Health Care System Policies That Can Promote Safer Opioid Prescribing

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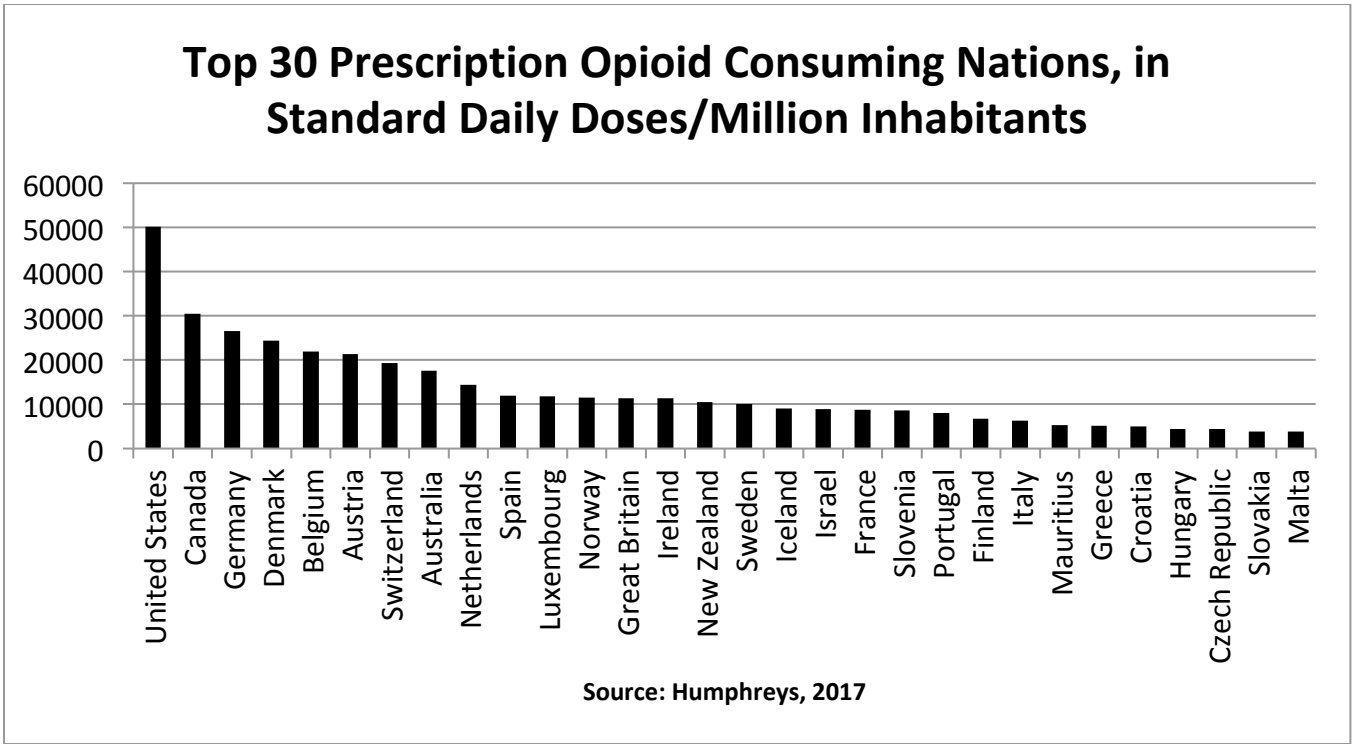
Beginning in the mid-1990s, U.S. opioid prescribing began rising at an unprecedented rate, nearly quadrupling in the next 15 years and bringing the U.S. to a per capita prescribing rate many times that of other developed countries (see Figure). For some individuals who otherwise would have endured untreated pain (e.g. after an injury or surgery), the expansion of opioid prescribing may have improved well-being. But in many cases opioid overprescribing led to ineffective pain relief, reduced function, opioid dependence, addiction, overdose, and/or death (Humphreys, 2017).



