



THE OPIOID CRISIS IN AMERICA
Domestic and International Dimensions

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Preventing opioid misuse and addiction

New thinking and the latest evidence

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BROOKINGS

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Executive summary

Drug policy often comprises efforts to reduce the supply of drugs, to provide health and social services to addicted individuals, and to prevent the development of addiction in the first place. The last of these efforts—prevention—is the subject of this paper. The scientific literature on drug policy offers some insights on the relative effectiveness and cost-effectiveness of different strategies for preventing traditional opioid misuse and related harm. But these insights don't apply perfectly to the current opioid crisis in the U.S. and Canada, due to many important differences between today's epidemic and those of the past (e.g., heroin in the 1960s and 1970s). School-based universal primary prevention programs, for example, will probably remain only modestly effective, mainly because it is mostly adults, rather than adolescents, who initiate opioid use through prescription drugs. However, there are new opportunities for prevention, including promoting safer opioid prescribing, and issuing public health warnings about fentanyl's dangers and the need to keep prescription opioids locked up.

Importantly, the audience for these prevention interventions can include prescribers and pharmacists, not just potential users, and the mechanisms should involve incentives and nudges, not just information and education. Classic drug law enforcement against retail sellers and their suppliers may become even less effective than it has been in the past. However, other forms of supply control are possible because most of the prescription opioids that get misused come from legal and regulated distribution. Because prescription opioids remain the dominant route through which opioid use disorder is initiated, reducing its incidence can translate over time into reduced deaths not only from prescription opioids, but also from heroin and fentanyl. Enforcement against licensed producers and distributors may perform well even if enforcement against traditional dealers does not, and there are a wide range of actions vis-a-vis these licensees that do not require arrest or incarceration.

Looking across the preventive strategies reviewed in this paper, four meta-lessons emerge:

- Regions not yet exposed to black market fentanyl should use every tool available, including traditional drug law enforcement, to delay its arrival; but such enforcement should be recognized as a holding action, not a long-term solution.
- Elements of the legal opioid industry whose corporate tactics violate laws and regulations—at home or abroad—should be treated like illicit drug cartels, including potential criminal prosecution of their leadership.
- Well-meaning clinicians, patients, and pharmacies need nudges and system redesign, not just education, to avoid becoming unwitting accomplices in the opioid crisis.
- A small subset of clinicians, patients, and pharmacies are criminals; they should be investigated aggressively, and their activities stopped.

Introduction

U.S. drug overdose deaths have been growing exponentially since at least 1979 (Hawre et al., 2018) and opioid overdoses account for more deaths than firearms, auto crashes, or suicides. Indeed, until the coming of COVID-19, the rate of acute death from the opioid crisis was higher than that of any epidemic (including HIV/AIDS) since the 1957-58 “Asiatic flu” outbreak. Opioid death rates are nearly as high in Canada, despite its lower inequality, universal health care, and more extensive provision of health and social services for addicted individuals (Humphreys, 2019). U.S. household surveys detect 2.1 million people living with opioid use disorder (OUD), which is almost surely a significant underestimate (Pardo et al., 2019). OUD creates enormous suffering for those with the condition, their families, and society more generally (Florence et al., 2018).

This paper addresses how best to prevent more individuals from developing opioid misuse and addiction. We focus on actions that could be taken in the U.S., but because American companies play a leading role in spreading the prescription opioid epidemic abroad, these actions could have benefits beyond U.S. borders. We begin by describing how the nature of the current opioid crisis reduces the relevance of some historical findings from research on the prevention of drug abuse problems (Babor et al., 2018; Surgeon General of the United States, 2016). We then turn to what policies can prevent opioid-related problems today, including approaches that were ineffective or irrelevant in prior drug crises.

The classic story of heroin up through the latter half of the 20th century is well-known. In broad strokes, initiation spread “contagiously” by word-of-mouth among youth and young adults (including soldiers) beginning in the late 1960s. Initiates encouraged friends to try the drug. Most used briefly without suffering great harm, but some progressed to dependent use over time. Once heroin’s dangers were widely appreciated, initiation ebbed, leaving behind a residual pool of aging and addicted users.

Heroin reached illicit retail markets through multi-layered international supply chains. Peasants in distant lands grew poppies that were harvested and refined into heroin. Although heroin fetched a good price in its source country, its value exploded when criminal networks trafficked it to wealthy countries for retail sale. Most heroin was consumed by a relatively small number of addicted users who were concentrated in disadvantaged populations in major metropolitan centers.

