in presuming that unrestricted opioid provision can only improve public health. The faith of some advocates that opioids are safe as long they are not derived from illicit markets (eg, heroin contaminated with fentanyl) is impossible to reconcile with the hundreds of thousands of overdose deaths from legal, pharmaceutical grade opioids that preceded the introduction of fentanyl into US and Canadian heroin markets.²²⁶

Care providers should also consider that many patients with OUD have serious, unaddressed psychiatric, medical, family, employment, and housing issues that medication alone will not solve.²¹⁴ The provision of medication only has generated resentment among some addiction recovery activists, who feel that they are being managed rather than treated.²²⁷ Opioid medications can be powerful and effective in the treatment of OUD, but should not be used as an informal system of pharmacological sedation of poverty.

Domain 3: Building integrated, well supported, enduring systems for the care of substance use disorders

Health-care systems and policy makers often react to a surge in some form of addiction as if they are facing a transient, novel challenge. The attention of the US and Canadian public, media, and policy makers was transfixed by heroin in the late 1960s and 1970s, cocaine in the 1980s, methamphetamine in 1990s, and opioids in this century. Use of those drugs indeed spiked in those periods, and each presented some unique challenges. Yet when these particular drugs seized public attention, tens of millions of people used many other drugs (including licit drugs like alcohol and tobacco) and experienced addiction. Even at an individual level, addiction rarely involves only one drug at a time. For example, 30% of opioid overdoses involve concomitant use of a benzodiazepine,²²⁸ and many others involve concurrent consumption of alcohol, cocaine, or methamphetamine.²²⁹

At any given historical moment, addiction might seem like a newly prevalent occurrence involving a single drug. However, the prevalence of addiction has been increasing since the 19th century, when innovations in chemistry, global commerce, and global travel combined to substantially expand access to addictive drugs. Addiction will always be part of human experience because human brains have evolved to be highly drawn to, and influenced by, particular molecules that are available in the modern world at a level beyond anything that evolution prepared us for.²³⁰ Nothing illustrates this fact better than the steady rise in drug-related deaths in the USA for decades despite different drugs coming in and out of fashion.²³¹

From this observation, it follows that health and social care systems have to be equipped to respond to OUD and other substance use disorders—not only to the opioid

problems that are ascendant at present, but to all other drugs that could harm health now and in the future. Yet services for substance use disorders have never been made a permanent, integrated part of health and social care as a result of two inter-related factors: stigma and financing.

In many societies, including the USA and Canada, addiction has long been stigmatised as a moral failing meriting punishment rather than a disorder requiring treatment.²³² Stigma is expressed and reinforced through many mechanisms, including the use of derogatory terms for people with addictions (such as “junkie” or “pillhead”), the unwillingness of insurers to cover care for addiction, and overly pessimistic beliefs about the ability of people to recover from addiction.^{233,234} Stigma is intensified when an addiction crisis disproportionately affects oppressed racial groups (eg, crack cocaine in the 1980s) or low-income groups (eg, methamphetamine in the 1990s). One highly important consequence of stigma is government underinvestment in care for substance use disorder, which partly reflects sentiments among some policy makers and the public that the population in need does not deserve quality treatment or cannot benefit from it.²³⁵

The USA, for example, spends below the point at which return on investment turns negative on care for patients with substance use disorders (ie, even if human welfare concerns were set aside, it would be cheaper to increase financial investment).²³⁶ In other words, even budget-minded officials not moved by the humanitarian case for addiction treatment would in many cases be more responsible stewards of the public purse if they spent more, rather than less, on such care.

But the amount of money alone is not the only important factor: the form of financing heavily influences the form of a society’s health and social care services. For example, the US Federal Government provides a substance abuse prevention and treatment block grant that is detached from all other federal health-care financing and goes to substance use-specific state agencies, which are rarely embedded in mainstream health-care administrative units. Predictably, this approach produces a system of care for substance use problems that is poorly integrated with the rest of health care, thereby causing stigma, reducing quality and accessibility, and making it harder for patients and providers to secure the range of services that many patients need. Studies^{237,238} done in the past two decades suggest that fewer than half of treatment programmes in the USA have a full-time physician or nurse on staff, which shows how poorly the treatment system for substance use disorder is integrated with mainstream medicine. Because this treatment system relies heavily on these annual lump sum block grant payments from the US Government to support its services, the availability of services for everyone who needs them is not guaranteed. Rather than automatically receiving

more resources from insurers when demand increases, as happens in the rest of the health-care system, a block grant programme simply runs out of money in such situations, creating wait lists for essential services such as residential treatment and methadone maintenance.^{239,240}

The US Federal Government has responded to the opioid crisis mainly by providing more fixed-amount, short-term grants to states. Grants can be useful for one-time investments (eg, building a new clinic), but as a source of treatment financing they perpetuate the separation of addiction-focused services from mainstream health care. This funding approach also creates systemic instability because potential employers, employees, and patients are hesitant to rely on a system supported by a time-limited grant. Relative to areas of medical care with enduring, stable, financial commitments, the precariousness of financing for care for substance use disorder reduces accessibility and organisational stability and increases disparities in access and stigma.

Low and inconsistent financing also reduces the willingness of clinicians to specialise in the care of substance use disorder and of educational institutions to provide training in this area. Substance use contributes to one in six deaths among adults globally,²⁴¹ but fewer than 1% of physicians in the US and Canada specialise in addiction. Specialisation in addiction is also rare among nurses, social workers, and psychologists. Importantly, non-specialist health and social care professionals receive minimal training about substance use disorder.²⁴² Medical students might receive perhaps a few hours of training devoted to a disorder that they will encounter almost every day in their career (whether or not substance use disorder is the official reason for care), which they not only will have to manage but also will need to avoid inadvertently causing. Not incidentally, training in pain management is also minimal.¹⁶⁹

Recommendations for building integrated, well supported care systems for substance use disorder

Health and social care systems should make an enduring commitment to provide services for people with substance use disorders that are fully integrated with mainstream care, are accessible to all people in need, and target a range of outcomes, not only the elimination of illicit drug consumption

In one sense, nothing new is needed to design high-quality care systems for substance use disorder, because comprehensive models of population health management are already in use for other serious chronic health problems.²⁴³ Chronic care systems include population-based and clinically based early detection approaches, offer less extensive treatments for early-stage disorders, and provide more involved treatments for serious cases. In such systems, primary care physicians and other generalists work individually or in interdisciplinary teams to manage cases to the limits of their expertise. When those limits are reached, generalists call on

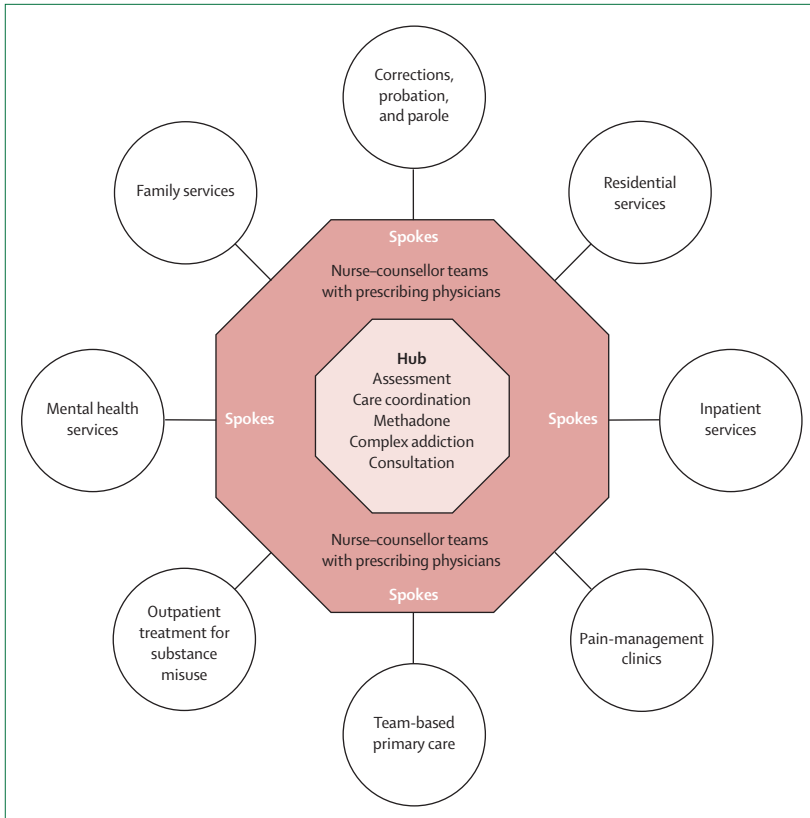


Figure 7: Hub-and-spoke model of addiction treatment

specialist support for collaborative care. Interventions that improve function and reduce morbidity and mortality are considered valuable even if they do not restore the individual to perfect health. The patient’s family is educated about the nature and management of the disorder, and their needs are cared for too. Further services are provided for other problems that patients might have (eg, homelessness, joblessness, parenting challenges) irrespective of whether they are causally linked to the core health problem. Long-term recovery support services are provided to ensure that early gains are routinised and spread to other aspects of the patient’s life. This basic lesson can be applied in the design of accessible and effective care systems for substance use disorders (figure 7).

The hub-and-spoke model^{244,245}—which integrates regional specialty addiction treatment centres (hubs) and geographically dispersed health-care settings (spokes) that can provide ongoing, community-based care—is a promising approach for providing such care. Certified opioid treatment programmes staffed by addiction specialists form the hubs, providing methadone maintenance, buprenorphine induction, and naltrexone as indicated. Spokes—which include primary care, mental health care, outpatient addiction treatment, and clinics specialising in management of chronic pain—provide maintenance medications for OUD and links

to other social services. Vermont²⁴⁶ and California²⁴⁷ are among the states that have greatly increased buprenorphine access with this model, which is also being rolled out in at least a dozen other states.²⁴⁸

The specific elements that should comprise care systems for substance use disorders have been elaborated elsewhere and need not be reiterated in detail here. Broad categories of care include emergency interventions for managing acute crises (eg, naloxone and emergency care for overdose, detoxification and stabilisation units), case-finding in the community and in medical settings (eg, addiction consultation liaison services in emergency departments and medical wards), outpatient and residential settings providing behavioural and pharmacological addiction treatments, mutual help groups and long-term recovery support services (eg, peer coaching, recovery housing), and efforts to prevent and treat common medical comorbidities (eg, hepatitis B vaccination, antiviral treatment for hepatitis C virus infection). Care should also include mental health services responsive to the psychiatric disorders (eg, depression, post-traumatic stress disorder) and adverse experiences (eg, child abuse, sexual assault, violence) that are prevalent in the population.^{249,250} The system should assist affected people at all stages of the cascade of care,²⁵¹ an organising concept pioneered in HIV care. Building a cascade of care requires increasing the proportion of affected individuals that is identified and diagnosed, the proportion of diagnosed individuals who are linked to care, the proportion linked to care who receive effective services, the proportion who receive effective services who are retained for at least 6 months, and the proportion of those retained who transition to long-term recovery.²⁵² Useful guides to the elements of such systems and the evidence behind them include the American Society of Addiction Medicine’s levels of care,²⁵³ and the US Surgeon General’s Report on Alcohol, Drugs and Health.²⁵⁴

Whereas in many areas of health care, removal of illness is (often appropriately) considered the highest success in treatment, people who experience addiction often aspire to more—namely, recovery.²⁵⁴ Although everyone defines recovery from addiction in their own way, common themes are the building or rebuilding of relationships with other people, contributing to the wellbeing of one’s family, friends, and community, being esteemed and valued by others, adopting productive roles, and having a sense of purpose in life (panel 7). High-quality care systems help individuals to achieve these goals, often by linking patients to recovery-supporting organisations (eg, mutual help groups) and support services.^{260,261}

To enhance the coordination of services, as well as the culture within which services are provided, the Commission also recommends that health workers in the field unify under the well established and deservedly respected label of public health. To do so would require

the abandoning of factional, internecine debates about whether one form of recovery is better than another, or whether use reduction or harm reduction is a better goal. Politics are inherently and justifiably a part of how health policy is made,²⁶² but the costs and benefits of individual service options can still be assessed based on scientific evidence rather than ideology (panel 8). And, in any event, the needs, problems, strengths, and goals of people with substance use disorders vary, and responsive care systems should make space for many paths to better health. Moreover, the alleged contradictions between different philosophies reflect ideological abstractions that are not practically meaningful. For example, interventions that are putatively about reducing harm rather than reducing drug use (eg, needle exchanges) often lead to reduced drug use,²¹³ and interventions putatively focused on abstinence rather than harm reduction often result in people continuing to use drugs but with less functional impairment.²⁶⁵ Furthermore, individuals often integrate components of allegedly opposing approaches into their efforts to have a healthier life. For example, people taking opioid agonist therapy who attend abstinence-focused 12-step mutual-help organisations have better outcomes than those who do not.^{266–68} If those who access services can peaceably integrate diverse models that help them, people who provide such services can do so too.

Funding mechanisms that marginalise and destabilise care for substance use disorders should be replaced with core, enduring funding via mainstream public and private financing mechanisms (eg, regulation of private insurance)

Funding for care of OUD and other substance use disorders should be expanded within the enduring financing mechanisms that support the rest of the health-care system. In the USA, this expansion can be achieved via several mechanisms. First, the public Medicaid insurance programme has become an increasingly important part of financing for treatment of substance use disorder in states that expanded Medicaid in some form under the provisions of the 2010 Affordable Care Act.^{269–71} Yet a number of states, including some with serious opioid-related problems, refused to expand Medicaid to cover more of the population. These states could improve care of OUD and related conditions (eg, pain, depression) if they expanded Medicaid.^{272,273} Medicaid expansion has been linked to increased receipt of substance use disorder treatment and decreases in overdose deaths.^{274–76}

Second, the US Federal Government should require coverage for the full continuum of substance use disorder care in Medicaid and Medicare, its two largest public health insurance programmes. Despite improvements in coverage, many state Medicaid programmes do not cover all the treatment services for substance use disorder that the American Society for Addiction Medicine deem essential.²⁷⁷ For example, Medicare and many state

Panel 7: Voices of people in recovery from addiction

“For me, recovery wasn’t an overnight process—it was a series of events dating back to my active using days—but my journey started at the needle exchange. The very first person I met who had successfully kicked heroin and stayed off for many years was a staff person at the exchange. By talking with us, encouraging us, and simply being there, the staff and volunteers reinforced that all drug users are human beings, deserving of compassion.”

Tracey Helton Mitchell²⁵⁵

“I am one of the lucky ones. And I know my continuing sobriety is not the result of my actions alone. I have a loving family and an extensive support network. I have 12-step and the guidance of my sponsors. I have good health insurance. I have the money, time, and resources to help me save myself.”

Nikki Sixx, Mötley Crüe bassist²⁵⁶

“During the ten years of my life I was using opioids, I never had a real friend. But once I put the drugs down, I started to find my people. That’s how it is in recovery. We make friends quickly. We know what it’s like out there. We’ve all survived the same nightmare.”

Ryan Hampton²⁵⁷

“I got tired of being a junkie, and I got tired of being a patient. I help take care of my grandma now. She has Alzheimer’s, and I do a lot of things for her, just like taking care of a little baby. My mom says I take even better care of her [Grandma] than she does ... I want to be well, and hold onto my dignity as long as I can. I can think again, and I’m doing art again, and that feels really good.”

Diana⁴⁴

“I started Homecomings: From Prison to Positivity. It’s for people who’ve been to prison, come home, and tried to keep their recovery. I know the struggles. I know the anxieties. We started meeting every Tuesday from eleven to twelve, and this room got so packed that I had to add another day ... We focus on getting better, whatever we’re recovering from.”

Tarah Dorsey²⁵⁸

“When we started MARS [Medication Assisted Recovery Support] in 2006, I would talk to groups of patients [who were receiving pharmacotherapy for substance use disorders] and ask who is in recovery? Rarely more than a few would raise their hands. They had been conditioned to believe that recovery was something that happened after they were off medication. Now thanks in part to [our] trainings around the US, it is much higher.”

Walter Ginter²⁵⁹

Panel 8: The controversy about supervised drug consumption sites

Three decades after the first supervised drug consumption site opened, fewer than 200 exist across Australia, Canada, the USA, and Europe. These sites allow people to use drugs they procure themselves in the presence of health professionals, who can administer aid in the event of overdose, teach safer injection practices, and provide health information, including about the availability of other services. Critics have attacked such sites for allegedly increasing drug use and crime,²⁶³ and for imposing costs on neighbouring residents and businesses. Research on supervised drug consumption sites is methodologically weak, but generally suggests that the risk of death from overdose is lower at such sites than outside of them. However, there is no evidence that accessing a site lowers an individual's risk of fatal overdose over time, or that sites lower community overdose rates.²⁶⁴ Rigorous research on supervised consumption sites would be useful. Because of the high cost of maintaining brick-and-mortar sites and how few people who use drugs access these sites when they do exist, supervised consumption might have more potential to affect population health if it works via technology (eg, smartphones) to offer monitoring to people using drugs irrespective of location.

Medicaid programmes do not cover residential treatment or recovery support services.²⁷⁸ State Medicaid programmes that contract with managed care entities should explicitly stipulate the terms of coverage for substance use disorder care. Medicaid is the largest payer of substance use disorder care in the USA, and ensuring coverage for the full continuum of treatment under this programme could improve access for as many as one million individuals with OUD.

Third, qualified health plans need better guidance about what constitutes coverage for substance use disorder care as specified in the Essential Health Benefit, which is a set of categories of services that all health insurance plans created under the Affordable Care Act must cover. The Affordable Care Act and subsequent final rules issued by the Centers for Medicare and Medicaid Services give states substantial discretion to define the scope of substance use disorder care within their state benchmark minimum requirements for coverage, including for insurance plans operating within the state exchanges (so-called marketplace plans).²⁷⁹ Consequently, some states required plans to cover the full continuum of treatment services and medications for substance use disorder recommended by the American Society of Addiction Medicine, whereas others required coverage for only the most basic outpatient services.²⁸⁰ The Commission therefore recommends that states provide more specific guidance regarding what services and medications have to be covered to ensure adequate access to substance use disorder care.

Fourth, in their benefit design, most private insurance companies are now required by federal and state parity laws not to impose utilisation-management policies (eg, previous authorisation, quantity limits, cost sharing) on care for substance use disorder that are more stringent than those applied to coverage of other medical and surgical services. Some insurers have not complied with parity laws and have thereby deprived individuals in need of care. Individual states have successfully brought suit against insurers who have violated parity laws,²⁸¹ but routine oversight and enforcement should be systematic across the USA. Within the profit-driven US health-care system, substance use disorder is one of the few conditions financed mainly by public sources, which reduces access to care and the availability of highly trained providers. Shepherding more private funding into the system by enforcing the parity law should thus be a major priority.

Mainstreaming the financing of substance use disorder care would have the added benefit of simultaneously imposing the workforce and regulatory standards of the rest of health care on care providers for substance use disorders. Reflecting its underfunding and segregation from the rest of health care, the substance use disorder treatment system has extremely uneven quality of care.²⁸² Low-quality care is bad for patients and also reduces the willingness of payors to purchase services in the future, creating a negative feedback cycle. Investment in services coupled with quality standards and related improvement efforts would create a positive feedback cycle.^{283,284}

Public and private payors and regulators should curtail provision of addiction-focused health care services that have substantial potential for harm

One of the tragedies of the opioid epidemic is that even though treatment funding is in short supply, it is sometimes expended on approaches that probably make patients worse off—eg, treatment programmes that actively discourage patients from using approved medications or that promote bogus therapies (such as cannabis as a cure for heroin addiction), and detoxification-only services with no follow-up, which may actually increase harm by lowering tolerance and thereby increasing overdose risk. Disappointingly, treatment programmes accredited by external auditors are as likely to offer ineffective services as those that are unaccredited.²⁸²

The most effective way to curtail harmful services is to stop purchasing them. The Commission recommends that government insurance programmes like Medicare and Medicaid, treatment block grants, and drug court funding no longer reimburse such services, and encourage private insurers to follow the same course. The Commission also recommends that public and private accreditation bodies prioritise elimination of services that have substantial potential to harm patients.