For this reason, many stakeholders have pursued efforts to make opioid prescribing safer. In most cases "safer" is taken to mean fewer opioid prescriptions or lower morphine milligram equivalents (MMEs) per patient. However, it can also mean prescribing opioids at the same level but in a less risky fashion (e.g., avoiding co-prescribing with benzodiazepines, monitoring high dose patients more closely, reducing diversion to non-patients).

LJAF has commissioned two reviews of efforts to promote prescribing that reduces the risk of harm and increases the likelihood of patient benefit. One review, currently underway and led by Corey Davis, J.D., focuses on state-level law and policies, for example those increasing availability of the overdose rescue drug naloxone and changing licensing regulations for pain clinics. The present review complements that legally-focused review by examining what health care system policies can do to promote safer opioid prescribing.

Specifically, this paper describes what health care system policies have been implemented and what evidence exists on their impact. Almost by definition policies touching one part of the health care system spill over into others, but for ease of presentation this paper organizes policies into five different foci: (1) Prescribers, (2) Patients, (3) Pharmacists, (4) Insurers, and (5) Pharmaceutical Industry. The paper then discusses how to evaluate iatrogenic policy effects across domains before closing with a summary of key themes.

(1) Prescriber-Focused Policies

Evidence-based prescriber education. Prescribers are bombarded with information about prescription drugs that is not necessarily scientific, most obviously from pharmaceutical industry promotion (e.g., sales staff visits to clinical offices, hired key opinion leaders speaking at continuing medical education events, advertising in journals, brochures handed out at conferences). Other potentially non-scientific information may be imparted through anecdotes by patients, colleagues and the media. As a counter-weight 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 various efforts to provide education that has a basis in past and emerging research.

One method for educating providers is to develop clinical practice guidelines. The most recent and high-profile guidelines for opioid prescribing were produced by The Centers for Disease Control and Prevention (Dowell, Haegerich & Chou, 2016). Their dissemination appears to have accelerated the recent decrease of opioid prescribing in the U.S. (Bohnert, Guy, & Losby, 2018).

Providers may also receive education in their medical school and residency training, at conference talks, at grands rounds in their hospital, and at continuing medical education courses, among other venues. Brennan and Mattick's (2013) comprehensive review of studies of provider education programs found that that most common effect identified on better prescribing was "moderate" with many studies finding no effect and in a few cases actually finding that prescribing became less safe (on this last point, the fact that at least some education programs have been covertly designed and funded by the pharmaceutical industry is worthy of consideration).

Franklin and colleagues (2012) for example found that issuing a guideline discouraging high-dose opioid prescribing within a workers' compensation program was followed by a 35% drop in the number of individuals receiving greater than 120 morphine-equivalent dose per day and a 50% decrease in deaths. However, this was not a randomized study and occurred in an environment of rising concern about opioids that may have contributed to the observed outcomes. In a more rigorous (and more

discouraging) study, Pimlott and colleagues' (2013) randomized trial with 374 physicians found that education and practice guidelines had no significant effect on risky prescribing of opioids or benzodiazepines.

Virtually everyone who works in or studies the health care system recognizes that patients rarely make a significant behavioral change solely based on information absent some incentives and supports for that change. Yet this lesson is often forgotten when we try to change prescriber behavior. The fact that education alone typically has only a modest effect (and sometimes no effect) on how clinicians prescribe should not really be that surprising.

Sometimes physicians agree with the contents of a new clinical practice guideline, but feel that they lack the skills to follow it or that the system in which they work will not allow them to do so (Cabana et al., 1999). Thus, as with patients, education may matter more when coupled with appropriate incentives and supports. Incentives can be positive (i.e., the prescriber gets something for changing) or negative (i.e., the prescriber loses something by not changing). Supports include education that provides new information in an interactive format, but can also include policies like implementing reimbursed time to learn and practice new prescribing skills, expanding coverage in the health care system of alternatives to opioids (e.g., physical therapy), and removing barriers (e.g., paperwork) to changed prescribing.