With respect to heroin and other agriculturally-derived drugs (e.g., cocaine), research consistently reached broad conclusions concerning the effectiveness of the four pillars of drug control (Babor et al., 2018):

1. Making the production and sale of drugs illegal keeps prices extremely high, which deters use. But expanding efforts to curtail supply to a level beyond routine enforcement produced little incremental benefit. Prisons could be rapidly filled, but retail dealers and other low-level players could be replaced just as rapidly when incarcerated.
2. Treatment could not “cure” addiction, but it was nonetheless cost-effective, particularly so for heroin addiction because of the effectiveness of pharmacotherapies such as methadone maintenance treatment that substituted safer, medical opioids for heroin.
3. Many popular prevention programs, such as the early versions of Drug Abuse Resistance Education (DARE), were not effective. Even evidence-based (“model”) programs were only modestly effective in absolute terms but they could still be cost-effective because they were cheap and what they prevented was so damaging.

4. Drug-related harms could be targeted directly even if use continued. Providing injection heroin users with clean syringes, for example, helped to reduce the spread of blood-borne diseases, notably HIV/AIDS.

In such drug crises, individual-level prevention programs played a minor supporting role, and while arresting dealers might have been effective in the early, explosive growth stages of a drug epidemic, once a market was well-established, stamping it out was virtually impossible.

Only some of these historical lessons apply to the modern opioid epidemic, which differs in at least two fundamental ways. First, most people today who overdose on opioids purchased in illegal (“street”) markets began by misusing pharmaceutical opioids that were produced, prescribed, and delivered within a regulatory system overseen by the Drug Enforcement Administration, Food and Drug Administration (FDA), and individual states. The motivation for initial opioid use may or may not have been recreational, and those first doses may or may not have been prescribed to the actual user. But legal opioids started a chain of events that progressed to the “trading down” to black market opioids and culminated in wide-scale overdoses, whether or not those overdoses involved prescription opioids.

Second, the recent arrival of fentanyl in illicit markets (particularly in western Canada and the eastern and midwestern U.S.) has radically increased death rates and begun to fundamentally alter the nature of drug supply chains. Unlike in prior epidemics, opioid deaths are soaring due to rising lethality rather than rising prevalence of use. Fentanyl multiplies the mortality risk of illicit opioid use well beyond the already terrifying historical norm of 1 or 2 per 100 person-years (Degenhardt et al., 2019).

Fentanyl also differs by entering markets more due to supply considerations rather than user demand. Fentanyl costs about one-tenth as much as heroin and is about 17 times as potent (Pardo et al., 2019). Wholesale dealers mix heroin with fentanyl to cut their raw materials cost, not because users are initially clamoring for it (though over time, some users do start to demand it as their tolerance grows).

Having discussed how the modern opioid problem differs from past epidemics, we now turn to what this means for preventing further OUD in the current crisis. We look at prevention in four domains: conventional drug supply control; population-focused prevention for youth; interventions with prescribers and pharmacists; and industry regulation.

Conventional drug supply control

Maintaining self-control in the presence of a tempting good (e.g., a doughnut or a bag of heroin) is more challenging than not consuming something that isn’t readily available (Ainslie, 1975). This is a primary rationale for drug supply control. In an ideal world, supply control would make a given drug physically unavailable. That ideal has actually been achieved sometimes, in some places. For many rural and suburban dwellers in the 1970s, buying heroin was simply not an option. Drug law enforcement created physical scarcity that spared everyone in those communities, not just those whose demand had been restrained by protective influences.

More commonly, supply control succeeds in driving up the price and reducing the convenience of obtaining drugs. Prohibition has historically made heroin remarkably scarce and expensive. A semi-refined agricultural product akin to tea, heroin is 100 times more expensive per unit of weight (ONDC, 2016).

The collapse of cannabis prices after the substance was legalized shows that prohibition per se is enormously effective at raising drug prices (Smart et al., 2017), but increasing prohibition enforcement beyond some base level brings fewer added benefits at greater cost (Pollack and Reuter, 2014). For example, the massive 1980s expansion of drug-related incarceration may have slowed the drop in heroin's price (Kuziemko and Levitt, 2004) but could not stop the price decrease entirely (Caulkins and Chandler, 2006).

This pessimistic judgment about intensifying enforcement applies even more acutely to fentanyl. Fentanyl production does not rely on plants that require farm labor, arable land, favorable weather, and a pliant or weak national government: any chemist anywhere with access to precursor chemicals can produce fentanyl (Humphreys, Caulkins, & Felbab-Brown, 2018). Further, rather than being based in a low-income country which wealthy consumer countries can readily influence, fentanyl production is currently centered in China, a nuclear-armed superpower (Pardo et al., 2019). Supply control is further complicated by fentanyl's extraordinary potency. Even a single kilogram is a large wholesale quantity, and kilogram-sized parcels can be shipped around the world in the mail, bypassing portions of the traditional criminal drug distribution networks.