Health-care policy makers and educators should invest in addiction-related training for specialist and generalist health professionals

Many addiction-focused curriculums have been developed by educators, researchers, clinicians, and professional societies. But at all levels of medical education, from undergraduate through to residency programmes, such training is infrequently provided.²⁸⁵ Years of exhortation on this point have not produced change, so the Commission believes that such training needs to be mandatory. Bodies responsible for the education of health professionals—most notably schools of medicine, nursing, pharmacy, and dentistry, as well as professional associations and societies that provide continuing professional education and certify professional training programmes—should agree on minimum standards for substance use disorder-related instruction that must be met for accreditation across the curriculum. Much of the training can be directed at generalists and professionals focused on other disorders (eg, training in how to manage alcohol use disorder in cardiology care, how to detect substance use disorders in family medicine clinics, how to treat substance use disorder in patients undergoing psychotherapy for depression, how to detect and manage OUD in pain clinics, and how to respond to OUD presentations in the emergency department).

In the USA, physicians who wish to prescribe buprenorphine for OUD to more than 30 patients are required to undergo additional addiction-focused continuing education. The Commission prefers a broader approach—specifically, it recommends that education in managing addiction and on the risks of addiction to prescribed medication should be required before any health professional is granted a licence to prescribe controlled substances.

Specialty training programmes should also be expanded to meet the enormous need for addiction treatment. Among specialties, psychiatry has historically done the most to treat addiction, but addiction medicine should not be regarded as only a psychiatric subspecialty. Indeed, one of the most positive developments of the past 10 years is the 2015 recognition of addiction medicine as a medical specialty, paving the way for a diverse set of physicians to receive additional training in addiction medicine under the auspices of the US Accreditation Council of Graduate Medical Education.¹⁹⁸ Addiction medicine and addiction psychiatry fellowships provide advanced fellowship training to a diverse range of specialists (eg, specialists in family medicine, internal medicine, psychiatry, and emergency medicine). Such fellowships should be expanded to increase the workforce targeting substance use disorders. Student loan repayment incentives should be expanded to encourage professionals to specialise in the addiction field.

Domain 4: Maximising the benefit and minimising the adverse effects of the involvement of the criminal justice system with people addicted to opioids

The criminal justice system is the fourth of the seven domains analysed by the Commission. The mantra that “we can’t arrest our way out of drug problems” is correct yet also implies something that is untrue, namely that there will or should ever be a time when the criminal justice system is not involved with people with addiction issues.²⁸⁶ Contrary to some popular narratives, contact between the criminal justice system and people who use addictive and intoxicating substances will be prevalent whether drugs are legal or illegal. Alcohol, which is legal, is a factor in more arrests, violence, and incarceration than any other drug.²⁸⁷ The criminal justice system will always have a role in responding to drug use because people who are intoxicated disproportionately engage in harmful conduct, including but not limited to physical violence. A famous conceptualisation in the field²⁸⁸ characterised addiction as a chronic disorder akin to asthma, type 2 diabetes, or hypertension. This conceptualisation is accurate in terms of addiction being a chronic condition with genetic and behavioural risk factors that merits high-quality health care, and everyone working in the criminal justice system should recognise these realities.²⁸⁶ But people with asthma, diabetes, or hypertension do not have disproportionately high rates of violent and other crimes, and hence the criminal justice system is less relevant to them than it is to people experiencing addiction.

The question therefore becomes how the criminal justice system can increase beneficial activities regarding OUD and decrease harmful activities, while still protecting crime victims. Because addiction is possibly the most common health problem among people who are incarcerated,²⁸⁹ offering addiction care tailored to individual need in all correctional health-care systems is the most prominent example of increasing beneficial effects within the criminal justice system.²⁹⁰ Incarceration is intended as a punishment for the individual concerned and a deterrent to others who might engage in the same crime, but for both humanitarian and utilitarian reasons, it is simultaneously an opportunity for rehabilitation.

Some correctional officials worry that pharmacotherapies (eg, methadone) might be diverted by patients and become part of black-market economies in prisons. This risk is typically manageable—for example by implementing observed dosing for oral medications and by offering injectable extended-release formulations.²⁹¹ It should be noted that not making pharmacotherapies available can also create management problems (eg, the smuggling of opioids into prisons, protracted opioid withdrawal leading some incarcerated people to be combative).

Transition services extending beyond release from incarceration are of paramount importance in OUD treatment. Contrary to popular lore, obtaining a regular

Panel 9: Expansion of treatment of opioid use disorder (OUD) in prisons

Starting in July, 2016, the Rhode Island Department of Corrections enacted several changes to improve treatment of OUD during incarceration and to reduce post-incarceration overdose deaths.²⁹³ Executive and legislative leadership were key in the success of the initiative. The Governor of Rhode Island requested US\$2 million for the programme, which was approved by the state General Assembly. Jails and prisons began screening for OUD on admission and offering to induct individuals onto their pharmacotherapy of choice. Treatment was maintained throughout incarceration, and the Department of Corrections partnered with community-based providers to prevent post-release disruptions to care. At the same time, 12 centres of excellence focused on treatment of substance use disorder were established across the state. These centres served as additional linkage locations for people released from incarceration to maintain pharmacotherapy for OUD. Early assessment of these programmes found high uptake and satisfaction with treatment during incarceration, substantial rates of continued engagement with treatment after release, and a 60% reduction in overdose deaths after release (compared with deaths in the period before programme implementation).²⁹³⁻²⁹⁵

supply of illicit opioids while incarcerated is in fact difficult.²⁹² As a result, most incarcerated people with OUD go through partial or complete withdrawal. Individuals who have not used opioids for an extended period lose tolerance, making their previous usual dose potentially deadly. The risk of death from opioid overdose in the immediate post-release period is appallingly high.⁴¹ Even individuals who have been receiving medications for OUD while incarcerated can be at risk if care services do not continue immediately after release or if naloxone is not provided for overdose emergencies. Prisons that have created smooth transition services from incarceration back to freedom have generated sizable public health benefits (panel 9).

Community supervision systems (eg, probation, parole) are another opportunity to deliver OUD treatment within the criminal justice system. One model for doing so are drug courts, which can be effective presuming they allow use of all evidence-based pharmacotherapies.^{213,296} Encouraging evidence suggests that contingency-management approaches, combined with regular drug testing (sometimes termed swift, certain, and fair monitoring), in community-based supervision settings could reduce substance use, crime, and likelihood of incarceration.²⁹⁷

These potential positive opportunities should lead no one to overlook the harms of criminal justice involvement with people addicted to opioids—particularly in the USA, where the criminal justice system is so large and powerful that it

has frightening potential to make the opioid crisis worse, most notably for low-income individuals and African Americans. Three specific policies are particularly destructive.

First, even though incarceration in a prison for possession of a personal supply of illicit opioids (or of syringes) virtually never happens in the USA or Canada,²⁹⁸ some arrested individuals spend time in local jails. The common results are withdrawal (dangerous in itself) and loss of tolerance (more dangerous because it increases risk of overdose on release).²⁹⁹

Second, during the height of the USA's war on drugs, many states and the federal government passed laws applying long-term, sometimes permanent collateral penalties for individuals convicted of drug-related crimes. Collateral penalties include bans on public assistance, exclusion from public housing, denials of student loans, and bars to certain types of employment.³⁰⁰ These penalties were often applied as supplements rather than alternatives to criminal penalties (eg, arrest and incarceration), and extended the term of punishment beyond that typically applied for more serious offences, up to and including an individual's lifetime.

Third, several states in the USA punish the use of alcohol and other drugs during pregnancy as a form of child abuse.³⁰¹ Such policies comprise laws that consider substance use during pregnancy to be criminal child abuse, policies that allow civil commitment (forced inpatient treatment) during pregnancy (justified as protecting the fetus from substance use), and clinician mandatory reporting laws. In some cases, courts have even viewed a mother's use of opioid agonist therapy for OUD negatively in child welfare cases.

Maximising the benefit and minimising the adverse effects of criminal-justice involvement in care

Addiction-related health services, including medications, should be available to all individuals with opioid use disorder during incarceration and after release

Rehabilitation is one of the core missions of criminal justice systems, which have a responsibility to treat health conditions such as addiction. Indeed, in the Plata decision in 2010, the US Supreme Court held that providing inadequate health care in prison violated the eighth amendment to the US Constitution's injunction against cruel and unusual punishment.³⁰² Even if it were not a legal requirement and an ethical imperative, there are additional practical reasons to treat OUD and other substance use disorders in prison: the marginal costs of providing addiction care to people who are incarcerated is small relative to the potential public health and safety benefits of such care.

Because prison-based addiction treatment without continuing services after release is less effective (some studies suggest that it is not effective at all),²¹³ and because the period immediately after release is so high risk, the

Commission also recommends that community re-entry services after release should be universally provided and adequately resourced. In addition to addiction treatment, incarceration should also be treated as an opportunity to attend to all other health needs, including offering prenatal care, providing hepatitis B vaccines,³⁰³ treating sexually transmitted infections, caring for psychiatric disorders, and offering overdose education and naloxone distribution (which could have radiating benefits for other people upon release³⁰⁴).

In the USA, the Commission recommends making addiction-related services available in prisons by passing the Medicaid Re-Entry Act,³⁰⁵ which is under consideration in Congress at the time of writing. Medicaid does not generally cover services provided in prisons, which hampers both in-facility service provision and re-entry services (because once Medicaid coverage is stopped upon incarceration, there can be paperwork hassles and delays before benefits are reactivated after release). The Medicaid Re-Entry Act reactivates Medicaid coverage to cover addiction treatment provided in the final month of an individual's incarceration.³⁰⁵ This funding could allow prison staff to provide the care themselves, but in most cases the probable division of responsibility will be Medicaid-funded contracts given to community health-care providers to care for incarcerated people both before and after release.

Incarceration for illicit possession of opioids or drug-related equipment intended for personal use should be abandoned because it creates public health risks without producing public health or safety gains

Incarceration of people with OUD raises the risk of overdose death.²⁹⁹ Reducing incarceration for illicit possession of small amounts of illicit opioids (eg, defelonisation in California) has not adversely affected public health or safety.³⁰⁶ Some people might argue that incarcerating people for illicit opioid possession has an offsetting public health benefit of deterring use by others. Legal sanctions have some deterrent effects on drug use, but there is no evidence that these effects are unique to incarceration.^{306,307} Moving to penalties other than incarceration or to therapeutic diversion programmes is very unlikely to increase population opioid use.^{286,308} It could also benefit the health of people with OUD by reducing their risk of incarceration-precipitated overdose and engaging them with treatment services.³⁰⁹ Although not a health harm per se, trust in the criminal justice system is not improved when heroin users are punished more severely than the Purdue Pharma executives who in 2007 pleaded guilty to knowingly helping to trigger the opioid crisis, none of whom—shamefully and shockingly—spent even a day in prison. The Commission therefore recommends an end to incarceration for illicit possession of opioids or drug-use equipment intended for personal use.

Collateral penalties for people who commit drug-related crimes should be abandoned because they hamper people's ability to maintain recovery from addiction

Collateral penalties do not distinguish individuals who continue to engage in illegal behaviour (eg, using or dealing heroin) after incarceration from those who do not (eg, someone who enters recovery and leaves involvement in the drug trade behind them). The Commission considers this system unjust and foolish: punishing people for engaging in desired behaviours benefits neither the individual nor society. Furthermore, these laws create barriers for individuals to enter and remain in recovery, for example by making it difficult to pursue education, employment, and housing.

State and federal officials in the USA should abandon policies that punish opioid use, opioid use disorder, or opioid agonist therapy during pregnancy

Pregnancy-focused punishments create barriers to disclosing illicit opioid or other substance use or entering treatment. Penalising opioid agonist therapy for addiction during pregnancy based on the theory that therapy harms the developing fetus has no medical basis.³¹⁰ The Commission recommends that states pursuing such policies abandon them and instead focus on establishing priority-access pathways to high-quality services in both the pregnancy and post-partum period.

Domain 5: Creating healthy environments that can produce long-term declines in the incidence of addiction

Addictive drugs provide short-term rewards via an increase in positive experiences (eg, intense pleasure) or a decrease in negative experience (eg, escape from anxiety or withdrawal), or both. Neuroscience and behavioural economics teach that the value of all such rewards is relative—ie, it depends on what other positive rewards are available in the environment, and, how much the environment produces states that would be desirable to avoid (eg, fear, alienation, a sense of worthlessness). Very broadly speaking, one would expect that when a supply of drugs is present, they would be consumed more by individuals with more environmental stressors and fewer alternative rewards than by those with fewer stressors and more rewards, and that of all people who use drugs, those in stressful environments with few alternative rewards available would be most likely to develop addictions. This hypothesis is not easy to test in an ecologically valid and ethical fashion. However, experimental research with primates has supported the concept by showing that the strains of being at the bottom of a social hierarchy increase consumption of available drugs,³¹¹ while the rewards of being at the top seem to make addictive drugs relatively less attractive.³¹²

The characteristics of environments that increase risk of addiction vary, but have historically included political

and economic upheaval, racial and ethnic persecution, and chronic exposure to violence and disorder. When an addiction crisis lasts for more than a generation, as has the US and Canadian opioid crisis, high-risk environments can also include areas where large numbers of children are growing up with parents who are addicted, contributing to child abuse, neglect, and abandonment. In one of the most influential analyses of the roots of the opioid epidemic, Anne Case and Angus Deaton document that the crisis originally took hold in regions affected by deindustrialisation and sustained loss of living-wage employment.³¹³ This account of the origins of the epidemic is sometimes misread and often invoked in public debate to dismiss the influence of any causal factor other than poverty, which does a disservice both to reality and to the nuanced analysis that Case and Deaton offer. As the pair highlight, the explosion of opioid prescribing began increasing opioid overdose deaths in an era of declining national inequality (the 1990s), and the death rate was unaffected by the 2008 financial crisis.

When matters are complex and have high stakes, many people see within murky evidence a validation of their political preferences. For example, some people see addiction as a symptom of a root cause, namely poverty and inequality.³¹⁴ If this hypothesis is correct, it would follow that economic interventions aimed at reducing inequality (eg, increased transfer payments, changes in taxation) would necessarily translate into substantial alleviation of the opioid crisis, and perhaps addiction more generally. These propositions are probably untrue, for five reasons. First, the degree of prescription opioid marketing and supply explains the geographical distribution of overdose deaths better than does the degree of economic privation.^{315,316} Second, religiously or culturally rooted abstinence from all substance use is more common in lower-income groups than in higher-income groups,³¹⁷ and abstinent people cannot become addicted. Third, addiction often moves up and down the income scale (eg, tobacco and cocaine in the USA both went from being drugs of upscale urban sophisticates to stigmatised drugs used by low-income people).^{318,319} Fourth, when poor nations experience rising wealth, their population's consumption of addictive substances tends to rise sharply.³²⁰ Fifth, even if one accepts that an economic shock has increased the prevalence of addiction, causes do not necessarily become solutions when reversed: knowing that an egg is broken because it fell to the ground does not imply that hurling its fragments skyward will reassemble it. More concretely, someone whose opioid addiction started ten years ago when the local coal mine shut down does not become unaddicted if the mine re-opens.

More generally, as Case and Deaton note, "Many of the things people care about are not reducible to money or measurable in monetary terms."³¹³ Domain 3 of this report discussed how, for many individuals, recovery

from addiction involves more than a change in substance use, and also incorporates strengthened connections to other people, the filling of responsible roles, respect in the eyes of others, and a subjective sense of meaning and purpose in life. Although it could never be tested in a randomised trial, it is reasonable to speculate that the presence of these same factors could lower the likelihood that individuals would develop addictions in the first place.

Policy makers should attempt to alleviate poverty and inequality because of the human misery they cause. But they should not put forward the false promise that macroeconomic policy is a powerful or specific lever for reducing the prevalence of addiction. In the USA, drug-related deaths have been rising for at least 40 years through a series of diverse macroeconomic policies and economic situations.²³¹ Nevertheless, policy makers have at their disposal evidence-informed strategies for improving human environments that have long-term potential to reduce addiction.

The highest-priority investments in this domain focus on children and adolescents. Neuroscience, developmental, and epidemiological research all point strongly to youth as the time when the incidence of substance use disorders is most concentrated.²³⁰ Youth is also the time of life when the acquisition of skills and capacities is most easily facilitated and when doing so has the largest effect on an individual's life course.

The availability of specific substances in the environment, and attitudes and beliefs individuals hold about particular drugs, are risk factors that prevention programmes should address. Indeed, the Commission's preceding recommendations about promoting safer opioid prescribing address risks particular to that specific class of drug. But most risk factors for developing addiction and a wide range of other problems are generic,³²¹⁻²³ including chaotic, unrewarding environments, unremitting stress, social exclusion, violence and other trauma, sexual assault, child abuse and neglect, and individual risk factors (eg, difficulty managing emotions, coping with challenges, and exercising behavioural self-control).

Prevention programmes could target these generic risk factors rather than focusing on any one drug or drugs in general. Examples include the COMBINE project in Australia³²⁴ and Communities that Care in the USA,³²⁵ both of which were shown to positively affect several youth outcomes, including use of multiple substances, mental health, and academic performance. Panel 10 details Iceland's unusually energetic effort to improve young people's environments as an addiction prevention strategy, and also shows the range of settings (beyond traditional sites, such as schools) in which preventive efforts can be implemented.

Risk and protective factors exist within children, within their environments, and within the interaction between the two. The most effective substance use prevention programmes will focus on all these risk and protective

factors. The Good Behavior Game, in which teachers specifically reward students for cooperation, has some long-term evidence of reducing substance use and instilling emotional self-regulation in children and also improves the classroom environment.²⁵⁴ Restrictions on youth-targeted advertising of addictive drugs (eg, alcohol, tobacco, cannabis, pharmaceuticals)^{230,332} are another example of valuable prevention efforts that keep the environment in mind.

Prevention programming is generally directed at children of school age. Infants, toddlers, and pre-school children generally do not use drugs, so it does not make sense to offer them informational or persuasive programming on the risks of drugs. However, during this developmental period, programmes that aim to strengthen health, wellbeing, and school readiness, and to improve interactions between them and their parents, could have remarkable long-term effects (potentially even extending, as in the case of Head Start, which increases the school readiness of young children from low-income families, into the next generation).³³³ These effects could include reduced risk for addiction. Such programmes should thus be appreciated and supported in this light, even though prevention of addiction is not their primary purpose.

The Nurse–Family Partnership provides home visits to first-time mothers during pregnancy and infancy.³³⁴ Nurses teach positive health behaviours and effective parenting skills and support parental health and personal development. Most recipients are low-income, unmarried teenagers. The most replicated effects of the programme are reduced rates of child abuse or neglect and second teenage pregnancy, and increased child educational attainment.³³⁴ These effects were evident in four of five randomised clinical trials³³⁴ (the exception was a UK study in which participants in the control group received home visits via the National Health Service, and the results could thus be interpreted to suggest the value of home visits rather than as a critique of nurse–family partnerships). Some but not all trials showed that, compared with controls, infants of people who were assigned to receive visits from the Nurse–Family Partnership, had lower rates of substance use and related characteristics (eg, poor impulse control, involvement with the criminal justice system) in adolescence and adulthood.³³⁴

The Perry Preschool Project provided high-quality educational instruction to low-income, 3–4-year old African American children. Children randomly assigned to the programme were arrested for drug-related offences by age 27 years at less than a third the rate of that among controls (who received no intervention).^{335,336} Similar findings were presented for the Abecedarian Early Childhood Project, which provided full-time educational support for low-income children from infancy to age 5 years.³³⁷ Studies of both of these programmes had methodological weaknesses, including attrition over time from samples that were small

Panel 10: Iceland's experiment with community-wide prevention

From 1995 to 2015, the number of tenth graders (ie, aged around 16 years) in Iceland who had ever used alcohol decreased from nearly 80% to under 35%.³²⁶ The proportion who had used cannabis or smoked cigarettes dropped as well during the same period. These declines occurred during the implementation of the Icelandic Prevention Model,³²⁷ which supports national investment in adolescent wellbeing grounded in sociological and criminological theories that view so-called problem behaviour as emerging from environmental features rather than individual characteristics.³²⁸ This approach is also consistent with neuroscientific and behavioural economic conceptualisations of the frequency of substance use as partly reflecting the richness of alternative rewards available in the same environment. The main features of the Icelandic Prevention Model include laws restricting the purchase of alcohol and tobacco by young people, restricting advertising of these products, a curfew for 13–16-year-olds, strengthening ties between schools and parents, an emphasis on quantity of parental time spent with children, and increased state funding for organised sports, art, and music classes for young people.³²⁹

Because declines in youth drinking were also noted in other Nordic countries over the same period,³³⁰ it would be premature to attribute Iceland's falling prevalence of youth substance use solely to the prevention model. Iceland's results are nonetheless worthy of assessment in other settings. As of 2020, 111 communities in 32 countries have implemented components of the Icelandic approach.³³¹ As data from these diverse settings become available, they might illuminate which aspects of the model have replicable effects on youth substance use.

at the outset (each programme enrolled fewer than 125 participants), but their findings remain consistent with the hypothesis that generic investments in young children's wellbeing can have long-term protective effects in the substance use domain.