One incentive that seems to increase the impact of education is how the prescriber is perceived by peers or by organizational leadership. For example, dental professionals are substantially more likely to screen for substance use disorders when they perceive such interventions are valued components of their own professional roles (Parish, et al. 2015). Looking more at the negative incentive side, a Canadian study of 138 physicians taking a 2-day long 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 on the physician created by the College's referral may have provided a motivation to apply the lessons of the course.

More studies of prescriber education in the abstract are probably not a productive future research focus; rather the research opportunity is to find tailored incentives and supports that make prescribers more likely to apply the lessons that particular educational programs teach. System-change interventions are a good venue to explore these issues, as explained below.

System-change interventions. The above policies focus on individual prescribers and their beliefs, knowledge, and habits. Some interventions embrace the importance of the above but also attempt to more broadly disrupt the ecology of the health care system. Such efforts are not readily possible for independent practitioners, but can be undertaken in the various

self-contained, organized, health care systems such as Kaiser Permanente, the Veterans Health Administration and the like (see, e.g., Del Giorno et al., 2018; Saunders et al., 2015).

The Opioid Safety Initiative in the Veterans Health Administration is almost certainly the largest scale of such interventions in the U.S. and so is highlighted here to illustrate the possibilities of system-wide change. Education on safe prescribing was taken to a qualitatively different level by assigning almost 300 pharmacists to provide in-person instruction to VHA 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 as well as managers were given the computerized capability to easily monitor the prescription drug use history and risk profile of patients. In 2018 this was taken even further when VHA began to post its facility-level prescribing rates on the Internet for anyone to see.

VHA also became the first large health care system to dramatically expand provision of naloxone education and distribution, and to expand a range of 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 (30.9% to 36.7%), complementary/alternative medicine (2.2% to 3.3%), psychosocial therapy (40.0% to 44.9%) and specialty pain clinic care (9.8% to 11.9%) from 2010-11 to 2015-16 (Frank et al., 2018). Prescriptions for most but not all non-opioid medications also became more common for pain (Frank et al., 2018).

In the three years following the launch of the Opioid Safety Initiative in 2013, the number of patients prescribed an opioid each quarter had dropped by 25% and the number receiving high-dose opioids decreased by 36%. The number receiving the risky combination of opioids and benzodiazepines declined even more (47%). The program was implemented systemwide so there wasn't a no-intervention comparison condition against which to judge these decreases. At the same time, the changes in prescribing are so large that it seems unlikely that they occurred spontaneously.

The VHA Opioid Safety Initiative is like most effective system-change interventions in that it combined education with incentives ranging from "everyone on the team is working on this now and I want to be a part of it", to "the boss is paying attention and I don't want to be called out". The initiative also provided many supports for change including using new training procedures and hiring of new staff to give prescribers realistic options for patients in pain, including expanded physical therapy, cognitive-behavioral psychotherapy, and pain management psychoeducation.

Key policy evaluation questions are raised by system-change interventions. First, rather than throw everything against the wall and see

what sticks which has been a common approach in such efforts to date, is there a way for health care systems to know which specific elements of system change most strongly affect opioid prescribing and improve patient well-being? Similarly, when a system change intervention does not work, what element or elements are most likely to be the sticking point? These sorts of questions are important because for many systems an effort on the scale VHA can mount is out of reach and they thus have to focus on a subset of high-impact strategies.

The other key policy evaluation question is to determine the costs of system-change interventions. This does not just refer to financial cost, but also attentional cost in that when everyone in a health care system is focusing on one goal they are by definition not focusing on other areas of clinical care, for which performance could slip. Once these costs were specified by research, it would then be possible and desirable to evaluate the cost-effectiveness of system change initiatives.

Prescription Nudges in the Electronic Medical Record. A different, almost absurdly simple, way to change opioid prescribing does not require changing attitudes, mounting elaborate educational efforts, or championing system-wide reinvention. Rather, it relies on the human tendency to accept defaults when making many decisions. Manipulating choice architecture, often referred to as "nudging" can have substantial influence on prescribing at low cost.