The aforementioned supply-control challenges, coupled with fentanyl being dramatically cheaper than heroin, will almost certainly depress retail illicit opioid prices eventually (Reuter & Kleiman, 1986; Caulkins & Reuter, 2010). Indeed, in the long run, illicit opioids could possibly become so cheap and readily available that supply control has to content itself with preventing violence and brazen selling, rather than driving up prices to deterrent levels. Drug law enforcement nonetheless still has a role to play. At least as of 2017-2018, fentanyl and other synthetic opioids had not yet become widely available outside certain North American markets. Given that those drugs currently end the lives of about 30,000 people per year in just part of the U.S. and Canada, anything that delays their spread could save tens of thousands of others. Delaying their spread to other continents could save even more.

Implications for youth-focused prevention

Traditional drug prevention efforts assume that adolescents experiment with drugs for a range of reasons, such as a desire to fit in with peers, an expression of autonomy from parents, a need to cope with negative emotions, a lack of appreciation of the risks of drugs, or a desire for new and exciting sensations. The prototypical prevention program targets children in middle school, hoping to reduce or delay such experimentation, thereby reducing harm (including the development of addiction) down the road. Although often referred to as “drug education”, the goal is changing behavior—not enhancing knowledge per se. Unfortunately, there have been few rigorous evaluations, and most widely-used programs do not have significant power to reduce drug use in general (Flynn et al., 2015) or in middle school in particular (Onrust et al., 2016).

Inasmuch as most drug prevention programs are not substance-specific, these ideas are germane to the modern opioid problem. Misuse of prescription opioids can begin at young ages, there can be myths to dispel, and preventing initiation is one good way to reduce overdose deaths over time (Chen et al., 2019). Indeed, some randomized controlled trials conclude that evidence-based universal prevention programs can reduce prescription drug misuse (e.g., Spoth et al., 2013; Crowley et al., 2014; Surgeon General of the United States, 2016).

Adolescents are sometimes prescribed opioids and can also filch opioids prescribed to family members. That said, many cases of opioid addiction—past and present—have begun with a prescription from a doctor and an instruction to take opioids, and most people who head down that path are adults. Among opioid-naïve adults, within four years of being prescribed an opioid, almost 5 percent will have a diagnosed opioid use disorder (Burke et al., 2020), and 38 percent of American adults are prescribed an opioid each year (Han et al., 2017). Youth-focused universal prevention programs will thus likely make only a modest difference to the course of the North American opioid crisis.

Media-based attempts to discourage use of drugs available in illicit markets have generally had little success (Hornik et al., 2008). Prescription drug use disorder does present new opportunities however, such as Utah’s “Use only as directed” campaign which included sensible and potentially useful messages such as “keep your medications locked in a safe place” (Johnson et al., 2011).

Policies focused on preventing unsafe opioid prescribing

U.S. opioid prescribing began soaring in the mid-1990s and nearly quadrupled (in morphine milligram equivalents) over the next 15 years. Although rates began dropping around 2012, U.S. per capita prescribing remains many times that of other developed countries (Humphreys, 2017), including those with similar levels of population pain (Humphreys, 2018). The silver lining is that policymakers have more tools available to reduce opioid supply within the health care system than they do in illicit markets. In doing so, policymakers can likely reduce future illicit opioid deaths because in many cases where fentanyl ultimately caused death, the underlying addiction began years earlier with an unwisely prescribed opioid.

Excessive prescribing has allowed some people with opioid use disorder to obtain extra pills by fraudulent methods and then sell them into the black market. Those pills can initiate or exacerbate opioid use in other people, who may themselves seek multiple prescriptions and sell some of those pills into the black market, continuing a positive feedback loop of epidemic spread. This chain reaction is dramatically different than the earlier situation with heroin. Heroin users may have introduced others to heroin use (contagious spread of demand), and some turned to criminal activity for income by working as retail sellers, but they never produced additional supply. With the current diversion of prescription opioids, those turning to criminal activity (fraudulent diversion) are actually expanding the black-market supply (contagious spread of supply). Curtailing excessive prescribing can disrupt this positive feedback loop.

Because only a modest proportion of people with opioid use disorder turn to reselling, this might seem like a minor matter. But consider that opioid prescribing from just one class of medical procedure—surgery—results in 3.3 billion unused pills accumulating in American homes every year (Plan Against Pain, 2017). Each pill may fetch \$20 on the black market, meaning the street value of excess prescribing from that one procedure matches or exceeds that of the entire U.S. heroin market (Midgette et al., 2019). Safer prescribing thus not only lowers the direct risk of generating opioid use disorder, it also cuts off a pool of suppliers who could potentially addict others.

Many safer prescribing initiatives could also be useful in addressing other types of drug use disorder. Opioids are only one of many heavily prescribed medications that result in significant harm to public health and also support illicit markets. A safer prescribing effort—such as a

prescription drug monitoring program—that targeted not only opioids but also benzodiazepines and stimulants could ameliorate problems with those drugs as well.