A final comment on building healthy environments: the obvious fact that the smaller the quantity of opioids readily available, the less likely people are to begin using them, should not be overlooked. Although many parents worry that their children could be offered opioids by a drug dealer or a friend, opioids are often more accessible in children's home environment. More than a sixth of Canadian adults and a third of American adults receive an opioid prescription each year,^{36,338} and the typical recipient takes only some of the pills dispensed (one study³³⁹ reported that 73% of opioid pills dispensed after surgery are not used by the patient). A simple way to create healthier environments that reduce the likelihood of opioid-related problems in young people and adults is to get rid of the billions of excess opioid pills in homes.³⁴⁰

Recommendations for creating healthy environments that could decrease the incidence of addiction

Policy makers in the USA should implement effective procedures to reduce the supply of excess opioid pills

In most high-income countries, governments require opioid manufacturers and distributors to fund widely available drug disposal programmes at convenient locations, such as community pharmacies.^{341,342} The USA, by contrast, tightly regulates drop-off procedures and does not ask the private sector to absorb the costs. For the first 15 years of the opioid crisis, efforts to reduce the prevalence of unused pills were limited to prescription drug take-back days operated once or twice a year by law enforcement. These efforts are valuable, but insufficient as a national policy response because opioids constitute only a tiny proportion of the drugs returned during such events.^{343,344} In 2010, Congress expanded the number and types of organisations (eg, pharmacies, hospitals) that can be licensed to collect and destroy unused controlled drugs, but as of 2017, only 2·5% of eligible sites operated take-back programmes.³⁴⁵

The Commission recommends that the USA follow the example of countries (including Canada) that operate more effective drug take-back programmes by mandating that hospital-based and community pharmacies have to accept unused medications. As in other countries, the cost of these programmes should be borne by pharmaceutical manufacturers and distributors. As with the early days of glass recycling, a financial incentive might initially be needed for the public to adopt the habit of returning unused medications until the behaviour becomes widespread and normalised. Policy makers should consider experimenting with requiring opioid manufacturers to fund a programme that would reward pharmacy customers returning the unused portion of controlled-substance prescriptions—eg, a discount coupon for in-store purchases.

Substance use prevention efforts should be horizontal,³⁴⁶ building healthy environments and strengthening individual capacities that protect against a broad range of difficulties, not limited to drug use

Narrowly targeted prevention programmes are wasteful if delivered to children who are not destined to develop the specific problem targeted. For efficiency and effectiveness, the Commission recommends that prevention initiatives be combined rather than implementing, for example, a programme discouraging smoking, a separate programme promoting healthy diets and exercise, and another focused on making classrooms more socially supportive.

Moving to a horizontal prevention model will require substantial changes in funding, management, and accountability in a field where efforts are often siloed. For example, people who work in alcohol prevention sometimes see themselves as doing something fundamentally different from those who work in bullying prevention. However, the benefits to children of

making substance use only one focus among many targeted by prevention efforts more than justifies the dissolution of such bureaucratic boundaries and the creation of a horizontal prevention funding streams.

Implementation of horizontal prevention programmes on a broad scale will not cause the current opioid epidemic to dissipate. Prevention is a long-term investment that societies should make today for benefits a decade or more down the line, when the most acute drug epidemic might concern alcohol, stimulants, opioids, psychedelics, or some other drug that no one has heard of yet. Indeed, the crisis averted might not even be in the drug domain: the benefits of investment in prevention might be less self-harm, depression, violence, or other adverse outcome that we should rejoice for the next generation to avoid no matter what its specific nature.

Early childhood enrichment programmes for low-income families should be expanded as a long-term strategy for reducing addiction, among many other benefits

As mentioned, studies of early childhood enrichment programmes such as the Nurse–Family Partnership, the Perry Preschool Project, and the Abecedarian Early Childhood Project, suggest long-term developmental benefits in a range of areas. None of these programs has any substance-specific content, nor are their chief benefits necessarily related to substance use. Yet the Commission believes that these types of programmes deserve more attention in discussions of long-term preventive strategies for reducing population substance use. Because the incentives in politics are typically to focus on short-term effects, advocacy for these programmes is particularly important because any potential benefits are likely to accrue in the long term.

Domain 6: Stimulating innovation in responses to addiction

The range and effectiveness of treatments for many chronic health problems (eg, depression, asthma, hypertension, sleep apnoea, cardiovascular disease) have improved substantially in the past 25 years. Sadly, the same is not true for OUD nor for treatment of addiction more generally. The dominant psychological and behavioural treatments used in front-line addiction care have changed very little in the 21st century. Since the FDA approved methadone maintenance as an OUD therapy in 1972, only two other medications (buprenorphine and naltrexone) have made it to market in the USA, both of which are also specifically focused on the brain's opioid system. No pharmacotherapies have been approved for stimulant use disorder or cannabis use disorder. The treatment of addiction is in dire need of innovation. New treatments, although crucial, will not solve the well documented lack of access^{277,347} to available OUD treatments.³⁴⁸ Innovations in implementation³⁴⁹—that is, finding new ways to get effective treatments to people who need them—are also crucial.

Innovation is also needed in pain management, particularly in the development of effective medications that do not carry risk of addiction. The main efforts of the pharmaceutical industry in this regard have been directed towards the creation of prescription opioids that are purportedly tamper-resistant (sometimes referred to as abuse-deterrent, a stigmatising term the Commission believes should be abandoned). Some of these products have been complete failures: OxyContin was touted as hard to misuse because of its long-acting formulation, but it was easily and widely crushed for injection and insufflation. Subsequent tamper-resistant opioid formulations, including that which replaced OxyContin, have moderate benefits in terms of reducing long-term population harm.³⁵⁰ An Australian study found that introduction of tamper-resistant formulations was associated with population-level drops in sales of controlled-release oxycodone but not with population-level changes in overdose indicators or treatment seeking.³⁵¹ Our Commission's modelling suggests that although tamper-resistant formulations moderately reduce mortality in the long term by lowering the rate of misuse initiation, in the short-term they drive some pill users to switch to illicit drugs.^{24,79} Also, no tamper-resistant formulation can entirely prevent opioid misuse because individuals can always simply orally consume more than the recommended dose.³⁵² Tamper-resistant opioids formulations thus have a moderate effect at most in an arena where greater strides are needed towards safe, effective, pain care.

Data systems intended to monitor opioid use, OUD, and the consequences thereof, are also in dire need of innovation. For example, epidemiological surveillance relies primarily on self-report surveys of individuals despite the well documented validity limits of such approaches.³⁵³ Governments lack credible estimates of how many people use heroin or fentanyl, or both, how many people are addicted to these drugs, how much these drugs are bought and sold for, and how users acquire them.³⁵⁴ In Canada, although quarterly surveillance reports on overdose mortality are comprehensive, national opioid-related mortality data were not collected before 2016.^{52,355} Epidemiological data for some issues prevalent among people with OUD, such as alcohol use disorder and suicide, also have validity problems.^{356,357} Decades into the worst drug epidemic in North American history, this situation is scandalous. The US National Drug Early Warning System, which was renewed in July, 2020, and includes some novel monitoring methods, is a good step towards improved epidemiological surveillance.³⁵⁸ Wastewater analysis is a widely used technology in Europe that, with a few exceptions, has been underexploited in North America.^{359,360} This method provides unique opportunities to rapidly monitor population-wide use patterns without the missing data and privacy concerns inherent in self-report surveys.

Law-enforcement strategies for reducing the supply and use of illicit opioids have also evolved little at the national level, despite promising pilots of alternative models.^{307,361} The field's lack of innovation has already been tragic enough in terms of opportunity costs—ie, lives that could have been saved but were not. Lack of innovation has become hugely damaging in the face of the rising availability of synthetic drugs such as fentanyl, which, because of their high potency and lack of dependence on agricultural production, pose fundamentally different challenges to public health and safety that current policies cannot meet.²⁶

Although the Commission calls for many individual innovations throughout this report, it also notes that lack of innovation is a more general problem for the field, which suggests the need for specific policies that foster an innovation-friendly environment.

Recommendations for stimulating innovation in responses to addiction

Policy makers should implement pro-innovation policies that correct for failures in patent law and market incentives

The USA's innovation climate is set up to reward goods that can be patented (eg, pharmaceuticals), and incentivises companies to create and then increase demand for habit-forming patented products. Patent law can also create barriers to access for some OUD treatments—by allowing drug companies to keep the price of a medication high due to lack of competition, for example. But other innovation policies could be introduced to reduce harms of medication exclusivity.³⁶² Policy makers should consider eliminating patent-related access barriers by purchasing products from patent owners and distributing them at low cost to patients or by purchasing patent rights and allowing generic production. For example, if the US government bought out Evzio's patents on the naloxone auto-injector, it could be made publicly available at cost.³⁶²

Public policy should also encourage innovation in pursuits unlikely to lead to substantial market rewards. Non-pharmacological treatments—whether for addiction or pain—do not fit into the usual system of patents or promised profits. Similarly, most public health interventions cannot be patented. Greater government funding through grants and prizes could help to drive innovation in areas where patents are not suitable incentives.³⁶² Public funding could also be more focused on projects that are unlikely to attract private sector investment. For example, government grants could have a section for applications to explain why the project would not otherwise be funded.

Pro-innovation policies work in concert with the health-care provision, training, and financing policies that the Commission recommended in Domain 3. As the number of individuals with insurance who seek care for opioid-related conditions increases, the reimbursement for those services and the number of

professionals providing them will increase too. These increases create demand-side pressure for innovation, thereby increasing the likelihood that supply-side efforts will meet with success.

Government research agencies and private industry should prioritise development of non-opioid analgesics and drugs targeting addiction and the redesign of opioids to separate their effects (eg, analgesia, euphoria, respiratory suppression)

As mentioned, tamper-resistant opioids are not entirely without merit, but at most make pain pharmacotherapy only slightly safer. A more effective innovation would be to design or discover drugs that do not carry risk of addiction, overdose, or other adverse effects of opioids. One route is to design opioid molecules with biased agonism,³⁶³ which would mean that they could relieve pain with less respiratory suppression and less activation of the brain reward circuitry underlying the acquisition of addiction.³⁶⁴ This approach has produced some promising preclinical findings,³⁶⁵ but these findings have not yet been replicated or rigorously tested in clinical studies.³⁶⁶ A non-competing alternative approach is to develop non-opioid drugs and interventions (eg, virtual reality and nerve stimulation devices) that could relieve pain or ameliorate addiction, or both.

The rapid development of effective vaccines for COVID-19 shows what is possible when governments make a massive, urgent commitment in the face of an epidemic. The same commitment is needed for the opioid crisis. Expansion of US National Institutes of Health initiatives, such as the Blueprint Neurotherapeutics Network for Small Molecule Drug Discovery and Development for Disorders of the Nervous System, and charging them with focusing more work on opioids, could be productive. Private industry could be incentivised to do similar work through tax credits for research and development (prize-based competitions make less sense, as the developer of any such interventions would probably reap enormous profits). Privately and publicly funded animal research is more likely to lead to life-saving innovations if guided by translational scientific models.

To promote rapid adoption of treatments for opioid use disorder, regulatory agencies should increase their willingness to approve drugs on the basis of data from trials done abroad

In high-income countries collectively, the range of medications used to treat OUD is broad and includes oral and injectable methadone, oral, injectable extended-release, and implanted buprenorphine, slow-release oral morphine, injectable hydromorphone, injectable and inhaled or smoked diacetylmorphine, and injectable extended-release and implanted naltrexone. Yet in any given country, only a subset of these medications is approved and available, which reduces opportunities to expand treatment options to a broader population and to tailor treatment to individual needs.

Regulatory agencies (eg, the FDA) often consider international evidence to an extent, but still require extensive in-country data collection before drug approval, including new safety and dosage studies for drugs that have been used for many years in other countries. Given the exigency of the opioid epidemic, relaxing these requirements legislatively and administratively could bring more treatments to patients with OUD more quickly.

Law-enforcement agencies should develop and implement innovative strategies to disrupt illicit fentanyl (and other novel synthetic opioid) transactions both physically and financially

In the USA and Canada, fentanyl and fentanyl precursors are sourced via online transactions with producers in China, either directly or via traffickers in Mexico.²⁶ Due to the volume and variety of consumer goods exported from China, universal screening of either packages or financial transactions based on country of origin is unlikely to be productive. The effectiveness of targeting specific actors might be short-lived, because chemical companies that produce fentanyl and fentanyl analogues rapidly change names and tweak opioid molecules to avoid penalties. Up-to-date knowledge of how organisations that produce fentanyl, fentanyl precursors, and novel psychoactive substances sell their wares is key to enacting any kind of strategy that will not rapidly become obsolete. A major challenge in the detection of fentanyl-related financial transactions is that, even when such transactions raise flags, they do not obviously differ from other potentially lower-priority money-laundering activities.³⁶⁷ Furthermore, fentanyl, fentanyl precursors, and novel synthetic opioids are often purchased in small quantities that can be easily hidden inside other consumer goods, and the size of the financial transaction are often small; thus they can easily escape notice.⁵⁸

Governments should incentivise technical solutions to these detection and interdiction challenges. Prizes have been used to drive innovation in fentanyl detection in the postal system: in 2019, the Opioid Detection Challenge awarded US\$1.5 million in prizes across eight teams.³⁶⁸ The winning team developed a three-dimensional CT scanning system with automated detection algorithms, similar to that used in airport baggage scanning. The runners up developed a quadrupole resonance technology that uses radio-frequency signals to search for specific materials, triggering an alarm when an illicit substance is detected. More prizes and efforts to pilot and scale up potential solutions deserve public investment.

The US Defense Advanced Research Projects Agency should be tasked with leading out-of-the-box demonstration projects focused on the opioid crisis

The US Defense Advanced Research Projects Agency was founded in response to the Sputnik launch to lead transformational change within and outside of

Panel 11: Possible demonstration projects

- Deliver substance-focused prevention or treatment services in unconventional settings. A randomised controlled trial³⁷⁰ showed that a hypertension intervention delivered in barbershops increased uptake of blood pressure checks,³⁷⁰ with effects still evident a year later.³⁷¹ Barbershops might also be a good setting for substance-focused programmes in some communities, while in others better results might be obtained in bowling alleys, dental offices, online chatrooms, gaming clubs, or faith communities.
- Interfere with online drug sales by using inexpensive tricks developed by hackers. For example, IP spoofing (using a false IP address to impersonate a trusted computing system) can be automated and scaled to overwhelm a website in a denial-of-service attack. A potential way to collapse online drug transaction websites offline would be to create many impersonating IP addresses to access the site until it crashes.
- Automate naloxone administration. Opioid users who overdose when alone cannot benefit from naloxone. A possible solution is a wearable device that automatically triggers a naloxone injection based on respiration rate, much like how insulin pumps administer insulin in the event of acute need. At users' discretion, the device could also be set to contact emergency medical services in the event of overdose.
- Mount creative and accurate public messaging campaigns to reduce drug-related risks—eg, promoting the role of designated rescuers akin to designated drivers, or campaigns informing people who use stimulants or pressed pills that fentanyl is not just a risk with heroin.
- Use technology to limit diversion of prescribed drugs to illicit markets. Smart pill bottles have not been particularly helpful for improving adherence in HIV treatment,³⁷² but perhaps they could be repurposed to reduce diversion of prescription opioids.
- Monitor places where people publicly discuss drugs to learn of emerging risks. Novel drugs like bromphine have shown up on the r/opiates thread on Reddit months before their existence was widely reported. Screen-scraping this and similar forums, including those on the dark web, could provide behavioural data to complement toxicological studies.
- Remove technical and legal barriers to the provision of telehealth care across state and provincial lines and international borders. For example, crisis counselling services could be made more available during relevant periods—ie, dusk to dawn—if counsellors working in other countries could take these shifts during their daytime hours.
- Develop machine learning algorithms that predict responses to pain and the risk of addiction and overdose in patients for whom opioids are being considered to inform decisions about medication choice, dosing, and co-prescription of naloxone (if an opioid is prescribed).
- Develop and test assessments of the incidence and prevalence of opioid use, addiction, and overdose that do not involve surveying individuals. These could include a combination of wastewater analysis, scraping of social media and internet search engine data, medical examiner data,²²⁹ and natural language processing of journalistic reports and chatroom dialogue from around the world.

government, with a focus on national defense. Its achievements are many: most notably it had a key role in developing the World Wide Web. The Commission recommends that the Defense Advanced Research Projects Agency be tasked to expand its focus to the opioid crisis. An alternative proposed by President Biden is the creation of a spinoff of the agency within the US National Institutes of Health.³⁶⁹

The range of projects that could be attempted is limitless. The Commission offers a non-exhaustive, illustrative list of ideas (panel 11). These ideas have not been tried, so we do not know how well they would work, but many would be relatively inexpensive and could be genuinely innovative.

Domain 7: Preventing opioid crises outside the USA and Canada

The seventh and final domain analysed by the Commission was the risk of the opioid crisis spreading to other nations. Whether out of fear or complacency, many people outside the USA have convinced themselves that the opioid crisis is something that could only happen in the USA's unique political and economic

context. As this report makes clear, this notion is clearly untrue: Canada had a similar explosion of opioid prescribing and now has an epidemic of OUD and overdose.³⁷

Several countries outside the USA and Canada show sharp increases in opioid prescribing (figure 8). Per-person opioid consumption in the Netherlands nearly doubled during the decade ending in 2017,³⁷³ and opioid-related hospital admissions and deaths tripled over the same period. The latest UN opioid prescription data showed that Iceland's consumption increased by 96% in the past 7 years; opioid overdose deaths are also up sharply, and Iceland now has the highest rate of overdose deaths among the Nordic countries.³⁷⁴ Between 1998 and 2016 in England,³⁷⁵ the per-person morphine equivalent dosage dispensed increased by 127%. Between 2009 and 2015, opioid prescriptions in Brazil increased by 465%.³⁷⁶ In Australia, between 1992 and 2012, opioid dispensing increased by a factor of 15.³⁷⁷ During the same period, hospitalisations associated with prescription opioid use more than doubled, and now outnumber hospitalisations associated with heroin. In Mexico, opioid dispensing increased by an average of 13% per quarter from 2015 to

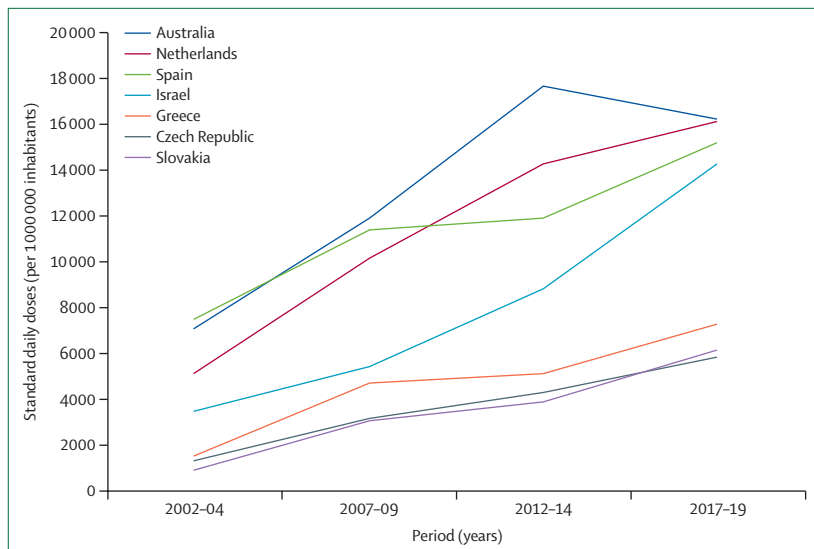


Figure 8: Selected countries with rising opioid consumption

2019, although the highest overall rate of dispensing was roughly 150 times lower than that in the USA at that time.^{81,378,379} The proportion of the Finnish population receiving opioid prescriptions rose from less than 1% in 1995, to 7% in 2016.³⁸⁰

“We’ve won the war on smoking” is a common expression invoked by public health officials and politicians in high-income countries. But this statement would only be true if exporting morbidity and mortality to the rest of the world while keeping the profits at home can be considered a victory.^{381,382} There is risk of a similar victory being declared with regard to prescription opioids.