For example, Chiu and colleagues (2018) changed the default number of post-surgical opioid pills in the electronic medical record from 30 to 12. Prescribers were under no constraints in their prescribing and therefore did not have to follow the default. Yet an extraordinary number of them did so, dropping the proportion of surgical procedures (n=2910) resulting in a prescription of 30 opioid pills from 39.7% to 12.8%. That the number of patients requesting refills did not change suggests that these lower doses were adequate for pain relief.

This was not an isolated demonstration of the power of nudges in medicine. Changing the University of Pennsylvania's health care system default from brand name to generic medications (again, with no constraints on what was prescribed) increased the proportion of prescriptions for generic medications by nearly a third (Patel et al., 2016). Defaults even influence decisions about extremely weighty matters, for example whether patients create advance directives that determine whether extraordinary measures are employed to save their lives in particular circumstances (Halpern et al., 2013).

The key policy evaluation now is whether nudges for opioid prescribing could be implemented in the most widely used electronic medical record systems (e.g., EPIC) in the country, with the goal of making an impact

nationwide rather than only on a single facility or network of facilities. Given the low cost and easy scalability of this approach, it should be a major policy evaluation priority, particularly if LJAF can identify an electronic medical record system producer with whom to partner. Such an evaluation would be particularly valuable if it could identify how patient care and well-being are affected by changes in opioid prescribing defaults.

Informing providers about opioid-related deaths. Sending a physician a letter informing them that their opioid prescribing is objectively higher than their peers and may be high risk does not seem to influence prescribing (Sacarny et al., 2016). However, one recent study has examined the effect of a potentially more potent letter-based intervention, and its results are sufficiently intriguing to merit mention here. In a randomized trial of 861 physicians, those who were provided a letter informing them that one of their patients had died of an overdose decreased their prescribing relative to physicians who were not aware of the patient's death (Doctor et al., 2018). In the subsequent three months, those who received the letter reduced their opioid prescribing by about 10%. This is an inexpensive, easily scalable intervention that could make a substantial difference in the health care system if the effects are generalizabile and non-transitory. But because many studies do not replicate, the first priority for research funders should be to evaluate this intervention in a different health care system than Doctor and colleagues studied, and, to extend the evaluation for a longer time period than three months and to other outcomes (e.g., patient well-being).

(2) Patient-focused policies

In one sense, there are no "patient-focused" health care system policies in that, while we can train, reward, license, mandate, pressure, and nudge people who work for the system, no one needs a license, training program or even the system's permission to become a patient. At the same time, there are several areas where well-conducted clinical trials have identified procedures administered to patients that reduce demand for and misuse of opioids. Any of these could be translated into health care system policies, i.e., by adopting as a standing practice across all patients the implementation of such procedures. Three areas stand out as the strongest candidates.

Self-tapering facilitation. Benzodiazepines are a different class of medication than opioids, but they are addictive and also increase significantly the likelihood that a patient taking opioids will overdose (Sun et al., 2017). It is therefore of note that multiple clinical trials have shown that minimal clinical consultation coupled with printed information (e.g., a booklet) describing the risks of benzodiazepines and encouraging patients to taper on their own leads to substantial reductions in use, whether this

outcome is defined as reducing the dose or stopping entirely (e.g., Bashir et al. 1994; Cormack et al. 1994; Tannenbaum, Martin & Tamblin, 2014). These interventions require little work from clinical staff, meaning they could be easily scalable as system-wide policies, for example having an integrated care system or insurance plan automatically mail a self-tapering guide to all patients who had been taking benzodiazepines for 12 months and also encourage them to seek an in-person consultation. In addition to evaluating the effects of such a policy, it would be useful to do the same for policies governing opioids, presuming currently ongoing trials of opioid self-tapering prove safe and effective.

Treatment contracts. When physicians suspect that a patient may be misusing opioids or could start doing so in the future, they may implement a treatment contract. A treatment contract lays out expectations such as patients not taking more opioids than prescribed, not selling them, and, not combining them with alcohol. Treatment contracts also typically include a provision that the patient agrees to submit to a blood or urine test if so requested by the prescriber. The treatment contract is explained to the patient and then both the prescriber and patient sign it.