Although the U.S. and Canadian health care systems over-prescribe opioids, opioids remain essential medications that should not be denied to those who need them. The best policy goal is not a blanket restriction but safer prescribing practices. “Safer” can mean fewer prescriptions (e.g., not providing opioids to a disturbing 12 percent of patients with twisted ankles, Finney et al., 2019), lower doses, or prescribing in a less risky fashion (e.g., avoiding co-prescribing with benzodiazepines).

Finally, it bears mentioning that helping individuals taper off or down from high dose opioids they have been prescribed for long periods can pose risks, including return of pain, emotional anguish, or depression. Consensual and gradual tapering has a place in prescription opioid reduction efforts, but the lower hanging fruit—which is abundant in the U.S.— is avoiding initiating more opioid naïve patients into taking opioids when they are not medically necessary.

Measures that may enhance the safety of opioid prescription regimes include better education of prescribers, prescription nudges, and ensuring providers are informed about opioid-related deaths.

Evidence-based prescriber education

The pharmaceutical industry bombards prescribers with messages designed to promote drug sales (e.g., sales staff visits to doctors’ offices, hiring prescribers as speakers at medical education events, advertising in medical journals, etc.). As a counterweight to these influences—which are more potent than many clinicians would like to admit—medical schools, residency programs, professional societies, government agencies, and health care systems all make efforts to provide unbiased, scientifically-grounded education.

One example is clinical practice guidelines, such as the high-profile prescribing guidance produced by The Centers for Disease Control and Prevention (Dowell, Haegerich, & Chou, 2016). A pre-existing trend of decreasing U.S. opioid prescription showed a modest acceleration following the release of this guidance (Bohnert, Guy, & Losby, 2018).

Prescriber education also occurs in medical school and residency training, at conference talks, during grand rounds, and through continuing medical education courses. The most common effect identified of these education-oriented interventions was “moderate”, with many studies finding no effect (see Brennan and Mattick, 2013 for a review). Discouragingly, more rigorous studies are particularly unlikely to find beneficial effects. For example, a randomized trial with 374 physicians found that education and practice guidelines had no significant effect on risky prescribing of opioids or benzodiazepines (Pimlott et al., 2003).

Education may become more potent when coupled with supports such as reimbursing physicians for the time needed to learn new prescribing skills, expanding coverage of alternatives to opioids (e.g., physical therapy), and removing barriers (e.g., paperwork) to changed prescribing. Positive and negative incentives can also increase the impact of education. As an example of a positive (reputational) incentive, dental professionals are substantially more likely to screen for substance use disorders when they perceive such interventions as valued components of their own professional roles (Parish, et al. 2015). Looking more at the negative incentive side, a Canadian study of 138 physicians attending a workshop on safe prescribing found that participants did not prescribe less afterwards, *unless* they had been referred to the course by the College of Physicians and Surgeons of Ontario in response to a complaint (Kahan et al., 2013). The pressure created by the College’s referral may have provided motivation to apply the lessons of the course.

Prescription nudges

A low-cost way to alter opioid prescribing relies on the human tendency to accept defaults when making many decisions. Manipulating choice architecture, often referred to as “nudging” (Thaler and Sunstein, 2009), can have a substantial influence on prescribing (Patel et al., 2016).

In one example, Chiu and colleagues (2018) lowered the default number of post-surgical opioid pills in the electronic medical record from 30 to 12. Prescribers did not have to follow the default, yet many did, dropping by two-thirds the proportion of procedures that resulted in an opioid prescription of 30 pills. The number of patients requesting refills did not change, suggesting pain relief remained adequate.

Nudges have some theoretical risk of raising prescribing for low-prescribers (i.e., bringing a low prescriber up to a default). However, in the Chiu study there was no evidence that physicians who previously wrote prescriptions for fewer than 12 pills raised their prescribing in response to the changed default.

It should be inexpensive to apply such nudges at scale. Health system regulators, including chief technology officers in hospitals and state insurance commissioners, could mandate lowered defaults across all electronic medical record systems.

Informing providers about opioid-related deaths

Letters informing physicians that their opioid prescribing is higher than their peers doesn't influence prescribing (Sacarny et al., 2016), but letters informing them of a patient's overdose death may. In a randomized trial of 861 physicians, receiving such a death notice decreased opioid prescribing by about 10 percent (Doctor et al., 2018). This inexpensive intervention could make a substantial difference at scale if the effects are generalizable, non-transitory, and do not lead physicians to avoid prescribing opioids in cases where it is appropriate to do so.