Investigative journalists have shown that the Sackler family is expanding opioid markets through Mundipharma, using the same tactics that they used in the USA. Some of this expansion has been in high-income countries. A criminal investigation is ongoing in Italy, where two Mundipharma executives have been sentenced for involvement with a leading physician, who promoted opioids and allegedly laundered large cash payments from Mundipharma and another opioid manufacturer in exchange.³⁸³

Most of the expansion efforts are targeted at low-income and middle-income countries. According to an investigation by the *Los Angeles Times*,³⁸⁴ Mundipharma is attempting to promote OxyContin in countries including Brazil, China, Colombia, Egypt, Mexico, and the Philippines. Other investigative journalists have documented that Mundipharma is one of many Western companies promoting opioids in India^{385,386} and China using tactics pioneered in North America, including some that are now illegal there.³⁸⁷ Disturbingly, Furlan and colleagues have shown that in several low-income and middle-income countries, opioid manufacturers have been directly financially and personally involved in the production of opioid prescribing guidelines.³⁸⁸

We recognise the urgent need for better pain care in low-income countries. That the USA and Canada have an excess of prescription opioids should not distract policy makers from the fact that a lack of opioids causes untold misery in many low-income countries. The *Lancet* Commission on Palliative Care and Pain Relief⁷⁸ estimated that 25.5 million people die annually experiencing “serious health-related suffering”, over 80% of whom are in low-income countries where adequate palliative care is lacking. Low-income countries should not be forced to choose between letting their citizens suffer needlessly or giving in to corporate predation.

To increase the likelihood that opioid prescribing policies are geared toward maximising population health, the Commission urges all nations to consider our recommendations so far, particularly those designed to reduce regulatory corruption (eg, those under Domain 1). The following additional recommendations could further help protect nations outside the USA and Canada from having opioid crises of their own.

Recommendations to prevent export of the opioid crisis internationally

To avoid repeating the history of how the tobacco industry responded to increased regulation in high-income countries by finding new markets overseas, high-income nations where opioid manufacturers are based should extend restrictions and legal sanctions to global operations

US Government entities have won major civil cases against US based drug manufacturers and distributors.⁴ In addition to securing damage settlements, these cases have curtailed some deceptive practices that helped to trigger the opioid crisis, such as misleading prescribers by overstating the benefits and understating the risks of prescription opioids, making secret payments to key opinion leaders to promote their products, and engaging in false advertising.⁴

However, these court decisions and legal agreements do not prevent companies or their owners from engaging in the same fraudulent conduct outside the USA. A vivid case in point is the Sackler family, which owns both the USA-based Purdue Pharma and a sister company, Mundipharma, which is active internationally. Purdue Pharma executives were found criminally and civilly responsible for destructive and fraudulent tactics promoting OxyContin in the USA in 2007,⁴ and the company itself was found criminally and civilly liable in another major case in 2020.³⁸⁹ Purdue Pharma will cease to exist as a result of the 2020 case, but the Sackler family can still continue the same activities internationally through another company.

Political officials are fundamentally responsible for the wellbeing of their own citizens, but have an ethical imperative to protect people in other countries too. They should therefore insist on legal settlements with the opioid industry in which fraudulent and dangerous practices are banned not only in domestic markets but

also internationally, including through subsidiaries or other companies with the same owners. Otherwise, epidemics of prescription OUD and overdose could become pandemic. This concern has particular urgency given the latest federal and state prosecutions against Purdue Pharma and the Sackler family, in which forcing the family to give up foreign sister companies like Mundipharma (and Napp Pharmaceuticals) is being considered. Preventing the family only from continuing fraudulent OxyContin promotion domestically while allowing them to continue to do so overseas through a different company would be a terrible failure of leadership.

To respond to pain relief and palliative care needs in low-income nations as well as to prevent such countries from being exploited by for-profit opioid manufacturers, international agencies should coordinate distribution of free, generic morphine to hospitals and hospices

Faced with the humanitarian tragedy of untreated pain, low-income countries might cede some regulatory control to the pharmaceutical manufacturers whose profit-seeking has been destructive in other nations. The international community has a moral responsibility to not force low-income nations to choose between relieving needless suffering and risking an opioid addiction epidemic brought on by multinational corporations.

Accordingly, WHO, with support of donor organisations, should coordinate delivery of generic morphine to hospitals and hospices in low-income countries. This action will require the support of the International Narcotics Control Board, which oversees the UN conventions on narcotics drugs and licences and regulates licit opioid production.

Without the influence of the profit motive, this model could help to relieve suffering without overpromotion and overprescription of opioids. And implementation costs are low: the cost of providing morphine-equivalent pain treatment to every child experiencing serious health suffering in low-income countries is only US\$1 million a year.³⁷⁸

Conclusion

Even in the era of COVID-19, the opioid crisis stands out as one of the most devastating public health disasters of the 21st century in the USA and Canada. The Commission's conclusions about the crisis are in one respect simple: unrestrained profit-seeking and multi-level, multi-system regulatory failure instigated the opioid crisis and can produce further epidemics of addiction in the future. Although the present crisis is concentrated in the USA and Canada, similar crises could emerge in any country. The public health case for the Commission's proposed reforms of pharmaceutical and medical regulation is thus strong, and the need urgent.

The Commission is unequivocal in its view that addiction is an enduring feature of population health, although in the future the main drugs of concern might

not be opioids. For this reason, provision of addiction-related services should be a permanent feature of health and social care systems, and should be financed and organised as a core commitment.

In other respects, the Commission pleads for attention to nuance in an era characterised by simplistic viewpoints. Opioids are neither good nor bad in any absolute sense. Rather, they are a class of drug that is simultaneously essential to medical practice and fraught with serious risks. Some regions, particularly low-income countries, do not have sufficient opioids and should be supplied them through non-profit, public sector initiatives. Other regions, notably the USA and Canada, have a surfeit of opioids and population health suffers as a result, even as individuals within these nations simultaneously avoid needless pain that they might have had to experience in low-income countries. Implementation of restrictions on opioid prescriptions can avert cases of addiction but could potentially harm patients who are in pain or are dependent on prescription opioids, or both. Prescribing policies should be sensitive to the diverse and sometimes opposing needs of different subpopulations.

Nuance is also needed regarding the criminal justice system. Law enforcement officials cannot crush the opioid crisis through brute force, and attempts to do so destroy many lives. At the same time, the use of addictive drugs changes people's behaviour, including in ways that can lead to victimisation of other people, who will seek protection from the criminal justice system. Engagement of the criminal justice system in drug-related issues is thus inevitable, irrespective of whether drugs are legal or not. The goal should thus be to maximise the benefits and minimise the costs of that engagement, for the individuals concerned, their families, and for the community around them.

Nuanced thinking is also needed regarding poverty, inequality, and addiction. Alleviating poverty is a worthy goal for many reasons, but no simple promises should be made that reduced addiction will necessarily be the result. Human wellbeing is not a simple function of economics, but it can be augmented by programmes and policies that increase access to safe and rewarding environments. Cultivating health-promoting environments is a structural strategy that might translate into reduced addiction in future years, and could help to prevent other individual and social ills.

Few of the Commission's recommendations are easy to implement, but they will be easier to achieve if a culture of innovation is encouraged and if long-standing structural gaps in knowledge about the epidemic and about drugs more generally are closed. Even perfect attainment of all our recommendations will not eliminate the opioid crisis: tragically, many future deaths are inevitable at this point.^{24,79} Nevertheless, substantial gains in quality of life and reductions in loss of life are clearly attainable with sufficient resources and political will to pursue the bold policies set out here.

It took more than a generation of mistakes to create the North American opioid crisis. It might take a generation of wiser policies to resolve it. Such policies will have long-lasting gains if they curtail the power of health-care systems to cause addiction and maximise their ability to treat it.

Contributors

KH chaired the Commission, secured funding from Stanford University School of Medicine, and drafted most of the report. CLS, CMA, and MLB drafted individual sections. All Commissioners participated in deliberations, and reviewed and edited multiple drafts of the report.

Declaration of interests

KH has been supported by the Esther Ting Memorial Professorship at Stanford University School of Medicine and research grants from the US Veterans Administration Health Services Research and Development Service (RCS 04-141-3, HX-12-001, and HX002714-01A2), the US National Institute on Drug Abuse (3UG1 DA015815-17S4 and 2UG1DA015815-19), the US Food and Drug Administration, Wu Tsai Neurosciences Institute, the Silicon Valley Community Foundation, the County of Santa Clara California, and the American Board of Family Medicine. He has received speaking honoraria and travel expenses from the American College of Medical Toxicology, Arizona State University, Barclays Bank, Caron Foundation, the University of Florida, the New York Museum of Modern Art, Syracuse University, West Virginia University School of Medicine, and the West Virginia Medical Professionals Health Program. He has received writing honoraria or royalties from the Association of Psychological Science, American Academy of Political and Social Science, Brookings Institution, Cambridge University Press, and *Washington Monthly*. He has been a paid consultant to AELIS Pharma, Harvard Medical School, and Harvard University Press. CLS has been employed by Stanford University, the University of California, Los Angeles (UCLA), the Los Angeles County Department of Public Health, Heluna Health, and the Los Angeles LGBT Center. She has received research funding or stipends from the US National Institute on Drug Abuse (K01DA050771, T32DA035165), the RAND Opioid Policy Tools and Information Center), Wu Tsai Neurosciences Institute, and UCLA David Geffen School of Medicine, and speaking honoraria or travel expenses from Emory University, New York University, UCLA, the University of North Carolina at Chapel Hill, the University of Southern California, the University of Pittsburgh, the University of Chicago, the University of Western Ontario, the Nevada State Medical Association, RAND, the University of California, Irvine, the US Centers for Disease Control and Prevention, College on Problems of Drug Dependence, the Conference on Retroviruses and Opportunistic Infections, HIV Research for Prevention, Addiction Health Services Research, and the American Psychopathological Association. CMA has been supported by the Arnold School of Public Health at the University of South Carolina, and by research grants from the US National Institute on Drug Abuse (R01DA034634, K01DA041628, U2CDA050097, R01DA049776, and R01DA052425), the US National Institute on Alcoholism and Alcohol Abuse (R01AA029097 and R01AA029821), and the South Carolina Department of Alcohol and Other Drug Abuse Services, and has been a paid consultant to the Robert Wood Johnson Foundation, RTI International, the Medical University of South Carolina, the State of Pennsylvania Department of Public Health, and the State of Illinois Division of Health Care and Family Services. ASBB has been supported by grants from the US National Institutes for Health (R01 DA045705), the US Veterans Health Administration (IIR 13-322 and C19 21-278), the US Centers for Disease Control and Prevention (U01CE002780), Blue Cross Blue Shield of Michigan, the US Department of Defense, the Patient-Centered Outcomes Research Institute, the Michigan Health Endowment Fund, and the Substance Abuse and Mental Health Services Administration via sub-contracts from the Michigan Department of Health and Human Services, has received speaker honoraria or travel expenses from the Illinois Health and Hospital Association, the International Summit on Suicide Research, the Washington State Department of Labor & Industries, the

American Psychopathological Association, and the High Intensity Drug Trafficking Area program, has been paid as a consultant by New York University, and has received products from Fitbit at a reduced cost and Headspace for free for research purposes. MLB has been supported by research grants from the US Department of Veterans Affairs and the US National Institute on Drug Abuse (R37-DA15612), and a Koret Foundation gift for Smart Cities and Digital Living, has received travel expenses from the University of Maryland, the University of Auckland, Massachusetts Institute of Technology, the European Working Group on Stochastic Modeling, INSEAD, the University of Michigan, and the University of Oklahoma, and has been a paid consultant to Compass Lexecon and DE Shaw. JPC has received a National Science Foundation EAGER Grant on Detecting and Disrupting Illicit Supply Networks via Traffic Distribution Systems, is a consultant to the RAND Corporation's Drug Policy Research Center, has consulted with or received honoraria from the Actis—Norwegian Policy Network on Alcohol and Drugs, the Arnold Foundation, Bank of Montreal, Boston University, the Foreign Affairs, Justice Research and Statistics Association, Lisbon Addictions Conference, Massachusetts Institute of Technology, National Affairs, the National Institute of Justice, Oxford University Press, Pew, PIRE, the Russell Sage Foundation, Springer Verlag, Stanford University, the US State Department, Texas Research Society on Alcoholism, the US Veteran's Administration, *Washington Monthly*, and the WT Grant Foundation. JHC has received research support or funding from the US National Institutes of Health and National Library of Medicine (R56LM013365), the Gordon and Betty Moore Foundation (GBMF8040), the US National Science Foundation (SPO181514); Google (SPO13604), the Stanford Clinical Excellence Research Center, the Stanford Department of Medicine and Department of Pathology, and the Stanford Aging and Ethnogeriatrics Research Center (P30AG059307), which is part of the Resource Centers for Minority Aging Research programme led by the US National Institute on Aging at the National Institutes of Health, is the co-founder of Reaction Explorer (which develops and licenses organic chemistry education software), and has been paid consulting or speaker fees by the US National Institute of Drug Abuse Clinical Trials Network, Tuolc, Roche, and Younker Hyde MacFarlane. M-FC has served as president of the Carnegie Endowment for International Peace, a justice of the Supreme Court of California, the Herman Phleger Professor at Stanford Law School, a distinguished visiting jurist at the New York University School of Law, the Castle Distinguished Lecturer in Ethics, Politics, and Economics at Yale University, a member of the President & Fellows of Harvard College (the Harvard Corporation), a member of the board of directors of the William and Flora Hewlett Foundation, a member of the Council of the American Law Institute, chair of the board of directors of the Center for Advanced Study in the Behavioral Sciences, chair of the advisory board of the Seed Initiative at the Stanford Graduate School of Business, and a member of the advisory board at the Stanford Human-Centered Artificial Intelligence Institute. His work has been supported by Stanford Law School and by a grant from the Stanford Human-Centered Artificial Intelligence Institute, and he was previously chair of the advisory board of the AI Now Institute at New York University. YLH has received research grants from the US National Institute on Drug Abuse (DA050323, DA048613, DA008227, DA043247, DA030359, DA037317, and DA15446), research funding from GW Pharmaceuticals, speaking honoraria or travel expenses, or both, from the University of North Carolina, the American Society for the Advancement of Science, the Society for Neuroscience Public Education & Communication Committee, Washington University in St Louis, Temple University, Tufts School of Medicine, Indiana University, the American College of Neuropsychopharmacology, the Iowa Neuroscience Institute, the Franklin Institute, State University of New York Upstate Medical University, the Canadian Consortium for the Investigation of Cannabinoids, the University of Michigan, Cold Spring Harbor Laboratory, the US National Institutes of Health, Penn State Hershey College of Medicine, the US National Academy of Medicine, the Mediterranean Neuroscience Society, the Wu Tsai Neurosciences Institute, Society of Biological Psychiatry, International College of Neuropsychopharmacology, the Federation of European Neuroscience Societies, Gordon Research Conference, the National

Institutes of Health Center for Scientific Research Council, and the Society of Neuroscience. DNJ has received research grants from the Canadian Institutes for Health Research and the Ontario Ministry of Health, financial support from the departments of medicine at both the University of Toronto and Sunnybrook Health Sciences Centre, travel expenses or speaking honoraria from Dalhousie University, the University of Ottawa, the University of Saskatchewan, the University of Calgary, the Bloomberg Johns Hopkins School of Public Health, the American College of Physicians, the University of Alabama at Birmingham, the American Society of Nephrology, the Canadian Society of Internal Medicine, the Canadian Anesthesiologists' Society, The Canadian Society of Obstetricians and Gynecologists, the Western Canada Addiction Forum, and the Canadian House of Commons Standing Committee on Health, and payment for expert witness testimony from (and has been retained by) Sanis, a generic drug manufacturer and distributor to provide advice related to an ongoing Canadian class action, and is a volunteer member of Physicians for Responsible Opioid Prescribing. HKK has been supported by grants from the Robert Wood Johnson Foundation (77667, 74275, and 73359), the John Templeton Foundation (52125), the JPB Foundation (1085 and 439), and the Association of State and Territorial Health Officers (1584), has received honoraria from Jefferson University, Jefferson Health, the Perelman School of Medicine at the University of Pennsylvania, MaineHealth Center for Tobacco Independence, Harvard University Memorial Church, the Association of State and Territorial Health Officials, the University of Wisconsin Medical School, Wake Forest Baptist Health (in partnership with Shaw University), the Robert Wood Johnson Foundation advisory committee, the American College of Gastroenterology, and Tufts University School of Medicine, has been a consultant to the Commonwealth Fund, and is a member of the Community COVID Coalition Advisory Group, Phillips Academy Public Health Expert Advisory Panel, the Policy Advisory Group, the board of the Bipartisan Policy Center, the Palliative and Advanced Illness Research Center External Advisory Board (at the Perelman School of Medicine), the American Cancer Society Eastern New England Area Council of Advisors, the American University of Beirut International Advisory Council, the US National Advisory Board, the Culture of Health Year in Review Advisory Committee and Culture of Health as a Business Imperative Initiative of the Robert Wood Johnson Foundation, the editorial board of the *Journal of the American Medical Association*, the New England Donor Services board of trustees, the Josiah Macy Jr Foundation board of directors, and the *Lancet*-O'Neill Institute, Georgetown University Commission on Global Health and the Law. EEK has received research funding from the US Department of Veterans Affairs Health Services Research and Development (COR 19-489, 1I01HX003063-01A1, 5101HX001752-05, 5101HX002737-02, 5101HX001288-05, and 5101HX000911-06), the Patient Centered Outcomes Research Institute (OPD-1511-33052), the US National Center for Complementary and Integrative Health (5R01AT008387-04, 5UH3AT009761-04/5UG3AT009761-02, and 4UH3AT009765-03/5UG3AT009765-02), and the US National Institute of Diabetes and Digestive and Kidney Diseases (1U01DK123816-01), and travel expenses from the law firm Nix Patterson representing the state of Oklahoma (to serve as an expert witness in support of the state's litigation against opioid manufacturers), the American Society of Health-System Pharmacists, the Association of Academic Physiatrists, the Australian Pain Society, the Cleveland VA Medical Research and Education Foundation, the Duke-Margolis Center for Health Policy, the Foundation for Medical Excellence, the Foundation for Opioid Response Efforts, the Friends of VA Medical Care and Health Research, the Hennepin Healthcare Research Institute, the Indiana Institute for Medical Research, the US National Academies of Medicine, the US National Center for Complementary and Integrative Health, the National Governors Association, the North American Spine Society, the Patient Centered Outcomes Research Institute at Stanford University, the US Food and Drug Administration, and the Washington State Department of Labor & Industries. AL has received consulting fees for her work as a medical expert witness in federal and state litigation against opioid manufacturers, distributors, and pharmacies, book royalties from Johns Hopkins University Press and Dutton Penguin Random House,