In a systematic review, Starrels and colleagues (2010) identified 11 studies meeting a minimum methodological threshold. They were a combination of studies that evaluated the impact of contracts alone and contracts in combination with drug testing (e.g., urinalysis). The review concluded that contracts reduce opioid misuse in the range of 7-23% (Starrels et al. 2010). This is not a huge effect, particularly given that the research base includes no randomized trials, but it suggests that a useful policy research question would be whether adopting such contracts as standard practice in a healthcare system would have a favorable cost-benefit ratio for patients meeting a certain risk profile.

Preventive peri-operative management. There are about 50 million inpatient and 50 million outpatient surgeries in the U.S. each year, most of which result in an opioid prescription. One method of reducing post-surgical risk, discussed above, is to reduce opioid prescribing through nudges. Another is to manage the patient differently peri-operatively.

Some peri-operative procedures are psychological, for example relaxation training designed to ease the anxiety which can heighten the experience of pain and in turn the tendency to take opioids. But given the realities of the health care system, the most likely type of intervention to be broadly adopted is a pharmacologic one.

Many pharmacological agents have been tried, but most recently gabapentin had a positive outcome in a placebo-controlled randomized trial. Relative to controls, patients randomized to receive 4 doses of gabapentin in the 24 hours prior to surgery and 6 doses in the 48 hours after, continued

taking opioids after surgery for a 24% shorter length of time (Hah et al., 2018). The questions for policy research are first, whether this finding could be replicated in a different site, and second, if so, what would be the implications of routinizing it across broad swathes of U.S. surgical practice.

(3) Pharmacy-focused policies

Most interventions in the opioid prescribing arena focus on the patient or the prescriber, but there is a third point in the triangle of prescription medication access and use. The country's more than 250,000 pharmacists are an essential component of how controlled substances are dispensed. Also, practically speaking, pharmacists may in many cases have more knowledge about the specifics of a medication -- as well as more time to convey those specifics -- than do physicians.

Pharmacist counselling of patients. The typical method by which patients are intended to learn about the risks of opioids (e.g., the importance of taking them as directed, of avoiding alcohol consumption, adverse side effects) is via printed instructions included with the medication. Such instructions have no evidence of reducing the risks of misuse (Morris & Halperin 1979), which is unsurprising given that many patients do not look at them at all and those who do typically encounter complex text printed in a font size that is difficult for many patients to read.

However, the impact of risk and compliance information can be greatly enhanced by counselling from a pharmacist. For example, in a randomized trial of 178 patients being discharged from the hospital, those actively counselled by a pharmacist regarding their medication regime had a much lower rate of preventable adverse events (1% vs. 11% for controls, Schnipper et al. 2006). Other individual studies (e.g., Peveler et al. 1999) as well as systematic reviews of the literature (e.g., Roughead et al., 2005) provide evidence that pharmacist counselling increases compliance with the terms of the prescription. Not incidentally, Strand and colleagues (2018) have shown that pharmacists can learn how to screen patients for opioid-related problems and to respond accordingly, including providing naloxone or referring individuals to substance use disorder treatment.

The above evidence suggests a policy research question, namely how can the pharmacy system be incentivized to engage more broadly in patient screening and counseling regarding prescription opioids? Counselling patients takes time, and time is money within the health care system. Christensen and Farris (2006) point out that many pharmacists are under pressure to process a very large number of prescriptions each day, which lessens their ability to counsel patients. However, such counselling is more likely to occur when it is covered by insurance (Christensen and Farris 2006). This suggests that a cost-effectiveness study of pharmacist counseling about opioids would be useful as way to persuade insurers that

the costs of reimbursing it might be traded off by other savings (e.g., fewer adverse events and emergency admissions).

Requesting justification from extremely prolific prescribers. CVS Health identified 42 prolific prescribers who prescribed 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% of cases, the prolific prescriber either did not respond or gave implausible explanations, leading CVS to stop filling their scripts. There is a policy research opportunity to evaluate this strategy with other pharmacy chains, and perhaps as well to approach CVS about collaborating on a broader initiative given that their effort only touched less than a one hundredth of a percent of prescribers.