Legal and regulatory oversight of individual prescribers

Information alone can change prescriber behavior, but not always by a lot. Greater response may require a range of legal and regulatory measures, including restricting the length of prescriptions; using more restrictive scheduling; questioning prolific prescribers; and targeting enforcement on the most abusive prescribers.

Legislative restrictions on prescription length

Many U.S. states have passed laws restricting the length of initial opioid prescriptions for acute pain or injury (Davis et al., 2019). The restrictions vary in terms of which medications and settings are covered, and in terms of the length of prescription allowed (seven days is the mode, Davis et al., 2019). This crude approach lumps risky prescriptions in with potentially appropriate ones (e.g., knee surgery pain usually persists longer than seven days), but can be seen as a natural political consequence of medicine's failure to self-regulate. An initial evaluation across all states showed that such laws have not changed opioid prescribing (as measured by morphine milligram equivalents per 100,000 people, Davis et al., in press). However, an evaluation of New Jersey's law, which combined a five-day limit with an electronic

medical alert if a new prescription exceeded the limit, was followed by a 22 percent greater decrease in opioid dose per prescription than was seen in neighboring Pennsylvania (Lowenstein et al., 2019). This study did not measure how this change affected patients' well-being.

Rescheduling drugs

Moving controlled substances to a more restrictive federal or state schedule can reduce prescriptions. When the federal government moved hydrocodone combination products (e.g. Vicodin) from Schedule III to the more restrictive Schedule II, annual U.S. opioid prescriptions decreased by about 15 million (Jones, Lurie, & Throckmorton, 2016) despite some compensatory uptick in prescriptions for opioid drugs that were less restrictively scheduled (e.g., Tylenol #3 and #4, Seago et al., 2016). Similarly, Haynes et al. (2016) found reductions in hydrocodone exposures reported to Texas Poison Control centers, but increases in mentions of codeine, oxycodone, and tramadol. In a state-level study, Spiller et al. (2010) found that tramadol poisoning cases fell after Arkansas and Kentucky rescheduled tramadol, in comparison with two control states that did not reschedule it.

Prescription drug monitoring programs

Prescription drug monitoring programs (PDMPs) track data on prescriptions and make it accessible to prescribers, pharmacies, and/or other monitoring agencies. PDMPs vary in how well they are resourced, their technical details, what drugs they cover, and the extent to which prescribers actually use them. Unsurprisingly, this has led to inconsistent findings on the magnitude of their impact (Haffajee, 2019; Humphreys & Pollack, 2020). PDMPs can produce some substitution when prescribers decrease their use of medications tracked under the program, but increase their use of others (Humphreys & Pollack, 2020). However, the net effect appears beneficial, if modest.

As all states now have PDMPs, the policy question has shifted to what type of monitoring program is best. Pardo's (2017) study indicated that programs operated by law enforcement agencies produced larger benefits than those operated by other administrative bodies. In one of the most rigorous studies to date, Buchmueller and Carey (2018) found that PDMPs had no average benefit. But when coupled with laws requiring a PDMP check prior to controlled substance prescription, monitoring programs reduce doctor shopping and prescription opioid misuse. Similarly, Haffajee and colleagues (2018) found that "robust" state programs that required prescriber registration and regular checking reduced high-risk opioid prescribing. Other studies suggest that programs that proactively monitor prolific prescribers have more benefits than entirely passive models (Humphreys & Pollack, 2020).

Requesting justification from extremely prolific prescribers

Opioid prescribing is far more skewed than prescribing of other medications (Kiang et al., in press). That means a handful of truly extreme prescribers account for a sharply disproportionate share of prescribing, creating opportunities for tailored interventions. CVS identified 42 prescribers who prescribed at as much as 30 times the rate of other physicians within their specialty (Betses & Brennan, 2013). These prolific prescribers were sent a letter asking for justification if they wished for CVS to continue filling their prescriptions. In 86 percent of cases, the prolific prescriber either did not respond or gave implausible explanations, leading CVS to stop filling their scripts.

Targeted enforcement against destructive prescribers

Mercifully, few physicians are intentionally malignant: law enforcement must, nonetheless, prioritize such individuals because they can cause population-wide harm (Strang & Sheridan, 1997). A small group of unethical pain doctors running “pill mills” in Florida facilitated substantial opioid addiction and overdoses throughout the southeastern U.S. in the 2000s (Surratt et al., 2014). Following pill mill raids by law enforcement and the introduction of tighter regulations, Florida’s opioid-related overdose death rate fell significantly (Johnson et al., 2014; Surratt et al., 2014).

Pill mill customers can migrate to heroin/fentanyl markets. When there is law enforcement action against their suppliers, these individuals should be linked to treatment services rather than being left to fend for themselves. But the possibility of displacing existing customers does not diminish the benefits that shutting down pill mills creates in terms of reducing the inflow of people to opioid use disorder.