speaking honoraria or travel expenses, or both, from the Vanderbilt University School of Medicine, the Ohio State University School of Medicine, the University of Kansas School of Medicine (sponsorship of the Alpha Omega Alpha Visiting Professorship), the Oregon Pain Guidance, the Indiana Prosecuting Attorneys Council, the Perrin's Opioid Litigation Conference, the Public Funds Forum, the Baton Rouge Health District, the Montrose Colorado Annual Continuing Medical Education Conference, the PerformRX Pharmacy Benefits Manager Annual Conference, the American Academy of Psychiatry and the Law, the Psych Congress, the 69th Annual Canadian Refresher Course for Family Physicians, the Ohio State University Inter-Professional Summit, the University of Texas, the Geminus Community Partners Annual Conference of Indiana, the National Council on Alcoholism and Drug Abuse, the Stanford Sierra Camp Womens' Alumni Wellness Retreat, the American Psychiatric Association, the Association for Medical Education and Research in Substance Abuse, and the Southwestern Gynecologic Assembly. SCM has been supported by the Redlich Professorship and the Rosekrans Pain Research Endowment Fund at Stanford University School of Medicine and research grants awarded to Stanford University from the US National Institutes of Health (R61NS118651, R03HD094577, R01DA045027, R01NS109450, R01AT008561, K24DA02926207, R01DA035484, and P01AT00665105), the Patient Centered Outcomes Research Institute (PCORI OPD-1610- 370707), the Stanford Wu Tsai Neurosciences Institute, and the University of California, San Francisco—Stanford Center of Excellence in Regulatory Science and Innovation (FDA) (2U01FD005978-06), has received speaking honoraria or travel expenses from Walter Reed, Harvard University, the American Academy of Pain Medicine, Washington University, the US Food and Drug Administration, the US National Institutes of Health, the US National Institute of Neurological Disorders and Stroke, the University of Washington, George Washington University, New York University, Weill Cornell Medical College, Duke University, the University of Utah, the World Institute of Pain, and the Canadian Pain Society, has received payment for testimony (unrelated to opioids) from Lauria Tokunaga Gates and Linn, and has received payment for consulting (unrelated to opioids) from the American Society of Anesthesiology; Favros Law; Fain Anderson VanDerhoef Rosendahl O'Halloran Spillane; Cox, Wootton, Lerner, Griffin & Hansen; Lewis Brisbois Bisgaard & Smith; Muro & Lampe; McCormick Barstow; Schmid & Voiles; and the University of Oklahoma Health Sciences Center. LLO has received travel expenses or honoraria from Cardozo Law School, Claremont McKenna College, Duke University, ETH Zürich, Georgetown University, Harvard University, the Los Angeles Intellectual Property Law Association, Michigan State University, New York University, Northwestern University, the University of Chicago, the University of Houston, the University of Kansas, the University of Nebraska, the University of San Diego, the University of Texas, the University of Villanova, the World Intellectual Property Organization, and Yale University, has received a writing honoraria from the Brookings Institution (to write a policy proposal for the Hamilton Project), and is a paid consultant to the MITRE Corporation (to assist with evaluations of the US Patent and Trademark Office requested by the Department of Commerce). BS has received research support from the US National Institute on Alcohol Abuse and Alcoholism (R01 AA023650 and K23 AA023284), the US National Institute of Drug Abuse (R21 DA043181), the US National Institute of Mental Health (P50MH115838), and the US National Highway Transportation Safety Authority, has received royalties from a software licence to healthStratica, and has several invention disclosures with the University of Pittsburgh for digital behavioral interventions. CT has been supported by the US Department of Veterans Affairs (VA HSR&D IIR 15-298, IIR 18-253, IIR 20-058, and PPO 16-337) and the US National Institutes of Health (NIAAA 1R01AA024136-01).

Acknowledgments

The work of the Commission was funded by Stanford University School of Medicine (Stanford, CA, USA). The views expressed in this report are those of the authors and do not necessarily reflect the official position of Stanford University or of any governmental or non-governmental entity for which they work or that they advise.

References

- 1 Humphreys K, Caulkins JP, Felbab-Brown V. Opioids of the masses. *Foreign Aff* 2018; **97**: 118–29.
- 2 American Medical Association. Issue brief: Reports of increases in opioid- and other drug-related overdose and other concerns during COVID pandemic. 2020. <https://www.ama-assn.org/system/files/2020-12/issue-brief-increases-in-opioid-related-overdose.pdf> (accessed Dec 12, 2020).
- 3 US Food and Drug Administration. Timeline of selected FDA activities & significant events addressing opioid misuse & abuse. <https://www.fda.gov/media/85029/download> (accessed Dec 12, 2020).
- 4 Meier B. Pain Killer: An Empire of Deceit and the Origins of America's Opioid Epidemic. New York, NY: Random House, 2018.
- 5 Cuéllar M-F, Humphreys K. The political economy of the opioid epidemic. *Yale Law Policy Rev* 2020; **38**: 1–76.
- 6 Delgado MK, Huang Y, Meisel Z, et al. National variation in opioid prescribing and risk of prolonged use for opioid-naive patients treated in the emergency department for ankle sprains. *Ann Emerg Med* 2018; **72**: 389–400.
- 7 DeVries A, Koch T, Wall E, Getchius T, Chi W, Rosenberg A. Opioid use among adolescent patients treated for headache. *J Adolesc Health* 2014; **55**: 128–33.
- 8 Gossett TD, Finney FT, Hu HM, et al. New persistent opioid use and associated risk factors following treatment of ankle fractures. *Foot Ankle Int* 2019; **40**: 1043–51.
- 9 Suda KJ, Zhou J, Rowan SA, et al. Overprescribing of opioids to adults by dentists in the US, 2011–2015. *Am J Prev Med* 2020; **58**: 473–86.
- 10 US Centers for Disease Control and Prevention. Prescription painkiller overdoses in the US, November 2011. <https://www.cdc.gov/vitalsigns/painkilleroverdoses/index.html> (accessed Dec 26, 2021).
- 11 Canadian Institute for Health Information. Pan-Canadian trends in the prescribing of opioids, 2012–2016. <https://www.cihi.ca/sites/default/files/document/pan-canadian-trends-opioid-prescribing-2017-en-web.pdf> (accessed Dec 26, 2021).
- 12 Kaafarani HMA, Han K, El Moheb M, et al. Opioids after surgery in the United States versus the rest of the world: the International Patterns of Opioid Prescribing (iPOP) multicenter study. *Ann Surg* 2020; **272**: 879–86.
- 13 Humphreys K. Avoiding globalisation of the prescription opioid epidemic. *Lancet* 2017; **390**: 437–39.
- 14 International Narcotics Control Board. Narcotic Drugs 2013. 2013. https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2013/Narcotic_Drugs_Report_2013.pdf (accessed Dec 14, 2020).
- 15 Watson ST. Name of convicted donor coming off UB Pharmacy School building. 2019. https://buffalonews.com/news/local/name-of-convicted-donor-coming-off-ub-pharmacy-school-building/article_09388600-0b5a-51fe-9819-04a0b295ac87.html (accessed Nov 10, 2020).
- 16 Balko R. The war over prescription painkillers. 2012. https://www.huffpost.com/entry/prescription-painkillers_b_1240722 (accessed Dec 29, 2021).
- 17 US Centers for Disease Control and Prevention. Multiple Cause of Death 1999–2020. 2021. <http://wonder.cdc.gov/mcd-icd10.html> (accessed Dec 29, 2021).
- 18 Luo F, Li M, Florence C. State-Level economic costs of opioid use disorder and fatal opioid overdose—United States, 2017. *MMWR Morb Mortal Wkly Rep* 2021; **70**: 541–46.
- 19 Humphreys K. We can't fight opioids by controlling demand alone. 2019. https://www.washingtonpost.com/outlook/we-cant-fight-opioids-by-controlling-demand-alone/2019/07/05/d0253558e-7e2d-11e9-8ede-f4abf521ef17_story.html (accessed Dec 13, 2020).
- 20 Humphreys K. How legal drug companies helped revive the heroin trade. 2018. <https://www.washingtonpost.com/news/wonk/wp/2018/06/15/how-legal-drug-companies-helped-revive-the-heroin-trade/> (accessed Dec 1, 2020).
- 21 Quinones S. *Dreamland: The True Tale of America's Opiate Epidemic*. New York, NY: Bloomsbury, 2015.
- 22 Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. 2013. <https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm> (accessed Dec 27, 2021).
- 23 Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. *N Engl J Med* 2016; **374**: 154–63.
- 24 Pitt AL, Humphreys K, Brandeau ML. Modeling health benefits and harms of public policy responses to the US opioid epidemic. *Am J Public Health* 2018; **108**: 1394–400.
- 25 Frank RG, Pollack HA. Addressing the fentanyl threat to public health. *N Engl J Med* 2017; **376**: 605–07.
- 26 Pardo B, Taylor J, Caulkins JP, et al. The future of fentanyl and other synthetic opioids. Santa Monica, CA: RAND, 2019.
- 27 US National Institute on Drug Abuse. Prescription opioid use is a risk factor for heroin use. 2015. <https://www.drugabuse.gov/publications/research-reports/prescription-opioids-heroin/prescription-opioid-use-risk-factor-heroin-use> (accessed Dec 4, 2020).
- 28 Nechuta SJ, Tyndall BD, Mukhopadhyay S, McPheeters ML. Sociodemographic factors, prescription history and opioid overdose deaths: a statewide analysis using linked PDMP and mortality data. *Drug Alcohol Depend* 2018; **190**: 62–71.
- 29 Artiga S, Hill K, Orgera L, Damico, A. Health coverage by race and ethnicity, 2010–2019. San Francisco, CA: Kaiser Family Foundation, 2021.
- 30 Hoffman KM, Trawalter S, Axt JR, Oliver MN. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc Natl Acad Sci USA* 2016; **113**: 4296–301.
- 31 Morden NE, Chyn D, Wood A, Meara E. Racial inequality in prescription opioid receipt — role of individual health systems. *N Engl J Med* 2021; **385**: 342–51.
- 32 Alberta Health. Opioids and substances of misuse among First Nations people in Alberta. 2017. <https://open.alberta.ca/dataset/cb00bdd1-5d55-485a-9953-724832f373c3/resource/31c4f309-26d4-46cf-b8b2-3a990510077c/download/Opioids-Substances-Misuse-Report-FirstNations-2017.pdf> (accessed Dec 4, 2020).
- 33 McGramahan D, Parker T. The Opioid Epidemic: A Geography in Two Phases. Washington, DC: US Department of Agriculture, 2021.
- 34 Horwitz S, Cenziper D, Rich S. As opioids flooded tribal lands across the U.S., overdose deaths skyrocketed. 2020. <https://www.washingtonpost.com/graphics/2020/national/investigations/native-american-opioid-overdose-deaths/> (accessed Dec 8, 2021).
- 35 Webster PC. Indigenous Canadians confront prescription opioid misuse. *Lancet* 2013; **381**: 1447–48.
- 36 Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription opioid use, misuse, and use disorders in US adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med* 2017; **167**: 293–301.
- 37 Belzak L, Halverson J. The opioid crisis in Canada: a national perspective. *Health Promot Chronic Dis Prev Can* 2018; **38**: 224–33.
- 38 Baggett TP, Hwang SW, O'Connell JJ, et al. Mortality among homeless adults in Boston: shifts in causes of death over a 15-year period. *JAMA Intern Med* 2013; **173**: 189–95.
- 39 Yamamoto A, Needleman J, Gelberg L, Kominski G, Shoptaw S, Tsugawa Y. Association between homelessness and opioid overdose and opioid-related hospital admissions/emergency department visits. *Soc Sci Med* 2019; **242**: 112585.
- 40 Martins SS, Sampson L, Cerdá M, Galea S. Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. *Am J Public Health* 2015; **105**: e29–49.
- 41 Merrall ELC, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction* 2010; **105**: 1545–54.
- 42 Hedegaard H, Bastian BA, Trinidad JP, Spencer MR, Warner M. Regional differences in the drugs most frequently involved in drug overdose deaths: United States, 2017. *Natl Vital Stat Rep* 2019; **68**: 1–16.
- 43 Spencer MR, Warner M, Bastian BA, Trinidad JP, Hedegaard H. Drug overdose deaths involving fentanyl, 2011–2016. *Natl Vital Stat Rep* 2019; **68**: 1–19.
- 44 Lembke A. *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop*. Baltimore, MD: Johns Hopkins University Press, 2016.
- 45 Levin D. The class of 2000 'could have been anything.' Until opioids hit. 2019. <https://www.nytimes.com/interactive/2019/12/02/us/opioid-crisis-high-school-teenagers.html> (accessed Nov 1, 2020).

- 46 Lynch B. What a difference a year makes: woman focused on detox after addiction. 2017. https://www.wvgazette.com/news/health/what-a-difference-a-year-makes-woman-focused-on-detox-after-addiction/article_8366e4cb-4209-5bf1-be53-94e1e52c13f2.html (accessed Nov 1, 2020).
- 47 Bramham D. 'I don't want Nick to be only a statistic.' 2020. <https://vancouver.sun.com/news/daphne-bramham-i-dont-want-nick-to-be-only-a-statistic> (accessed Oct 10, 2020).
- 48 Krebs EE, Bergman AA, Coffing JM, Campbell SR, Frankel RM, Matthias MS. Barriers to guideline-concordant opioid management in primary care—a qualitative study. *J Pain* 2014; **15**: 1148–55.
- 49 US Centers for Disease Control and Prevention. HIV surveillance—United States, 1981–2008. *MMWR Morb Mortal Wkly Rep* 2011; **60**: 689–93.
- 50 US Census Bureau. US and world population clock. 2021. <https://www.census.gov/popclock/world/ca> (accessed Dec 29, 2021).
- 51 Jonah L, Bourgeois AC, Edmunds M, Awan A, Varsaneux O, Siu W. AIDS in Canada—surveillance report, 2016. *Can Commun Dis Rep* 2017; **43**: 257–61.
- 52 Special Advisory Committee on the Epidemic of Opioid Overdoses. Opioid and stimulant-related harms in Canada. Ottawa, ON: Public Health Agency of Canada, 2021.
- 53 Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. 2021. <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm> (accessed Jan 3, 2022).
- 54 Shover CL, Falasinnu TO, Dwyer CL, et al. Steep increases in fentanyl-related mortality west of the Mississippi River: recent evidence from county and state surveillance. *Drug Alcohol Depend* 2020; **216**: 108314.
- 55 American Medical Association. Issue brief: drug overdose epidemic worsened during COVID pandemic. 2021. <https://www.ama-assn.org/system/files/issue-brief-increases-in-opioid-related-overdose.pdf> (accessed Dec 29, 2021).
- 56 Friedman J, Mann NC, Hansen H, et al. Racial/ethnic, social, and geographic trends in overdose-associated cardiac arrests observed by US emergency medical services during the COVID-19 pandemic. *JAMA Psychiatry* 2021; **78**: 886–95.
- 57 Pardo B. Supplying synthetic opioids during a pandemic: an early look at North America. *Int J Drug Policy* 2021; **93**: 102833.
- 58 Westhoff B. Fentanyl, Inc: How Rogue Chemists Created the Deadliest Wave of the Opioid Epidemic. New York, NY: Grove Atlantic, 2019.
- 59 Palamar JJ, Le A, Carr TH, Cottler LB. Shifts in drug seizures in the United States during the COVID-19 pandemic. *Drug Alcohol Depend* 2021; **221**: 108580.
- 60 US Department of Health and Human Services. Practice guidelines for the administration of buprenorphine for treating opioid use disorder. 2021. <https://www.federalregister.gov/documents/2021/04/28/2021-08961/practice-guidelines-for-the-administration-of-buprenorphine-for-treating-opioid-use-disorder> (accessed Dec 29, 2021).
- 61 Alexander GC, Stoller KB, Haffajee RL, Saloner B. An epidemic in the midst of a pandemic: opioid use disorder and COVID-19. *Ann Intern Med* 2020; **173**: 57–58.
- 62 Clarke H, Weinrib A, Kotteeswaran Y, Katz J, Yu A, Tanguay R. Remote buprenorphine-naloxone initiation as an essential service for people with chronic pain and opioid dependence during the COVID-19 pandemic: case reports, clinical pathways, and implications for the future. *Can J Pain* 2020; **4**: 224–35.
- 63 Cance JD, Doyle E. Changes in outpatient buprenorphine dispensing during the COVID-19 pandemic. *JAMA* 2020; **324**: 2442–44.
- 64 Clark SA, Davis C, Wightman RS, et al. Using telehealth to improve buprenorphine access during and after COVID-19: a rapid response initiative in Rhode Island. *J Subst Abuse Treat* 2021; **124**: 108283.
- 65 Huskamp HA, Busch AB, Uscher-Pines L, Barnett ML, Riedel L, Mehrotra A. Treatment of opioid use disorder among commercially insured patients in the context of the COVID-19 pandemic. *JAMA* 2020; **324**: 2440–42.
- 66 Duncan A, Sanders N, Schiff M, Winkelman TNA. Adaptations to jail-based buprenorphine treatment during the COVID-19 pandemic. *J Subst Abuse Treat* 2021; **121**: 108161.
- 67 Bandara S, Kennedy-Hendricks A, Merritt S, Barry CL, Saloner B. Early effects of COVID-19 on programs providing medications for opioid use disorder in jails and prisons. *J Addict Med* 2020; **14**: e257–60.
- 68 Donelan CJ, Hayes E, Potee RA, Schwartz L, Evans EA. COVID-19 and treating incarcerated populations for opioid use disorder. *J Subst Abuse Treat* 2021; **124**: 108216.
- 69 Volkow ND. Collision of the COVID-19 and addiction epidemics. *Ann Intern Med* 2020; **173**: 61–62.
- 70 Shover CL, Falasinnu TO, Freedman RB, Humphreys K. Emerging Characteristics of isotonitazene-involved overdose deaths: a case-control study. *J Addict Med* 2021; **15**: 429–31.
- 71 Connecticut Office of the Chief Medical Examiner. Statistics. <https://portal.ct.gov/OCME/Statistics> (accessed Jan 3, 2022).
- 72 Cook County Government. Medical examiner case archive. <https://datacatalog.cookcountyil.gov/Public-Safety/Medical-Examiner-Case-Archive/cjeq-bs86> (accessed Jan 3, 2022).
- 73 Tarrant County, TX. Medical examiner's case records. <https://mepublic.tarrantcounty.com/> (accessed Jan 3, 2022).
- 74 British Columbia Coroners Service. Illicit drug toxicity deaths in BC January 1, 2011–October 31, 2021. 2021. <https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicit-drug.pdf> (accessed Dec 29, 2021).
- 75 King County. Overdose deaths. 2020. <https://www.kingcounty.gov/depts/health/examiner/services/reports-data/overdose.aspx> (accessed May 1, 2020).
- 76 National Academies of Sciences, Engineering, and Medicine. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. Washington, DC: National Academies Press, 2017.
- 77 National Academies of Sciences, Engineering, and Medicine. Advancing Therapeutic Development for Pain and Opioid Use Disorders Through Public–Private Partnerships: Proceedings of a Workshop. Washington, DC: National Academies Press, 2018.
- 78 National Academies of Sciences, Engineering, and Medicine. Medications for Opioid Use Disorder Save Lives. Washington, DC: National Academies Press, 2019.
- 79 Rao IJ, Humphreys K, Brandeau ML. Effectiveness of policies for addressing the US opioid epidemic: a model-based analysis from the Stanford–Lancet Commission on the North American Opioid Crisis. *Lancet Reg Health Am* 2021; **3**: 100031.
- 80 Goodman-Meza D, Medina-Mora ME, Magis-Rodríguez C, Landovitz RJ, Shoptaw S, Werb D. Where is the opioid use epidemic in Mexico? A cautionary tale for policymakers south of the US-Mexico border. *Am J Public Health* 2019; **109**: 73–82.
- 81 Goodman-Meza D, Friedman J, Kalmin MM, et al. Geographical and socioeconomic disparities in opioid access in Mexico, 2015–19: a retrospective analysis of surveillance data. *Lancet Public Health* 2021; **6**: e88–96.
- 82 Keefe PR. Empire of Pain: The Secret History of the Sackler Dynasty Hardcover. New York, NY: Doubleday, 2021.
- 83 Keefe PR. The family that built an empire of pain. 2017. <https://www.newyorker.com/magazine/2017/10/30/the-family-that-built-an-empire-of-pain> (accessed Dec 12, 2020).
- 84 Herper M. An opioid spray showered billionaire John Kapoor in riches. Now he's feeling the pain. 2016. <https://www.forbes.com/sites/matthewherper/2016/10/04/death-kickbacks-and-a-billionaire-the-story-of-a-dangerous-opioid/?sh=b23d5186e3f9> (accessed Dec 29, 2021).
- 85 Higham S, Horwitz S, Rich S. 76 billion opioid pills: newly released federal data unmasks the epidemic. 2019. https://www.washingtonpost.com/investigations/76-billion-opioid-pills-newly-released-federal-data-unmasks-the-epidemic/2019/07/16/5f29fd62-a73e-11e9-86dd-d7f0e60391e9_story.html (accessed Dec 13, 2020).
- 86 Eyre E. Death in Mud Lick: A Coal Country Fight Against the Drug Companies That Delivered the Opioid Epidemic. New York, NY: Simon and Schuster, 2020.
- 87 Johns MW. Self-poisoning with barbiturates in England and Wales during 1959–74. *BMJ* 1977; **1**: 1128–30.
- 88 Lembke A, Papac J, Humphreys K. Our other prescription drug problem. *N Engl J Med* 2018; **378**: 693–95.
- 89 Agarwal SD, Landon BE. Patterns in outpatient benzodiazepine prescribing in the United States. *JAMA Network Open* 2019; **2**: e187399.
- 90 Watson GL, Arcona AP, Antonuccio DO. The ADHD drug abuse crisis on American college campuses. *Ethical Hum Psychol Psychiatry* 2015; **17**: 5–21.