Engaging pharmacies in drug take-back programs. The billions of excess opioid pills that are prescribed each year and end up forgotten in Americans' medicine cabinets are a significant aggravator of the opioid epidemic (Bicket et al., 2017). To attempt to drain off this enormous reserve of pills, law enforcement agencies in recent years 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, and even were they all opioids it would still constitute only a small proportion of the known excess (Albert et al. 2011; Stewart et al. 2015).

Drug take back days can be analogized to the early days of bottle and newspaper recycling: special events organized by a motivated few that while useful only scratched the surface of the possible. The quantum leap in the scope of glass and paper recycling came when it became routinized as something everyone does every day without thinking. The key policy question today is can this same transformation happen for the return of excess opioids?

Congress has dramatically expanded the number of organizations that can be licensed to collect unused opioids 365 days a year. CVS Health has done the most to act on these new powers, but even it has only a small proportion of its outlets recycle. At other chains and other approved takeback sites (e.g., hospitals), adoption has been even slower. Nationally, only 2.5% of eligible sites operate take back programs (Government Accountability Office, 2017).

Two useful policy experiments would be to test what financial incentive (e.g. funding for the required secure storage box?) would be necessary to encourage more pharmacies to become take back sites. Relatedly, it would be valuable to determine what incentives would make more patients return their excess opioid pills. In the early days of bottle recycling, those who returned bottles received a nickel or dime in deposit paid at purchase (either by themselves or someone else). Eventually these incentives were no longer necessary once returning cans and bottles became routine for the

population. A useful policy study – potentially conducted in collaboration with a pharmacy chain or opioid manufacturer – would be to determine the impact of different sizes of financial incentive on willingness to return excess opioids. Longer term, the policy question would become whether this incentive could be phased out once returning excessive opioids became a normative behavior much as bottle and can recycling has become.

(4) Insurer-focused policies

Policies in this section are those that can be carried out via insurers in the private or public sector. Some but not all of the below policies could also be implemented by pharmacy benefit managers (Brennan et al., 2017).

Preferred drug lists. Preferred drug lists in some way harken back to the earlier discussion of nudges, although they are established mainly by payers and are sometimes intended to shape consumer behaviour directly rather than only affecting prescribers. Usually drugs are designated as preferred based on costs (e.g., a generic version that works as well as a brand name may be designated "preferred") but drugs can also be designated as preferred based on patient safety.

Methadone is an excellent medication for opiate agonist therapy for heroin addiction, but has a high-risk profile for use in chronic pain. In response, some Medicaid programs have classified methadone for pain as non-preferred. In one study, this change was associated with reduced methadone overdose deaths (Faul, Bohm, Alexander, 2017), presumably because prescribers shifted to preferred drugs with better safety profiles for pain patients. Modelling the impact of extending this practice nationally would be a useful service to policy makers.

Reimbursement benefit and design on opioids and alternatives. There is little doubt among policy analysts that features of the U.S. insurance system have contributed to the opioid epidemic. To take an obvious example, while a physician may have to fight with an insurer to secure coverage for an opioid-addicted patient to start buprenorphine maintenance treatment and also be wary of not hitting the cap for how many such patients s/he can treat, handing the same patient another prescription for OxyContin typically requires no advance insurer approval and can be done an infinite number of times because there is no comparable cap.

Lin and colleagues (2018) recently analysed insurance benefits in Medicaid, Medicare Advantage, and commercial insurance plans. Although their study was focused on low back pain-related benefits, it raises more general issues regarding what are likely the more broadly critical questions in benefit design.

Lin et al. (2018) noted that plans vary on the following dimensions: (a) Relative coverage of opioid vs non-opioid medication, (b) Relative

coverage of short vs. long-acting opioids, (c) Degree of imposition of quantitative or qualitative limits (e.g, prior approval, non-opioid "fail first") for opioids, (d) Degree of product tiering and patient cost-sharing for medications. This framework sets the stage well for the key policy research question: how do each of these policies individually and in combination affect opioid prescribing and outcomes in covered populations?