Interventions at the health system level

The above policies focus on individual prescribers. Other interventions attempt to disrupt the ecology of entire self-contained, organized, health care systems such as Kaiser Permanente, the Veterans Health Administration (VHA), and the like (see, e.g., Del Giorno et al., 2018; Saunders et al., 2015).

The VHA Opioid Safety Initiative, which is almost certainly the largest such intervention in the U.S., illustrates the possibilities of system-wide change. Almost 300 pharmacists proactively provided in-person instruction to VHA medical staff around the country. The relevance of this education was accentuated by providing individual, service-level, and hospital-level information on opioid prescribing and continuing to monitor it throughout the initiative. Clinicians and managers were equipped with computerized tools and skills to easily monitor patients’ prescription drug use history and risk profile. In 2018, the VHA began posting facility-level prescribing rates on the Internet for anyone to see.

VHA also became the first large U.S. health care system to dramatically expand provision of naloxone, and to expand non-opioid pain treatments (Gellad, Good, & Shulkin, 2017). In a study of over two million VHA patients with incident chronic pain, increases occurred in the proportion receiving physical/occupational therapy (31 percent to 37 percent), complementary/alternative medicine (2 percent to 3 percent), psychosocial therapy (40 percent to 45 percent) and specialty pain clinic care (10 percent to 12 percent) from 2010-11 to 2015-16 (Frank et al., 2018). Prescriptions for most non-opioid medications also became more common for pain (Frank et al., 2018).

After three years, the number of patients prescribed an opioid each quarter had dropped by 25 percent and the number receiving high-dose opioids decreased by 36 percent. The number receiving the risky combination of opioids and benzodiazepines declined even more (47 percent). This wasn’t a randomized trial, but the changes are so large that it seems unlikely that they occurred spontaneously.

Because prescribing-reduction initiatives can harm chronic pain patients through rapid, forced tapering, it is worth noting that more than 90 percent of the reduction in long-term prescription opioid use in VHA resulted from reducing the number of new long-term patients rather than withdrawing opioids from existing long-term patients (Minegishi & Frakt, 2018).

Pharmacist-focused policies

Over a quarter million pharmacists practice in the U.S. They are an essential component of how controlled substances are dispensed, not least because they sometimes have more knowledge about the specifics of a medication—and more time to convey those specifics—than do prescribers. There are thus several ways in which pharmacists—and policies that govern their practice and reimbursements—can play a vital role in curtailing opioid use disorder.

Pharmacist counselling of patients

There is no evidence that printed instructions included with medications reduce misuse (Morris & Halperin 1979), which is unsurprising given that many patients do not read them; those who do typically encounter complex text in small print. Counselling from a pharmacist may be more important. In a randomized trial of 178 patients being discharged from the hospital, those actively counselled by a pharmacist had a much lower rate of preventable adverse events (1 percent vs. 11 percent for controls, Schnipper et al., 2006). Other individual studies (e.g., Peveler et al., 1999) as well as systematic reviews (e.g., Roughead et al., 2005) indicate that pharmacist counselling increases compliance with the terms of the prescription.

Counselling patients takes time, and time is money. Christensen and Farris (2006) point out that many pharmacists are under pressure to process a very large number of prescriptions each day. Reimbursement policy can be helpful here, because such counselling is more likely to occur when it is covered by insurance (Christensen and Farris, 2006).

Engaging pharmacies in drug take-back programs

Billions of excess opioid pills are prescribed each year but not used by the patient. Some are discarded improperly, with adverse environmental effects. Others accumulate in medicine cabinets and are a significant aggravator of the opioid epidemic (Bicket et al., 2017). In an attempt to diminish this enormous reserve of pills, law enforcement agencies have organized “take-back” events. Literally hundreds of tons of medication are turned in at such events, but only a small proportion of them are opioids. Even if all these pills were all opioids, this would still constitute only a small proportion of the known excess (Albert et al., 2011; Stewart et al., 2015).

Occasional drug take-back days can be compared to the early days of bottle and newspaper recycling: special events organized by a motivated few. While useful, their efforts only scratched the surface. The quantum leap in glass and paper recycling came when collection became routine, convenient, and widely practiced.

Congress has dramatically expanded the number and types of organizations (e.g., pharmacies, hospitals) that can be licensed to collect unused opioids 365 days a year. But only 2.5 percent of eligible sites operate such take-back programs (Government Accountability Office, 2017). Congress could go further and simply require that all pharmacies be willing to take back prescriptions, much as some states require all automobile service stations to accept motor oil from do-it-yourself oil changers.

Customer incentives could help here too. In some states, those who return bottles receive a nickel or dime refund of a deposit paid at purchase. Similarly, opioid manufacturers could be required to fund a program that would reward pharmacy customers returning the unused portion of a controlled-substance prescription with a discount coupon for in-store purchases.