- 91 Schwartz LM, Woloshin S. Medical marketing in the United States, 1997–2016. *JAMA* 2019; **321**: 80–96.
- 92 Hadland SE, Cerdá M, Li Y, Krieger MS, Marshall BDL. Association of pharmaceutical industry marketing of opioid products to physicians with subsequent opioid prescribing. *JAMA Intern Med* 2018; **178**: 861–63.
- 93 Nguyen TD, Bradford WD, Simon KI. Pharmaceutical payments to physicians may increase prescribing for opioids. *Addiction* 2019; **114**: 1051–59.
- 94 Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *Am J Public Health* 2009; **99**: 221–27.
- 95 Hadland SE, Rivera-Aguirre A, Marshall BDL, et al. Association of pharmaceutical industry marketing of opioid products with mortality from opioid-related overdoses. *JAMA Network Open* 2019; **2**: e186007.
- 96 Taitsman JK, VanLandingham A, Grimm CA. Commercial influences on electronic health records and adverse effects on clinical decision-making. *JAMA Intern Med* 2020; **180**: 925–26.
- 97 US Department of Justice Office of Public Affairs. Electronic health records vendor to pay \$145 million to resolve criminal and civil investigations. 2020. <https://www.justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0> (accessed Dec 29, 2021).
- 98 Ventola CL. Direct-to-consumer pharmaceutical advertising: Therapeutic or toxic? *P&T* 2011; **36**: 669–84.
- 99 Office of Budget. HHS FY2016 budget in brief. 2015. <https://www.hhs.gov/about/budget/fy2016/budget-in-brief/index.html> (accessed Dec 13, 2020).
- 100 Garcia A. Super Bowl drug ad spurs big backlash. 2016. <https://money.cnn.com/2016/02/11/news/super-bowl-painkiller-constipation-ad/index.html> (accessed Dec 12, 2020).
- 101 Horwitz S, Higham S, Bennett D, et al. Inside the opioid industry's marketing machine. 2019. <https://www.washingtonpost.com/graphics/2019/investigations/opioid-marketing/> (accessed Dec 12, 2020).
- 102 Shapiro BT. Positive spillovers and free riding in advertising of prescription pharmaceuticals: the case of antidepressants. *J Polit Econ* 2018; **126**: 381–437.
- 103 Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. *JAMA Intern Med* 2014; **174**: 1668–73.
- 104 Shover CL, Davis CS, Gordon SC, Humphreys K. Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proc Natl Acad Sci USA* 2019; **116**: 12624–26.
- 105 Humphreys K, Saitz R. Should physicians recommend replacing opioids with cannabis? *JAMA* 2019; **321**: 639–40.
- 106 Shover CL, Vest NA, Chen D, et al. Association of state policies allowing medical cannabis for opioid use disorder with dispensary marketing for this indication. *JAMA Network Open* 2020; **3**: e2010001.
- 107 Fain KM, Alexander GC. Mind the gap: understanding the effects of pharmaceutical direct-to-consumer advertising. *Med Care* 2014; **52**: 291–93.
- 108 Tufts University Office of the President. Important announcement. 2019. <https://president.tufts.edu/news/2019/12/05/important-announcement/> (accessed Dec 29, 2021).
- 109 Yurko RJ, Salvesen DW, Remz SF. Report and recommendations concerning the relationship of the Sackler family and Purdue Pharma with Tufts University, 2019. <https://president.tufts.edu/wp-content/uploads/Final-Report-Tufts-Sackler-and-Purdue-Pharma-December-2019.pdf> (accessed Dec 29, 2021).
- 110 Persaud N. Questionable content of an industry-supported medical school lecture series: a case study. *J Med Ethics* 2014; **40**: 414–18.
- 111 Larkin I, Ang D, Steinhart J, et al. Association between academic medical center pharmaceutical detailing policies and physician prescribing. *JAMA* 2017; **317**: 1785–95.
- 112 Eisenberg MD, Stone EM, Pittell H, McGinty EE. The impact of academic medical center policies restricting direct-to-physician marketing on opioid prescribing. *Health Aff* 2020; **39**: 1002–10.
- 113 Gregory A. Scientists quit back pain campaign over links to opioid giant Grünenthal. 2020. <https://www.thetimes.co.uk/article/scientists-quit-back-pain-campaign-over-links-to-opioid-giant-gruenenthal-txtclkdvd> (accessed Dec 14, 2020).
- 114 Daly R. More states explore laws on gifts to physicians. 2010; https://psychnews.psychiatryonline.org/doi/full/10.1176/pn.45.6.psychnews_45_6_014 (accessed Dec 29, 2021).
- 115 Sullivan T. Massachusetts Pharmaceutical and Device Code of Conduct: companies won't have to report payments covered by Federal Sunshine Act; gift ban still in place. 2018. <https://www.policymed.com/2014/06/massachusetts-pharmaceutical-and-device-code-of-conduct-companies-wont-have-to-report-payments-covered-by-federal-sunshin.html> (accessed Dec 29, 2021).
- 116 Dieners P, Kemmner C. Germany: Pharmaceutical Advertising Laws and Regulations 2021. 2021. <https://iclg.com/practice-areas/pharmaceutical-advertising-laws-and-regulations/germany> (accessed Dec 29, 2021).
- 117 Government of Canada. Restricting the marketing and advertising of opioids. 2019. <https://www.canada.ca/en/health-canada/services/substance-use/problematic-prescription-drug-use/opioids/responding-canada-opioid-crisis/advertising-opioid-medications.html> (accessed Dec 13, 2020).
- 118 Shaheen J. Shaheen re-introduces bill to stop big pharma from exploiting advertising tax loophole. 2021. <https://www.shaheen.senate.gov/news/press/shaheen-reintroduces-bill-to-stop-big-pharma-from-exploiting-advertising-tax-loophole> (accessed Dec 29, 2021).
- 119 Biden Harris Presidential Campaign Platform. Healthcare. 2020. <https://joebiden.com/healthcare/> (accessed Dec 12, 2020).
- 120 Council of Medical Specialty Societies. Code for interactions with companies. 2015. <https://cmss.org/wp-content/uploads/2016/02/CMSS-Code-for-Interactions-with-Companies-Approved-Revised-Version-4.13.15-with-Annotations.pdf> (accessed Dec 29, 2021).
- 121 Accreditation Council for Continuing Medical Education. Standards for commercial support: standards to ensure the independence of CME activities. 2021. <https://www.accme.org/publications/accme-standards-for-commercial-support> (accessed Dec 29, 2021).
- 122 Pillar C. Is FDA's revolving door open too wide? *Science* 2018; **361**: 21.
- 123 Sarasohn J. Tauzin to head drug trade group. 2004. <https://www.washingtonpost.com/archive/politics/2004/12/16/tauzin-to-head-drug-trade-group/71c7aad-c1e95-4f68-abbe-b09d5464c207/> (accessed Dec 14, 2020).
- 124 Higham S, Bernstein L. The drug industry's triumph over the DEA. 2017. <https://www.washingtonpost.com/graphics/2017/investigations/dea-drug-industry-congress/> (accessed Dec 29, 2021).
- 125 Keefe PR. The Sackler family's plan to keep its billions. 2020. <https://www.newyorker.com/news/news-desk/the-sackler-family-s-plan-to-keep-its-billions> (accessed Dec 12, 2020).
- 126 Bien J, Prasad V. Future jobs of FDA's haematology-oncology reviewers. *BMJ* 2016; **354**: i5055.
- 127 Rennie D. When evidence isn't: trials, drug companies and the FDA. *J Law Policy* 2008; **15**: 2.
- 128 US Food and Drug Administration. Postmarketing requirements and commitments: reports. 2020. <https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-reports> (accessed Dec 29, 2021).
- 129 Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing surveillance—lack of vigilance, lack of trust. *JAMA* 2004; **292**: 2647–50.
- 130 Spelsberg A, Prugger C, Doshi P, et al. Contribution of industry funded post-marketing studies to drug safety: survey of notifications submitted to regulatory agencies. *BMJ* 2017; **356**: j337.
- 131 Heyward J, Olson L, Sharfstein JM, Stuart EA, Lurie P, Alexander GC. Evaluation of the extended-release/long-acting opioid prescribing risk evaluation and mitigation strategy program by the US Food and Drug Administration: a review. *JAMA Intern Med* 2020; **180**: 301–09.
- 132 Guadamuz JS, Qato DM, Alexander GC. Use of risk evaluation and mitigation strategies by the US Food and Drug Administration, 2008–2019. *JAMA* 2020; **324**: 299–301.
- 133 Zisblatt L, Hayes SM, Lazure P, Hardesty I, White JL, Alford DP. Safe and competent opioid prescribing education: increasing dissemination with a train-the-trainer program. *Subst Abuse* 2017; **38**: 168–76.
- 134 Traynor K. Advisers say FDA's opioid REMS program needs improvement. *Am J Health Syst Pharm* 2016; **73**: 940–42.
- 135 US Food and Drug Administration. Transcript for the May 4, 2016 joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). 2016. <https://www.fda.gov/media/100451/download> (accessed Dec 29, 2021).

- 136 Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA risk evaluation and mitigation strategy for transdermal immediate-release fentanyl products. *JAMA* 2019; **321**: 676–85.
- 137 Angell M. FDA: this agency can be dangerous. 2010. <https://www.nybooks.com/articles/2010/09/30/agency-can-be-dangerous/> (accessed Dec 29, 2021).
- 138 US Food and Drug Administration. Prescription Drug User Fee Act; public meeting; request for comments. 2016. <https://www.federalregister.gov/documents/2016/07/19/2016-16916/prescription-drug-user-fee-act-public-meeting-request-for-comments> (accessed Dec 29, 2021).
- 139 US General Accounting Office. OxyContin Abuse and Diversion and Efforts to Address the Problem. Washington, DC: US General Accounting Office, 2003.
- 140 Baker DW. History of the Joint Commission's pain standards: lessons for today's prescription opioid epidemic. *JAMA* 2017; **317**: 1117–18.
- 141 WHO. Retraction of WHO guidance on opioid use. *Bull World Health Organ* 2020; **98**: 3.
- 142 de Shazo RD, Johnson M, Eriator I, Rodenmeyer K. Backstories on the US opioid epidemic. Good intentions gone bad, an industry gone rogue, and watch dogs gone to sleep. *Am J Med* 2018; **131**: 595–601.
- 143 Meier B. In guilty plea, OxyContin maker to pay \$600 million. 2007. <https://www.nytimes.com/2007/05/10/business/11drug-web.html> (accessed Dec 14, 2020).
- 144 Zaring DT. Against being against the revolving door. *Univ Ill Law Rev* 2013; **2013**: 507–50.
- 145 Baldwin TS. 2057 (115th). Pharmaceutical Regulation Conflict of Interest Act. 2017. <https://www.congress.gov/bills/115/congress/115th-congress/senate-bill/2057/text?r=81> (accessed Dec 29, 2021).
- 146 National Conference of State Legislatures. Revolving door prohibitions. 2020. <https://www.ncsl.org/research/ethics/50-state-table-revolving-door-prohibitions.aspx> (accessed Dec 29, 2021).
- 147 Maskell J. Post-employment, “revolving door,” laws for federal personnel. Washington, DC: Congressional Research Service, 2014.
- 148 Citizens United v Federal Election Commission. 08-205. US Supreme Court: Washington, DC, USA: Jan 21, 2010.
- 149 Mulvihill G, Whyte LE, Weider B. Drugmakers fought state opioid limits amid crisis. 2016. <https://www.heraldnews.com/news/20160918/drugmakers-fought-state-opioid-limits-amid-crisis> (accessed Dec 14, 2020).
- 150 Crowe K. Following the money between patient groups and big pharma. 2018. <https://www.cbc.ca/news/health/second-opinion-patient-advocacy-pharmaceutical-industry-funding-drug-prices-1.4539271> (accessed Dec 12, 2020).
- 151 Ornstein C, Weber T. American Pain Foundation shuts down as senators launch investigation of prescription narcotics. 2012. <https://www.propublica.org/article/senate-panel-investigates-drug-company-ties-to-pain-groups> (accessed Dec 14, 2020).
- 152 Ornstein C, Weber T. The champion of painkillers. 2011. <https://www.propublica.org/article/the-champion-of-painkillers> (accessed Dec 14, 2020).
- 153 American Pain Foundation. 2010 annual report: inspiring hope, empowering action, improving lives. 2010. <https://www.documentcloud.org/documents/277604-afp-2010-annual-report> (accessed Dec 30, 2020).
- 154 Charity Commission for England and Wales. Pain UK: regulatory compliance case conclusions. 2019. <https://www.gov.uk/government/publications/pain-uk-regulatory-compliance-case-conclusions/pain-uk-regulatory-compliance-case-conclusions> (accessed Dec 30, 2021).
- 155 McCoy MS, Carniol M, Chockley K, Urwin JW, Emanuel EJ, Schmidt H. Conflicts of interest for patient-advocacy organizations. *N Engl J Med* 2017; **376**: 880–85.
- 156 Rose SL, Highland J, Karafa MT, Joffe S. Patient advocacy organizations, industry funding, and conflicts of interest. *JAMA Intern Med* 2017; **177**: 344–50.
- 157 Ozieranski P, Csanádi M, Rickard E, Mulinari S. Under-reported relationship: a comparative study of pharmaceutical industry and patient organisation payment disclosures in the UK (2012–2016). *BMJ Open* 2020; **10**: e037351.
- 158 US Federal Trade Commission. FTC brings first case challenging fake paid reviews on an independent retail website. 2019. <https://www.ftc.gov/news-events/press-releases/2019/02/ftc-brings-first-case-challenging-fake-paid-reviews-independent> (accessed Nov 10, 2020).
- 159 Scott MJ. Ripping up the astroturf: regulating deceptive corporate advertising methods. *Iowa Law Rev* 2019; **105**: 431–61.
- 160 Humphreys K, Caulkins JP, Felbab-Brown V. What the US and Canada can learn from other countries to combat the opioid crisis. Washington, DC: Brookings Institute, 2020.
- 161 Kahneman D. *Thinking, Fast and Slow*. New York, NY: Farrar, Strous and Giroux, 2011.
- 162 Weick KE. Small wins: redefining the scale of social problems. *Am Psychol* 1984; **39**: 40–49.
- 163 US Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, MD, on agency's approval of Dsuvia and the FDA's future consideration of new opioids. 2018. <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-approval-dsuvia-and-fdas-future-consideration> (accessed Dec 30, 2021).
- 164 Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ* 2006; **174**: 1589–94.
- 165 Krebs EE, Gravelly A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. *JAMA* 2018; **319**: 872–82.
- 166 Humphreys K, Weisner C. Use of exclusion criteria in selecting research subjects and its effect on the generalizability of alcohol treatment outcome studies. *Am J Psychiatry* 2000; **157**: 588–94.
- 167 Lurie P, Sharfstein JM. Product approval and public health at the US Food and Drug Administration. *JAMA* 2021; **326**: 2469–70.
- 168 Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? *Stat Med* 1984; **3**: 409–22.
- 169 Institute of Medicine Committee on Advancing Pain Research, Care, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: National Academies Press, 2011.
- 170 Hoy D, March L, Brooks P, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; **73**: 968–74.
- 171 Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**: 1204–22.
- 172 Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018; **67**: 1001–06.
- 173 Buchbinder R, Underwood M, Hartvigsen J, Maher CG. The *Lancet* Series call to action to reduce low value care for low back pain: an update. *Pain* 2020; **161** (suppl 1): S57–64.
- 174 Dieleman JL, Cao J, Chapin A, et al. US health care spending by payer and health condition, 1996–2016. *JAMA* 2020; **323**: 863–84.
- 175 US National Institutes of Health. Estimates of funding for various research, condition, and disease categories (RCDC). 2020. <https://report.nih.gov/funding/categorical-spending/> (accessed Dec 13, 2020).
- 176 Interagency Pain Research Coordinating Committee. National pain strategy overview. 2021. <https://www.iprcc.nih.gov/national-pain-strategy-overview> (accessed June 12, 2021).
- 177 Humphreys K. Reconciling the present and the future in opioid prescription policy: an ethical dilemma. *Pain Med* 2018; **19**: 1514–15.
- 178 Webster F, Rice K, Katz J, Bhattacharyya O, Dale C, Upshur R. An ethnography of chronic pain management in primary care: the social organization of physicians' work in the midst of the opioid crisis. *PLoS One* 2019; **14**: e0215148.
- 179 Green CA, McCarty D, Mertens J, et al. A qualitative study of the adoption of buprenorphine for opioid addiction treatment. *J Subst Abuse Treat* 2014; **46**: 390–401.
- 180 Sinha CB, Bakshi N, Ross D, et al. Management of chronic pain in adults living with sickle cell disease in the era of the opioid epidemic: a qualitative study. *JAMA Network Open* 2019; **2**: e194410.