Reimbursement lock-in. Reimbursement lock-in is a different type of financial intervention which seeks to deter one low prevalence but high-risk pattern: "doctor shopping" for opioids. Many overdoses involve someone who has prescriptions from multiple prescribers (Hall et al., 2008). Payors can restrict a patient with many prescribers 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) was positive, including reduced doctor shopping, emergency room visits, and costs. North Carolina also showed a significant drop in prescribing in Medicaid, although some "locked-in" individuals switched to cash purchases outside of the Medicaid program (Roberts et al., 2016).

Medicare received authority to begin a reimbursement lock-in program in 2018, and there is currently active discussion between Congress and CMS regarding how broadly that program should operate and what the costs and benefits would be. An excellent short term policy research opportunity is to assemble all the evidence from states (much of which is unpublished or available only in internal reports) and provide evidence-based guidance on how Medicare should proceed. Given Medicare's more than 55 million enrollees and the certainty that doctor shopping for opioids occurs in the program, evidence-based policy in this domain is highly desirable.

(5) Pharmaceutical Industry-Focused Policies

Establishing constraints on industry product promotion. Purdue Pharma confessing in federal court in 2007 to criminal and civil liability for helping start the opioid epidemic validated what every thoughtful observer had long ago concluded: The explosion of opioid overprescribing would never have happened without the opioid manufacturers aggressively pushing their products, withholding information from regulators, and making donations to virtually every organization that would otherwise have been engaged in protecting patients (Lembke, 2016; Meier, 2018).

Any discussion of what policies might lessen opioid overprescribing thus must take on how the industry could be differently regulated. The question has only become more important with the ongoing class action against the industry in federal court, which could result in new constraints upon it just

as the tobacco master settlement forced alterations in the behavior of the tobacco industry.

One area for policy research is to evaluate prescribing practices in health care systems with different policies governing industry-prescriber interactions. Industry activities to persuade prescribers to use their products include gift-giving, in person "detailing" visits, funding of research, funding of continuing education programs, funding of patient advocacy groups (usually not acknowledged) that promote the use of opioids, and funding of professional societies and clinical practice guideline development groups. Although doctors tend to resist the idea that such promotion affects their behavior, much evidence suggests that it does (Brennan et al. 2006; Kassirer 2005, Wazana, 2000).

At least some health care systems (e.g., Stanford Medical School and Hospitals) have banned or severely curtailed such industry-prescriber interactions. A high impact policy research project would be to evaluate what happened to prescribing in such systems so that it could inform the federal court on whether such restrictions should be made universal in any settlement.

International comparative research would also be valuable regarding pharmaceutical advertising, which is ubiquitous on U.S. television but banned in all but one other developed country. This advertising does not include ads for opioids but does include "bank shot" ads (e.g., for laxatives designed to counter the constipation caused by opioids) and also may support more opioid prescribing by creating a general cultural expectation that patients should always demand pills from doctors for any problem they have. Documentation of such effects cross-culturally could support policies restricting pharmaceutical advertising, including ending the tax deduction for such marketing.

Expanding tamper-resistant/abuse-deterrent (TR/AD) opioid medication formulations. From the point of view of opioid manufacturers, the best response to the opioid crisis would be for prescribing to stay at its current high level while creating less risk of addiction and overdose. They have therefore invested heavily in tamper-resistant/abuse-deterrent (TR/AD) formulations of their products (Katz et al. 2007; Romach et al. 2013). TR/AD formulations change the design and/or composition of an opioid to make misusing it more difficult (e.g., crushing it for injection or inhalation).

For example, the drug marketed as 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 this feature seems to reduce if not eliminate misuse; this effect may be more pronounced when Suboxone is formulated as a film rather than as a pill (Comer et al., 2010; Lavonas et al., 2014).