Preferred drug lists

Preferred drug lists are established mainly by insurers (or pharmacy benefit managers, Brennan et al., 2017) and lower the cost of some drugs in preference to others in the same class. For example, methadone is an excellent medication for treating heroin addiction, but it has a high-risk profile for use in chronic pain. In response, some Medicaid programs have classified methadone for pain as non-preferred, a change associated with reduced methadone overdose deaths (Faul, Bohm, & Alexander, 2017).

Reimbursement lock-in

Reimbursement lock-in seeks to deter “doctor shopping”. Historically, many overdoses involved someone who had prescriptions from many prescribers (Hall et al., 2008). Payors can restrict such patients to a single provider who will write and be reimbursed for all future opioid prescriptions.

Lock-in programs reduce opioid provision (Roberts and Skinner 2014). The experience of Oklahoma (Katz et al., 2013) and Washington State (Franklin et al., 2015) in using such programs was positive: the results included reduced doctor shopping, emergency room visits, and costs. North Carolina also showed a significant drop in opioid prescribing in Medicaid (Roberts et al., 2016). Medicare received authority to begin a reimbursement lock-in program in 2018.

Regulation and enforcement addressing pharmaceutical manufacturers and distributors

Even though the consequences of OUD have been devastating to users, their families, and society as a whole, for some companies the epidemic has been a gold mine. OxyContin alone is estimated to have generated over \$35 billion in revenue for Purdue Pharma. Because the best customer is an addicted customer, protecting public health and safety requires strong regulation of the for-profit corporations that produce addictive products (Cuéllar & Humphreys, 2019). The evidence points to several regulatory and enforcement measures that may be effective in curbing the role of manufacturers and distributors in spurring the opioid crisis.

Constraining industry product promotion

Purdue Pharma executives confessed in federal court in 2007 to criminal and civil liability for misbranding OxyContin as less addictive and prone to abuse than they knew it to be. This validated what every thoughtful observer had long ago concluded: the explosion of opioid overprescribing was amplified by manufacturers aggressively pushing their products, withholding information from regulators, and making donations to virtually every organization that should have been protecting patients from them (Lembke, 2016; Meier, 2018).

Any discussion of policies to lessen opioid overprescribing thus must address industry regulation, designed to encompass the results of the ongoing class action lawsuit against the industry in federal court. That settlement could result in new constraints on pharmaceutical companies, just as the 1998 Master Settlement Agreement constrained the behavior of the tobacco industry.

One important tactic is curtailing industry-prescriber interactions such as gift-giving, in-person “detailing” visits, and industry funding of research, continuing education programs, patient

advocacy groups, professional societies, and clinical practice guideline-development groups. Although doctors may resist the idea that such promotion affects prescribing, much evidence suggests that it does (Brennan et al., 2006; Kassirer, 2005; Wazana, 2000).

Some countries and some individual health care systems within the United States have already banned or severely curtailed such industry-prescriber interactions. The constraints could be made national, with support from tax policy (e.g., removing promotion of controlled substances as a legitimate business expense).

Considering impacts beyond the user in FDA drug approval

Currently, the FDA assesses the safety and efficacy of medications by looking primarily at their impacts on the individuals to whom they will be prescribed. Yet opioids have significant adverse effects on other people: even living in a house where someone has been prescribed an opioid increases one's own risk of developing a problem. When deciding whether to allow an opioid onto the market, the FDA could consider the impact on people other than the patient (e.g., children in the same home), much as automobile regulators set safety standards based not just on the safety of drivers, but also on passengers.

Indeed, for any drug that has a high resale value in illegal markets, the regulatory process should presume that some of what is prescribed will be diverted. Oxycodone pills often fetch \$20 each on the black market. This means that an individual with prescriptions for 180 30 mg pills per month can earn about \$43,000 per year by selling rather than using those pills. Not only legitimate patients might be tempted by such a sum. Since there is no objective test for pain, criminals with no injury or ailment only need to "fake an ache" to secure a substantial tax-free income. Under these conditions, it is only common sense to assume that allowing take-home prescriptions for drugs that are highly valued in the black market will produce diversion. A regulatory process that blinds itself to that reality is not competent to protect public health or welfare.

Tamper-resistant/abuse-deterrent opioid medication formulations

Opioid manufacturers have invested heavily in developing tamper-resistant/abuse-deterrent (TR/AD) formulations of their products (Katz et al., 2007; Romach et al., 2013). These formulations change the drug's design and/or composition to make misusing it more difficult. For example, Suboxone is buprenorphine combined with an opioid antagonist (naloxone) that is released if the medication is crushed for injection or inhalation (Mastropietro & Omidian, 2013). Adding the naloxone seems to reduce misuse, particularly when Suboxone is formulated as a film rather than a pill (Comer et al., 2010; Lavonas et al., 2014).