- 181 Al Achkar M, Revere D, Dennis B, et al. Exploring perceptions and experiences of patients who have chronic pain as state prescription opioid policies change: a qualitative study in Indiana. *BMJ Open* 2017; **7**: e015083.
- 182 Frank JW, Levy C, Matlock D, et al. Patients' perspectives on tapering of chronic opioid therapy: a qualitative study. *Pain Med* 2016; **17**: 1838–47.
- 183 Wertli MM, Reich O, Signorell A, Burgstaller JM, Steurer J, Held U. Changes over time in prescription practices of pain medications in Switzerland between 2006 and 2013: an analysis of insurance claims. *BMC Health Serv Res* 2017; **17**: 167.
- 184 Gomes T, Mamdani MM, Paterson JM, Dhalla IA, Juurlink DN. Trends in high-dose opioid prescribing in Canada. *Can Fam Physician* 2014; **60**: 826–32.
- 185 Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain* 2008; **9**: 883–91.
- 186 Institute for Safe Medication Practices Canada. Opioid stewardship. 2021. https://www.ismp-canada.org/opioid_stewardship/ (accessed July 21, 2021).
- 187 Mackey S, Kao MC. Managing twin crises in chronic pain and prescription opioids. *BMJ* 2019; **364**: 1917.
- 188 UK Medicines and Healthcare products Regulatory Agency. Opioids: risk of dependence and addiction. *Drug Safety Update* 2020; **14**: 2–4.
- 189 Levy N, Lord LJ, Lobo DN. UK recommendations on opioid stewardship. *BMJ* 2021; **372**: m4901.
- 190 Canadian Deprescribing Network. The Canadian Deprescribing Network is dedicated to raising awareness of medication safety, deprescribing and safer alternatives to risky medications. 2020. <https://www.deprescribingnetwork.ca> (accessed Oct 11, 2020).
- 191 US Department of Health and Human Services. HHS guide for clinicians on the appropriate dosage reduction or discontinuation of long-term opioid analgesics. 2019. https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf (accessed Dec 30, 2021).
- 192 The US Attorneys Office Southern District of California. "Pill Mill" doctor pleads guilty to opioid distribution, admits signing prescriptions for dead and jailed patients. 2020. <https://www.justice.gov/usao-sdca/pr/pill-mill-doctor-pleads-guilty-opioid-distribution-admits-signing-prescriptions-dead> (accessed Dec 30, 2021).
- 193 The US District Attorney's Office District of Connecticut. APRN who received kickbacks from Insys Therapeutics for prescribing fentanyl spray is sentenced. 2019. <https://www.justice.gov/usao-ct/pr/aprn-who-received-kickbacks-insys-therapeutics-prescribing-fentanyl-spray-sentenced> (accessed Dec 30, 2021).
- 194 Funk C, Kennedy B. Public confidence in scientists has remained stable for decades. 2020. <https://www.pewresearch.org/fact-tank/2020/08/27/public-confidence-in-scientists-has-remained-stable-for-decades/> (accessed Dec 14, 2020).
- 195 Davis CS, Lieberman AJ, Hernandez-Delgado H, Suba C. Laws limiting the prescribing or dispensing of opioids for acute pain in the United States: a national systematic legal review. *Drug Alcohol Depend* 2019; **194**: 166–72.
- 196 Davis CS, Piper BJ, Gertner AK, Rotter JS. Opioid prescribing laws are not associated with short-term declines in prescription opioid distribution. *Pain Med* 2020; **21**: 532–37.
- 197 Funk C, Kennedy B, Johnson C. Trust in medical scientists has grown in US, but mainly among Democrats. 2020. <https://www.pewresearch.org/science/2020/05/21/trust-in-medical-scientists-has-grown-in-u-s-but-mainly-among-democrats/> (accessed Dec 30, 2021).
- 198 US National Academy of Medicine. First, Do No Harm: Marshaling Clinician Leadership to Counter the Opioid Epidemic. Washington, DC: National Academy of Medicine, 2017.
- 199 Gellad WF, Good CB, Shulkin DJ. Addressing the opioid epidemic in the United States: lessons from the Department of Veterans Affairs. *JAMA Intern Med* 2017; **177**: 611–12.
- 200 Frank JW, Carey E, Nolan C, et al. Increased nonopioid chronic pain treatment in the Veterans Health Administration, 2010–2016. *Pain Med* 2019; **20**: 869–77.
- 201 Hadlandsmayth K, Mosher H, Vander Weg MW, Lund BC. Decline in prescription opioids attributable to decreases in long-term use: a retrospective study in the Veterans Health Administration 2010–2016. *J Gen Intern Med* 2018; **33**: 818–24.
- 202 US Centers for Disease Control and Prevention. Prescription drug monitoring programs (PDMPs). 2020. <https://www.cdc.gov/drugoverdose/pdmp/index.html> (accessed Dec 13, 2020).
- 203 Furlan AD, MacDougall P, Pellerin D, et al. Overview of four prescription monitoring/review programs in Canada. *Pain Res Manag* 2014; **19**: 102–06.
- 204 McDonald DC, Carlson KE. Estimating the prevalence of opioid diversion by "doctor shoppers" in the United States. *PLoS One* 2013; **8**: e69241.
- 205 Pardo B. Do more robust prescription drug monitoring programs reduce prescription opioid overdose? *Addiction* 2017; **112**: 1773–83.
- 206 Buchmueller TC, Carey C. The effect of prescription drug monitoring programs on opioid utilization in Medicare. *Am Econ J Econ Policy* 2018; **10**: 77–112.
- 207 Chiu AS, Jean RA, Hoag JR, Freedman-Weiss M, Healy JM, Pei KY. Association of lowering default pill counts in electronic medical record systems with postoperative opioid prescribing. *JAMA Surg* 2018; **153**: 1012–19.
- 208 Delgado MK, Shofer FS, Patel MS, et al. Association between electronic medical record implementation of default opioid prescription quantities and prescribing behavior in two emergency departments. *J Gen Intern Med* 2018; **33**: 409–11.
- 209 Babor TF, Caulkins J, Fischer B, et al. Drug Policy and the Public Good: a summary of the second edition. *Addiction* 2019; **114**: 1941–50.
- 210 Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. *Drug Policy and the Public Good: evidence for effective interventions.* *Lancet* 2012; **379**: 71–83.
- 211 Fairley M, Humphreys K, Joyce VR, et al. Cost-effectiveness of treatments for opioid use disorder. *JAMA Psychiatry* 2021; **78**: 767–77.
- 212 Santo T Jr, Clark B, Hickman M, et al. Association of opioid agonist treatment with all-cause mortality and specific causes of death among people with opioid dependence: a systematic review and meta-analysis. *JAMA Psychiatry* 2021; **78**: 979–93.
- 213 Babor T, Caulkins JP, Fischer B, et al. *Drug Policy and the Public Good*, 2nd edn. Oxford: Oxford University Press, 2018.
- 214 Day E, Mitcheson L. Psychosocial interventions in opiate substitution treatment services: does the evidence provide a case for optimism or nihilism? *Addiction* 2017; **112**: 1329–36.
- 215 Best D, Harris J, Gossop M, et al. Use of non-prescribed methadone and other illicit drugs during methadone maintenance treatment. *Drug Alcohol Rev* 2000; **19**: 9–16.
- 216 Hall WD, Strang J. Alcohol problems need more attention in patients receiving long-term opioid substitution therapy. *Lancet Psychiatry* 2017; **4**: 265–66.
- 217 Tjagvad C, Skurtveit S, Linnert K, Andersen LV, Christoffersen DJ, Clausen T. Methadone-related overdose deaths in a liberal opioid maintenance treatment programme. *Eur Addict Res* 2016; **22**: 249–58.
- 218 Strang J, Hall W, Hickman M, Bird SM. Impact of supervision of methadone consumption on deaths related to methadone overdose (1993–2008): analyses using OD4 index in England and Scotland. *BMJ* 2010; **341**: c4851.
- 219 Best D, Day E, Morgan B, Oza T, Copello A, Gossop M. What treatment means in practice: an analysis of the delivery of evidence-based interventions in criminal justice drug treatment services in Birmingham, England. *Addict Res Theory* 2009; **17**: 678–87.
- 220 National Center for Injury Prevention and Control. Integrating & expanding prescription drug monitoring program data: lessons from nine states. 2017. <https://stacks.cdc.gov/view/cdc/45241> (accessed Dec 30, 2021).
- 221 McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA* 1993; **269**: 1953–59.
- 222 Carroll KM, Weiss RD. The role of behavioral interventions in buprenorphine maintenance treatment: a review. *Am J Psychiatry* 2017; **174**: 738–47.
- 223 Hunter SB, Dopp AR, Ober AJ, Uscher-Pines L. Clinician perspectives on methadone service delivery and the use of telemedicine during the COVID-19 pandemic: a qualitative study. *J Subst Abuse Treat* 2021; **124**: 108288.
- 224 Joseph G, Torres-Lockhart K, Stein MR, Mund PA, Nahvi S. Reimagining patient-centered care in opioid treatment programs: lessons from the Bronx during COVID-19. *J Subst Abuse Treat* 2021; **122**: 108219.

- 225 Ivsins A, Boyd J, Beletsky L, McNeil R. Tackling the overdose crisis: the role of safe supply. *Int J Drug Policy* 2020; **80**: 102769.
- 226 Lembke A. Unsafe supply: why making controlled prescription drugs available for unsupervised use will not target the syndemic of HIV, Hepatitis C, overdose, and COVID-19. *J Stud Alcohol Drugs* 2020; **81**: 564–65.
- 227 Brooks L. Scottish government urged to declare drug addiction emergency. 2019. <http://www.theguardian.com/society/2019/nov/01/scottish-government-urged-to-declare-drug-addiction-emergency> (accessed Oct 10, 2020).
- 228 Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *BMJ* 2017; **356**: j760.
- 229 Shover CL, Falasinnu TO, Dwyer CL, et al. Steep increases in fentanyl-related mortality west of the Mississippi River: recent evidence from county and state surveillance. *Drug Alcohol Depend* 2020; **216**: 108314.
- 230 Humphreys K, Malenka RC, Knutson B, MacCoun RJ. Brains, environments, and policy responses to addiction. *Science* 2017; **356**: 1237–38.
- 231 Jalal H, Buchanich JM, Roberts MS, Balmert LC, Zhang K, Burke DS. Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016. *Science* 2018; **361**: eaau1184.
- 232 Yang LH, Wong LY, Grivel MM, Hasin DS. Stigma and substance use disorders: an international phenomenon. *Curr Opin Psychiatry* 2017; **30**: 378–88.
- 233 Botticelli MP, Koh HK. Changing the language of addiction. *JAMA* 2016; **316**: 1361–62.
- 234 Kelly JF, Greene MC, Abry A. A US national randomized study to guide how best to reduce stigma when describing drug-related impairment in practice and policy. *Addiction* 2021; **116**: 1757–67.
- 235 Henderson S. Opioid crisis vs the war on drugs: a double standard? 2017. <https://wdet.org/posts/2017/07/12/85483-opioid-crisis-vs-the-war-on-drugs-a-double-standard/> (accessed Dec 30, 2021).
- 236 Meara E, Frank RG. Spending on substance abuse treatment: how much is enough? *Addiction* 2005; **100**: 1240–48.
- 237 D'Aunno T. Analysis of data from 346 clinics in the National Drug Abuse Treatment System Survey study. New York, NY: New York University School of Management, 2021.
- 238 McLellan AT, Carise D, Kleber HD. Can the national addiction treatment infrastructure support the public's demand for quality care? *J Subst Abuse Treat* 2003; **25**: 117–21.
- 239 Hoffman KA, Ford JH, Tillotson CJ, Choi D, McCarty D. Days to treatment and early retention among patients in treatment for alcohol and drug disorders. *Addict Behav* 2011; **36**: 643–47.
- 240 Andrews CM, Shin HC, Marsh JC, Cao D. Client and program characteristics associated with wait time to substance abuse treatment entry. *Am J Drug Alcohol Abuse* 2013; **39**: 61–68.
- 241 WHO. The top 10 causes of death. 2018. <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death> (accessed Dec 12, 2020).
- 242 Polydorou S, Gunderson EW, Levin FR. Training physicians to treat substance use disorders. *Curr Psychiatry Rep* 2008; **10**: 399–404.
- 243 Humphreys K, McGovern M, McLellan AT. Integrated care for substance use disorder. In: Miller SC, Fiellin DA, Rosenthal RN, eds. *The ASAM Principles of Addiction Medicine*. Washington, DC: American Society of Addiction Medicine, 2018: 423–32.
- 244 Medicaid Innovation Accelerator Program. Collaborative models for medication-assisted treatment: key elements of Vermont's hub-and-spoke system. 2019. <https://www.medicaid.gov/state-resource-center/innovation-accelerator-program/iap-downloads/reducing-substance-use-disorders/mat-key-elements-vt.pdf> (accessed Dec 30, 2021).
- 245 Rawson RA. Vermont Hub-and-spoke model of care for opioid use disorders: an evaluation. Burlington, VT: Vermont Center on Behavior and Health, 2017.
- 246 Brooklyn JR, Sigmon SC. Vermont hub-and-spoke model of care for opioid use disorder: development, implementation, and impact. *J Addict Med* 2017; **11**: 286–92.
- 247 Darfler K, Sandoval J, Pearce Antonini V, Urada D. Preliminary results of the evaluation of the California hub and spoke program. *J Subst Abuse Treat* 2020; **108**: 26–32.
- 248 US Substance Abuse and Mental Health Services Administration. TI-18-009 Individual Grant Awards. 2019. <https://www.samhsa.gov/grants/awards/2019/ti-18-009> (accessed Nov 2, 2020).
- 249 Stoffelmayr BE, Benishek LA, Humphreys K, Lee JA, Mavis BE. Substance abuse prognosis with an additional psychiatric diagnosis: understanding the relationship. *J Psychoactive Drugs* 1989; **21**: 145–52.
- 250 Douglas KR, Chan G, Gelernter J, et al. Adverse childhood events as risk factors for substance dependence: partial mediation by mood and anxiety disorders. *Addict Behav* 2010; **35**: 7–13.
- 251 Williams AR, Nunes EV, Bisaga A, Levin FR, Olfson M. Development of a cascade of care for responding to the opioid epidemic. *Am J Drug Alcohol Abuse* 2019; **45**: 1–10.
- 252 Yedinak JL, Goedel WC, Paull K, et al. Defining a recovery-oriented cascade of care for opioid use disorder: a community-driven, statewide cross-sectional assessment. *PLoS Med* 2019; **16**: e1002963.
- 253 American Society of Addiction Medicine. What are the ASAM levels of care? 2015. <https://www.asamcontinuum.org/knowledgebase/what-are-the-asam-levels-of-care/> (accessed Dec 13, 2020).
- 254 US Department of Health and Human Services Office of the Surgeon General. Facing addiction in America: the Surgeon General's spotlight on opioids. Washington, DC: US Department of Health and Human Services, 2018.
- 255 Mitchell TH. *The Big Fix: Hope After Heroin*. New York, NY: Seal Press, 2016.
- 256 Sixx N. Take it from a recovering addict, a lot more could be done to end the opioid crisis. 2017. <https://www.latimes.com/opinion/op-ed/la-oe-sixx-opioid-crisis-20170929-story.html> (accessed Nov 6, 2020).
- 257 Hampton R. *American Fix: Inside the Opioid Addiction Crisis—and How to End It*. New York, NY: All Points Books, 2018.
- 258 Dorsey T. *The Rooms Project: Tarah*. 2017. <http://www.theroomsproject.org/tarah/> (accessed Nov 2, 2020).
- 259 Woods JS, Joseph H. Reducing stigma through education to enhance medication-assisted recovery. *J Addict Dis* 2012; **31**: 226–35.
- 260 Humphreys K, Wing S, McCarty D, et al. Self-help organizations for alcohol and drug problems: toward evidence-based practice and policy. *J Subst Abuse Treat* 2004; **26**: 151–65.
- 261 Kelly JF, White WL. *Addiction Recovery Management: Theory, Research and Practice*. New York, NY: Humana Press, 2011.
- 262 Humphreys K, Piot P. Scientific evidence alone is not sufficient basis for health policy. *BMJ* 2012; **344**: e1316.
- 263 Rosenstein RJ. Fight drug abuse, don't subsidize it. 2018. <https://www.nytimes.com/2018/08/27/opinion/opioids-heroin-injection-sites.html> (accessed Dec 14, 2020).
- 264 Pardo B, Caulkins JP, Kilmer B. *Assessing the evidence on supervised drug consumption sites*. Santa Monica, CA: RAND Corporation, 2018.
- 265 Witkiewitz K, Kirouac M, Roos CR, et al. Abstinence and low risk drinking during treatment: association with psychosocial functioning, alcohol use, and alcohol problems 3 years following treatment. *Psychol Addict Behav* 2018; **32**: 639–46.
- 266 Harvey LM, Fan W, Cano MA, et al. Psychosocial intervention utilization and substance abuse treatment outcomes in a multisite sample of individuals who use opioids. *J Subst Abuse Treat* 2020; **112**: 68–75.
- 267 Weiss RD, Griffin ML, Marcovitz DE, et al. Correlates of opioid abstinence in a 42-month posttreatment naturalistic follow-up study of prescription opioid dependence. *J Clin Psychiatry* 2019; **80**: 18m12292.
- 268 Monico LB, Gryczynski J, Mitchell SG, Schwartz RP, O'Grady KE, Jaffe JH. Buprenorphine treatment and 12-step meeting attendance: conflicts, compatibilities, and patient outcomes. *J Subst Abuse Treat* 2015; **57**: 89–95.
- 269 Abraham AJ, Andrews CM, Grogan CM, et al. The Affordable Care Act transformation of substance use disorder treatment. *Am J Public Health* 2017; **107**: 31–32.
- 270 Andrews CM, Grogan CM, Smith BT, et al. Medicaid benefits for addiction treatment expanded after implementation of the Affordable Care Act. *Health Aff* 2018; **37**: 1216–22.