The street price of OxyContin declined by about a third when its TR/AD formulation was introduced (Severtson et al., 2016), suggesting that opioid misusers found it harder to snort or inject. Yet the price did not go to zero because the TR/AD protection is imperfect (see Bannwarth, 2012; Becker & Fiellin, 2017; Cicero & Ellis, 2015; Lourenco et al., 2013).

Data from poison-control center calls, treatment admissions, emergency room mentions, and deaths suggested that the TR/AD formulation of OxyContin was misused far less than the original formulation (Butler et al., 2013; Cicero et al., 2012; Coplan et al., 2013; Coplan et al., 2016; Sessler et al., 2014, Severtson et al., 2016). Small, but still notable, increases in prescriptions of some other non-TR/AD opioids suggests some users sought substitutes (Dart et al., 2015). Also, some opioid-addicted individuals likely reacted to the TR/AD formulation by switching to heroin. Recent modelling work suggests that this effect will lead to somewhat higher opioid-related mortality in the next five years, although after that time, TR/AD

reformulations will produce a larger net gain in saving lives as the benefits of not addicting new patients begin to exceed the costs of some opioid-addicted individuals switching to heroin (Pitt et al., 2018).

If the TR/AD drug is only added to the set of options available, rather than replacing the original form, dishonest doctors and/or fraudulent users may still seek the old formulations. So it may be primarily conscientious people—who would likely not have abused the drug—who get the newly patented, and more expensive, TR/AD drugs. In that scenario, health care costs and drug manufacturers' profits go up, but with less public health benefit than if the TR/AD reformulations were going to people who wanted to misuse.

Altering packaging

Dispensing higher risk medications in blister packs rather than as bottles of pills provides a different kind of physical barrier against misuse. A study of individuals who poisoned themselves with paracetamol found that those who had bottled pills were more likely (69 percent vs. 40 percent) to have taken a potentially fatal dose than were individuals who had the medication in blister pack form (Hawton et al., 1996). Congress recently required blister packs for some opioid medications.

Preventing pharmaceutical companies from exporting the opioid epidemic

Investigative journalists have documented how some opioid manufacturers are following the “Big Tobacco” playbook in attempting to spread addiction to other nations (e.g., India, Brazil, and China) now that some of the developed world is waking up to their conduct. The U.S. could reduce such spread by requiring that all regulations of U.S.-based companies apply worldwide, including to U.S.-owned “sister companies” that operate abroad (e.g., Mundipharma, which markets OxyContin to other nations and, like Purdue Pharma, is owned by the Sackler Family). This would be a favor to developing countries whose political systems may be unable to withstand the financial and political influence exerted by affected companies. Law enforcement professionals in countries with established opioid epidemics could also do good by liaising with their peers in other countries now being targeted by bad actors in the industry.

Although imprisonment only weakly deters street-level heroin dealers, who often have existing criminal records and few legal job prospects, it could be a greater deterrent to physicians operating pill mills and to the owners of manufacturers and distributors who engage in criminal conduct regarding opioids. If a monetary fine is the worst that can happen to a corporate official who reaps enormous profit from spreading addiction, a culture of impunity may prevail. Prison sentences should therefore be on the menu, and the U.S. could make extradition agreements with other countries for the return and prosecution of pharmaceutical industry officials, much as was done with the heads of cocaine cartels in the 1980s.

Conclusion

The modern opioid epidemic differs fundamentally from the heroin problem of the 1970s, '80s, and '90s. Those differences should alter judgments about what interventions are possible and

which are most promising. The primary negative conclusion is that traditional forms of primary prevention and drug law enforcement may have less effect now than in the past.

The primary positive conclusion flows from the observation that prescription opioids are responsible for much of the increase in opioid use disorder over the last 20 years, and that these opioids are prescribed by licensed clinicians, and produced, distributed, and sold by licensed and regulated firms. This creates opportunities to counter diversion from appropriate medical use that were simply not relevant for heroin. These countermeasures include interventions with individual doctors (e.g., education coupled with behavior-change incentives), system-wide changes such as have been implemented by the VHA, and measures targeting drug manufacturers.

Not enough has been done on these fronts. Even after recent reductions in opioid prescribing, the U.S. per capita rate is still three times higher than in the 1990s and far beyond that of any other nation. The opioid industry still has broad latitude and a growing profile overseas. With the White House Council of Economic Advisers estimating the damage of the epidemic at \$500 billion annually, this lack of action is economically foolish as well as morally unconscionable. We can't undo the past, but we can protect the future. Implementing the policies described here will require political courage and a financial investment, but will be well worth it.

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