- 271 Humphreys K, Frank RG. The Affordable Care Act will revolutionize care for substance use disorders in the United States. *Addiction* 2014; **109**: 1957–58.
- 272 Andrews CM, Humphreys K. Investing in Medicaid to end the opioid epidemic. *Psychiatr Serv* 2019; **70**: 537.
- 273 Humphreys K. How Medicaid can strengthen the national response to the opioid epidemic. *Am J Public Health* 2018; **108**: 589–90.
- 274 Sharp A, Jones A, Sherwood J, Kutsa O, Honermann B, Millett G. Impact of Medicaid expansion on access to opioid analgesic medications and medication-assisted treatment. *Am J Public Health* 2018; **108**: 642–48.
- 275 Saloner B, Levin J, Chang H-Y, et al. Changes in buprenorphine-naloxone and opioid pain reliever prescriptions after the Affordable Care Act Medicaid expansion. *JAMA Netw Open* 2018; **1**: e181588.
- 276 Kravitz-Wirtz N, Davis CS, Ponicki WR, et al. Association of Medicaid expansion with opioid overdose mortality in the United States. *JAMA Netw Open* 2020; **3**: e1919066.
- 277 Grogan CM, Andrews C, Abraham A, et al. Survey highlights differences in Medicaid coverage for substance use treatment and opioid use disorder medications. *Health Aff* 2016; **35**: 2289–96.
- 278 US Centers for Medicare and Medicaid Services. Medicare coverage of substance abuse services. 2016. <https://www.cms.gov/outreach-and-education/medicare-learning-network-mln/mlnmattersarticles/downloads/se1604.pdf> (accessed Dec 30, 2021).
- 279 US Department of Health and Human Services. Patient Protection and Affordable Care Act; HHS notice of benefit and payment parameters for 2019. 2018. <https://www.federalregister.gov/documents/2018/04/17/2018-07355/patient-protection-and-affordable-care-act-hhs-notice-of-benefit-and-payment-parameters-for-2019> (accessed Dec 30, 2021).
- 280 Tran Smith B, Seaton K, Andrews C, et al. Benefit requirements for substance use disorder treatment in state health insurance exchanges. *Am J Drug Alcohol Abuse* 2018; **44**: 426–30.
- 281 New York State Office of the Attorney General. AG Schneiderman announces settlement with Emblem Health for wrongly denying mental health and substance abuse treatment for thousands of New York Members. 2014. <https://ag.ny.gov/press-release/2014/ag-schneiderman-announces-settlement-emblem-health-wrongly-denying-mental-health> (accessed Dec 30, 2021).
- 282 Beetham T, Saloner B, Gaye M, Wakeman SE, Frank RG, Barnett ML. Therapies offered at residential addiction treatment programs in the United States. *JAMA* 2020; **324**: 804–06.
- 283 Harris AHS, Weisner CM, Chalk M, Capoccia V, Chen C, Thomas CP. Specifying and pilot testing quality measures for the American Society of Addiction Medicine's standards of care. *J Addict Med* 2016; **10**: 148–55.
- 284 Hoffman KA, Green CA, Ford JH 2nd, Wisdom JP, Gustafson DH, McCarty D. Improving quality of care in substance abuse treatment using five key process improvement principles. *J Behav Health Serv Res* 2012; **39**: 234–44.
- 285 Ayu AP, Schellekens AFA, Iskandar S, Pinxten L, De Jong CA. Effectiveness and organization of addiction medicine training across the globe. *Eur Addict Res* 2015; **21**: 223–39.
- 286 Koh HK, Kerlikowske RG, Botticelli MP. A smarter war on drugs. *JAMA* 2018; **320**: 2301–02.
- 287 Babor T. *Alcohol: No Ordinary Commodity*, 2nd edn. Oxford: Oxford Medical Publications, 2003.
- 288 McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 2000; **284**: 1689–95.
- 289 Compton WM, Dawson D, Duffy SQ, Grant BF. The effect of inmate populations on estimates of DSM-IV alcohol and drug use disorders in the United States. *Am J Psychiatry* 2010; **167**: 473–74.
- 290 Messina N, Grella CE, Cartier J, Torres S. A randomized experimental study of gender-responsive substance abuse treatment for women in prison. *J Subst Abuse Treat* 2010; **38**: 97–107.
- 291 McKenzie M, Nunn A, Zaller ND, Bazazi AR, Rich JD. Overcoming obstacles to implementing methadone maintenance therapy for prisoners: implications for policy and practice. *J Opioid Manag* 2009; **5**: 219–27.
- 292 Feucht TE, Keyser A. Reducing drug use in prisons: Pennsylvania's approach. 1999. <https://www.ojp.gov/sites/g/files/xyckuh241/files/archives/ncjrs/jr000241c.pdf> (accessed Dec 30, 2021).
- 293 Green TC, Clarke J, Brinkley-Rubinstein L, et al. Postincarceration fatal overdoses after implementing medications for addiction treatment in a statewide correctional system. *JAMA Psychiatry* 2018; **75**: 405–07.
- 294 Martin RA, Gresko SA, Brinkley-Rubinstein L, Stein LAR, Clarke JG. Post-release treatment uptake among participants of the Rhode Island Department of Corrections comprehensive medication assisted treatment program. *Prev Med* 2019; **128**: 105766.
- 295 Brinkley-Rubinstein L, Peterson M, Clarke J, et al. The benefits and implementation challenges of the first state-wide comprehensive medication for addictions program in a unified jail and prison setting. *Drug Alcohol Depend* 2019; **205**: 107514.
- 296 Logan MW, Link NW. Taking stock of drug courts: do they work? *Vict Offenders* 2019; **14**: 283–98.
- 297 Kilmer B, Caulkins J, DuPont RL, et al. Reducing substance use in criminal justice populations. In: Miller SC, Fiellin DA, Rosenthal RN, Saitz R, eds. *Principles of Addiction Medicine*, 6 edn. Washington, DC: American Society of Addiction Medicine, 2019: 1768–74.
- 298 Pfaff J. *Locked In: The True Causes of Mass Incarceration and How to Achieve Real Reform*. New York, NY: Basic Books, 2017.
- 299 Bird SM, McAuley A, Perry S, Hunter C. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006–10) versus after (2011–13) comparison. *Addiction* 2016; **111**: 883–91.
- 300 American Bar Association Criminal Justice Section. Collateral consequences of criminal convictions judicial bench book. 2018. <https://www.ojp.gov/pdffiles1/nij/grants/251583.pdf> (accessed Dec 30, 2021).
- 301 Haffajee RL, Faherty LJ, Zivin K. Pregnant women with substance use disorders—the harm associated with punitive approaches. *N Engl J Med* 2021; **384**: 2364–67.
- 302 Brown, Governor of California, et al v Plata et al. Number 563 US 2011. US Supreme Court: Washington, DC: May 23, 2011.
- 303 Charuvastra A, Stein J, Schwartzapfel B, et al. Hepatitis B vaccination practices in state and federal prisons. *Public Health Rep* 2001; **116**: 203–09.
- 304 Parmar MKB, Strang J, Choo L, Meade AM, Bird SM. Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths. *Addiction* 2017; **112**: 502–15.
- 305 Tonko PD. Tonko, Turner reintroduce bipartisan addiction treatment bill, 2019 <https://tonko.house.gov/news/documentsingle.aspx?DocumentID=816> (accessed Dec 30, 2021).
- 306 Bird M, Lofstrom M, Martin B, et al. The impact of Proposition 47 on crime and recidivism. San Francisco, CA: Public Policy Institute of California, 2018.
- 307 Kleiman MAR. *When Brute Force Fails: How to Have Less Crime and Less Punishment*. Princeton, NJ: Princeton University Press, 2010.
- 308 Anglin MD, Nosyk B, Jaffe A, Urada D, Evans E. Offender diversion into substance use disorder treatment: the economic impact of California's proposition 36. *Am J Public Health* 2013; **103**: 1096–102.
- 309 Bernard CL, Rao JJ, Robison KK, Brandeau ML. Health outcomes and cost-effectiveness of diversion programs for low-level drug offenders: a model-based analysis. *PLoS Med* 2020; **17**: e1003239.
- 310 US Substance Abuse and Mental Health Services Administration. Clinical guidance for treating pregnant and parenting women with opioid use disorder and their infants. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.
- 311 Nader MA, Czoty PW, Nader SH, Morgan D. Nonhuman primate models of social behavior and cocaine abuse. *Psychopharmacology (Berl)* 2012; **224**: 57–67.
- 312 Phillips KA, Bales KL, Capitanio JP, et al. Why primate models matter. *Am J Primatol* 2014; **76**: 801–27.
- 313 Case A, Deaton A. *Deaths of Despair and the Future of Capitalism*. Princeton, NJ: Princeton University Press, 2020.
- 314 Pickett K, Wilkinson R. *The Spirit Level: Why More Equal Societies Almost Always Do Better*. London: Bloomsbury, 2009.
- 315 Ruhm CJ. Deaths of despair or drug problems? 2018. <https://www.nber.org/papers/w24188> (accessed Dec 30, 2021).
- 316 Alpert A, Evans WN, Lieber EMJ, et al. Origins of the opioid crisis and its enduring impacts. 2019. <https://www.nber.org/papers/w26500> (accessed Dec 30, 2021).

- 317 Humphreys K, Gifford E. Religion, Spirituality, and the troublesome use of substances. In: Miller WR, Carroll KM, eds. *Rethinking Substance Abuse: What the Science Shows, and What We Should Do About It*. New York, NY: Guilford Press, 2006: 257–74.
- 318 Courtwright D. *The Age of Addiction: How Bad Habits Became Big Business*. Cambridge, MA: Harvard University Press, 2019.
- 319 Proctor RN. *Golden Holocaust: Origins of the Cigarette Catastrophe and the Case for Abolition*. Berkeley, CA: University of California Press, 2012.
- 320 UN Office on Drugs and Crime. *World drug report 2020*. 2020. <https://wdr.unodc.org/wdr2020/index.html> (accessed Jan 18, 2022).
- 321 Kilpatrick DG, Acierno R, Saunders B, Resnick HS, Best CL, Schnurr PP. Risk factors for adolescent substance abuse and dependence: data from a national sample. *J Consult Clin Psychol* 2000; **68**: 19–30.
- 322 Jones DJ, Lewis T, Litrownik A, et al. Linking childhood sexual abuse and early adolescent risk behavior: the intervening role of internalizing and externalizing problems. *J Abnorm Child Psychol* 2013; **41**: 139–50.
- 323 Esposito CL, Clum GA. Social support and problem-solving as moderators of the relationship between childhood abuse and suicidality: applications to a delinquent population. *J Trauma Stress* 2002; **15**: 137–46.
- 324 Teesson M, Newton NC, Slade T, et al. Combined prevention for substance use, depression, and anxiety in adolescence: a cluster-randomised controlled trial of a digital online intervention. *Lancet Digit Health* 2020; **2**: e74–84.
- 325 Fagan AA, Hawkins JD, Farrington DP, Catalano R. *Communities that Care: Building Community Engagement and Capacity to Prevent Youth Behavior Problems*. New York, NY: Oxford University Press, 2019.
- 326 Arnarsson A, Kristofersson GK, Bjarnason T. Adolescent alcohol and cannabis use in Iceland 1995–2015. *Drug Alcohol Rev* 2018; **37** (suppl 1): S49–57.
- 327 Jonsson G, Milkman H. Perspective: Iceland succeeds at preventing teenage substance use. In: Stephens M, El-Sholkamy MM, Moonesar IA, Awamleh R, eds. *Future Governments*. Bingley, UK: Emerald Publishing Limited, 2019: 315–24.
- 328 Kristjansson AL, Mann MJ, Sigfusson J, Thorisdottir IE, Allegrante JP, Sigfusdottir ID. Development and guiding principles of the Icelandic model for preventing adolescent substance use. *Health Promot Pract* 2020; **21**: 62–69.
- 329 Young E. How Iceland got teens to say no to drugs. 2017. <https://www.theatlantic.com/health/archive/2017/01/teens-drugs-iceland/513668/> (accessed Jan 19, 2017).
- 330 Raitasalo K, Kraus L, Bye EK, et al. Similar countries, similar factors? Studying the decline of heavy episodic drinking in adolescents in Finland, Norway and Sweden. *Addiction* 2021; **116**: 62–71.
- 331 Planet Youth. *Communities: countries introduced to the Icelandic model*. 2020. <https://planetyouth.org/get-involved/communities/> (accessed Nov 3, 2020).
- 332 Alcohol Public Policy Group. *Alcohol: No Ordinary Commodity—a summary of the second edition*. *Addiction* 2010; **105**: 769–79.
- 333 Barr A, Gibbs CR. Breaking the cycle? Intergenerational effects of an anti-poverty program in early childhood. 2019. <https://edworkingpapers.com/sites/default/files/ai19-141.pdf> (accessed Dec 30, 2021).
- 334 Social Programs that Work. *Evidence summary for the Nurse Family Partnership*. 2020. <https://evidencebasedprograms.org/document/nurse-family-partnership-nfp-evidence-summary/> (accessed Dec 30, 2021).
- 335 Schweinhart LJ. Benefits, costs, and explanation of the High/Scope Perry Preschool Program. 2003. <https://eric.ed.gov/?id=ED475597> (accessed Dec 30, 2021).
- 336 Barnett S, Belfield C, Montie J, et al. *Lifetime effects: the High/Scope Perry Preschool Study through age 40*. Ypsilanti, MI: High/Scope Press, 2005.
- 337 Campbell FA, Ramey CT, Pungello E, Sparling J, Miller-Johnson S. Early childhood education: young adult outcomes from the Abecedarian Project. *Appl Dev Sci* 2002; **6**: 42–57.
- 338 Canadian Institute for Health Information. *Opioid prescribing in Canada: how are practices changing?* Ottawa, ON: Canadian Institute for Health Information, 2019.
- 339 Howard R, Fry B, Gunaseelan V, et al. Association of opioid prescribing with opioid consumption after surgery in Michigan. *JAMA Surg* 2019; **154**: e184234.
- 340 Choose PT. In 2016 prescribed opioids resulted in 3·3 billion unused pills. <https://www.choosept.com/didyouknow/detail/in-2016-prescribed-opioids-resulted-in-3-3-billion> (accessed Dec 12, 2020).
- 341 Planet Ark Recycling Near You. *Unwanted and out-of-date medicines*. 2020. <https://recyclingnearyou.com.au/medicines/> (accessed Dec 13, 2020).
- 342 California Product Stewardship Council. *Products*. 2020. <https://www.calpsc.org/products> (accessed Dec 13, 2020).
- 343 Albert S, Brason FW 2nd, Sanford CK, Dasgupta N, Graham J, Lovette B. Project Lazarus: community-based overdose prevention in rural North Carolina. *Pain Med* 2011; **12** (suppl 2): S77–85.
- 344 Stewart H, Malinowski A, Ochs L, Jaramillo J, McCalk K 3rd, Sullivan M. Inside Maine's medicine cabinet: findings from the Drug Enforcement Administration's medication take-back events. *Am J Public Health* 2015; **105**: e65–71.
- 345 US Government Accountability Office. *Preventing Drug Abuse*. 2017. <https://www.gao.gov/assets/690/687719.pdf> (accessed Nov 8, 2020).
- 346 Stevens MP. Horizontal versus vertical infection prevention strategies. *Int J Infect Dis* 2014; **21**: 37.
- 347 Johnson K, Rigg KK, Hopkins Eyles C. Receiving addiction treatment in the US: do patient demographics, drug of choice, or substance use disorder severity matter? *Int J Drug Policy* 2020; **75**: 102583.
- 348 Shover CL, Humphreys K. Predictors of availability of long-acting medication for opioid use disorder. *Drug Alcohol Depend* 2019; **204**: 107586.
- 349 Lehman WEK, Simpson DD, Knight DK, Flynn PM. Integration of treatment innovation planning and implementation: strategic process models and organizational challenges. *Psychol Addict Behav* 2011; **25**: 252–61.
- 350 Humphreys K, Pollack HA. How should the United States respond to the opioid addiction and overdose epidemic? In: Goldman HH, Frank RG, Morrissey JP, eds. *The Palgrave Handbook of American Mental Health Policy*. New York, NY: Springer International Publishing, 2020: 259–95.
- 351 Larance B, Dobbins T, Peacock A, et al. The effect of a potentially tamper-resistant oxycodone formulation on opioid use and harm: main findings of the National Opioid Medications Abuse Deterrence (NOMAD) study. *Lancet Psychiatry* 2018; **5**: 155–66.
- 352 Becker WC, Fiellin DA. Abuse-deterrent opioid formulations—putting the potential benefits into perspective. *N Engl J Med* 2017; **376**: 2103–05.
- 353 Reuter P, Caulkins JP, Midgette G. Heroin use cannot be measured adequately with a general population survey. *Addiction* 2021; published online March 2. <https://doi.org/10.1111/add.15458>.
- 354 Kilmer B, Caulkins JP. Hard drugs demand solid understanding. 2014. <https://www.usatoday.com/story/opinion/2014/03/08/heroin-abuse-hoffman-research-column/6134337/> (accessed Nov 10, 2020).
- 355 Gladstone E, Smolina K, Morgan SG, Fernandes KA, Martins D, Gomes T. Sensitivity and specificity of administrative mortality data for identifying prescription opioid-related deaths. *CMAJ* 2016; **188**: E67–72.
- 356 Oquendo MA, Volkow ND. Suicide: a silent contributor to opioid-overdose deaths. *N Engl J Med* 2018; **378**: 1567–69.
- 357 Rockett IRH, Caine ED, Banerjee A, et al. Fatal self-injury in the United States, 1999–2018: unmasking a national mental health crisis. *eClinicalMedicine* 2021; **32**: 100741.
- 358 Pease, J. University of Florida named coordinating center for national drug abuse surveillance system. 2020. <https://ufhealth.org/news/2020/university-florida-named-coordinating-center-national-drug-abuse-surveillance-system> (accessed Dec 30, 2021).
- 359 European Monitoring Centre on Drugs and Drug Addiction. *Wastewater analysis and drugs—a European multi-city study*. 2020. https://www.emcdda.europa.eu/topics/pods/waste-water-analysis_en (accessed Nov 10, 2020).
- 360 Cornelius K. Sewage is helping cities flush out the opioid crisis. 2018. <https://www.scientificamerican.com/article/sewage-is-helping-cities-flush-out-the-opioid-crisis/> (accessed Dec 30, 2021).

- 361 Kennedy DM. Don't Shoot: One Man, a Street Fellowship, and the End of Violence in Inner-City America. New York, NY: Bloomsbury, 2011.
- 362 Hemel DJ, Ouellette LL. Innovation institutions and the opioid crisis. *J Law Biosci* 2020; 7: Isaa001.
- 363 Stanczyk MA, Kandasamy R. Biased agonism: the quest for the analgesic holy grail. *Pain Rep* 2018; 3: e650.
- 364 Zhu Y, Wienecke CFR, Nachtrab G, Chen X. A thalamic input to the nucleus accumbens mediates opiate dependence. *Nature* 2016; 530: 219–22.
- 365 Schmid CL, Kennedy NM, Ross NC, et al. Bias factor and therapeutic window correlate to predict safer opioid analgesics. *Cell* 2017; 171: 1165–75.e13.
- 366 Gillis A, Kliewer A, Kelly E, et al. Critical assessment of G protein-biased agonism at the μ -opioid receptor. *Trends Pharmacol Sci* 2020; 41: 947–59.
- 367 US. Financial Crimes Enforcement Network. Advisory to financial institutions on illicit financial schemes and methods related to the trafficking of fentanyl and other synthetic opioids. 2019. <https://www.fincen.gov/sites/default/files/advisory/2019-08-21/Fentanyl%20Advisory%20FINAL%20508.pdf> (accessed Dec 30, 2021).
- 368 US Department of Homeland Security. Prize winners announced in \$1.55M challenge for new solutions to detect opioids in international mail. 2019. <https://www.dhs.gov/news/2019/12/12/prize-winners-announced-155m-challenge-new-solutions-detect-opioids-international> (accessed Dec 30, 2021).
- 369 Collins FS, Schwetz TA, Tabak LA, Lander ES. ARPA-H: Accelerating biomedical breakthroughs. *Science* 2021; 373: 165–67.
- 370 Victor RG, Lynch K, Li N, et al. A cluster-randomized trial of blood-pressure reduction in Black barbershops. *N Engl J Med* 2018; 378: 1291–301.
- 371 Victor RG, Blyler CA, Li N, et al. Sustainability of blood pressure reduction in Black barbershops. *Circ* 2019; 138: 10–19.
- 372 Pellowski JA, Kalichman SC, White D, Amaral CM, Hoyt G, Kalichman MO. Real-time medication adherence monitoring intervention: test of concept in people living with HIV infection. *J Assoc Nurses AIDS Care* 2014; 25: 646–51.
- 373 Kalkman GA, Kramers C, van Dongen RT, van den Brink W, Schellekens A. Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study. *Lancet Public Health* 2019; 4: e498–505.
- 374 International Narcotics Control Board. Narcotic drugs—technical report. New York, NY: United Nations, 2020.
- 375 Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B. Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. *Lancet Psychiatry* 2019; 6: 140–50.
- 376 Krawczyk N, Greene MC, Zorzanelli R, Bastos FI. Rising trends of prescription opioid sales in contemporary Brazil, 2009–2015. *Am J Public Health* 2018; 108: 666–68.
- 377 Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *Br J Clin Pharmacol* 2014; 78: 1159–66.
- 378 Knaul FM, Bhadelia A, Rodríguez NM, Arreola-Ornelas H, Zimmermann C. The Lancet Commission on Palliative Care and Pain Relief: findings, recommendations, and future directions. *Lancet Glob Health* 2018; 6: S5–6.
- 379 US Centers for Disease Control and Prevention. US opioid dispensing rate maps. 2021. <https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html> (accessed Dec 30, 2021).
- 380 Böckerman P, Haapanen M, Hakulinen C, Karhunen H, Maczulskij T. Determinants of prescription opioid use: population-based evidence from Finland. *Addiction* 2021; 116: 170–75.
- 381 Action on Smoking and Health. ASH fact sheet: tobacco and the developing world. 2019. <https://ash.org.uk/wp-content/uploads/2019/10/Tobacco-Developing-World.pdf> (accessed Dec 30, 2021).
- 382 Brandt AM. FDA regulation of tobacco—pitfalls and possibilities. *N Engl J Med* 2008; 359: 445–48.
- 383 Galofaro C, D'Emilio FAP. Purdue foreign arm caught up in opioid probe in Europe. 2019. <https://apnews.com/article/d384c975e039474e8b93e11b9ace18e0> (accessed Dec 12, 2020).
- 384 Ryan H, Girion L, Glover S. OxyContin goes global—“We're only just getting started”. 2016. <https://www.latimes.com/projects/la-me-oxycontin-part3/> (accessed Nov 10, 2020).
- 385 Varney S. How big pharma is targeting India's booming opioid market. 2019. <https://www.theguardian.com/world/2019/aug/27/india-opioids-crisis-us-pain-narcotics> (accessed Nov 10, 2020).
- 386 Varney S. Opioid addiction rising in India as US drugmakers push painkillers. 2019. <https://www.theguardian.com/world/2019/aug/28/india-opioids-addiction-us-drugmakers-push-painkillers> (accessed Nov 10, 2020).
- 387 Kinetz E. Fake doctors, misleading claims drive OxyContin China sales. 2019. <https://apnews.com/article/china-united-states-opioids-shanghai-lawsuits-3ff1dfa05dac46ebb2615f729d947c0f> (accessed Dec 8, 2021).
- 388 Furlan AD, Harvey AM, Chadha R. Warning from Canada: Latin America, South Africa and India may face an opioid epidemic in the coming years. *J Glob Health* 2020; 10: 010324.
- 389 Mann B. Federal judge approves landmark \$8.3 billion Purdue Pharma opioid settlement. 2020. <https://www.npr.org/2020/11/17/936022386/federal-judge-approves-landmark-8-3-billion-purdue-pharma-opioid-settlement> (accessed Dec 9, 2020).

Copyright © 2022 Elsevier Ltd. All rights reserved.