Purdue Pharma released what they marketed as a TR/AD formulation of OxyContin in 2010. The street price of Oxycontin declined by about a third in response (Severtson, Ellis, Kurtz et al., 2016), indicating that opioid misusers (who obviously have relevant expertise) found it harder to snort/inject. At the same time, the price did not go to zero because the TR/AD protection is imperfect (see Bannwarth 2012; Becker & Fiellin, 2017; Cicero & Eillis, 2015; Lourenco et al. 2013). Data from poison control center calls, substance use disorder treatment admission, emergency room and mortality data 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). Note that although some of the positive studies of the TR/AD formulation were funded by Purdue Pharma, studies conducted by others have reached similar conclusions.

The introduction of the TR/AD OxyContin reformulation was also followed by smaller but still notable increases in prescriptions of some other non-TR/AD opioids (Dart et al. 2015). Also, some opioid-addicted individuals reacted to the TR/AD formulation of OxyContin by switching to heroin, exposing them to greater risk. Recent modelling work indicates that this effect is projected to make TR/AD reformulations lead to somewhat higher opioid-related mortality in the next 5 years, although after that point they 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).

Multiple policy research opportunities exist concerning TR/AD formulations. One priority is to examine how prescribers and patients (mis)understand them. It is likely than some patients as well as doctors believe incorrectly that one cannot get addicted to or misuse TR/AD formulations (Becker & Fiellin, 2017). Whether this creates a false sense of security that leads doctors to prescribe or patients to request opioids when they really shouldn't is important to evaluate, as such iatrogenic effects could counteract the potential benefits of new formulations.

Cost-effectiveness research should also be a priority. TR/AD formulations are significantly more expensive than older, non-TR/AD opioids. This means that even if they deliver some population health benefit, this could be cancelled out by economic costs, e.g., if Medicaid programs being required to purchase them leads to less funds being available for other services. Cost-effectiveness research on such questions could have a significant policy impact, particularly if the FDA moves towards requiring TR/AD formulations in for all prescription opioids.

Altering packaging. A different approach to creating physical barriers to misuse of opioid pills is to require changes in the container from which they are dispensed. Hospitals have long had automated dispensing machines

that reduce medication errors and diversion, but these are too large and expensive to be adopted in the homes of patients. However, a realistic alternative common in some countries is to dispense higher risk medications in blister packs rather than as bottles of pills.

A study of individuals who poisoned themselves with paracetamol found that those who had bottled pills were much more likely (69% vs. 40%) to have taken a potentially fatal dose than were individuals who had the medication in blister pack form (Hawton et al., 1996). FDA Administrator Gottlieb recently floated the idea of requiring blister packs for some opioid medications and Congress has incorporated this proposal into its current opioid-related legislative package.

Whether blister packs reduce opioid misuse or overdose is unknown at the moment, but there may be a policy research opportunity here. Specifically, it would useful for a funder to identify an opioid manufacturer and a health care system that were willing to experiment with blister packs for a designated period and evaluate whether they have systematic effects.

Conclusions

Potential iatrogenic effects of reducing opioid prescribing. Before summarizing key conclusions, it's worth mentioning an issue relevant to most of the policies and domains just discussed. Opioids are not particularly effective for chronic, non-cancer pain (Dowell, Haegerich & Chou, 2016) and indeed, for a subset of patients can increase pain sensitivity (Lembke, Humphreys & Newmark, 2016). That said, policies that reduce opioid prescribing almost certainly will cause at least some people in pain who would benefit from opioids to be denied them (Pitt et al., 2018). The extent of this adverse effect should be included in evaluations of the implementation of any of the foregoing policies.

Also worthy of study is the extent to which policy changes led some physicians to engage in harmful behaviour. These may include "firing patients" when they discover that patients have been misusing opioids, and, abruptly cutting off chronic pain patients from opioids because they feel – rightly or wrongly – policy pressure to reduce prescribing (Kertesz & Gordon, 2018). Forced, rapid tapering from prescription opioids could lead a patient to the black market to secure illicit opioids (e.g., heroin), exposing themselves to heightened risks. Careful weaning over time of patients from opioids is possible and generally results in improved function (Darnall et al., 2018; Lembke, Humphreys & Newmark, 2016; McPherson et al., 2018). Evaluating whether this sort of response versus a harmful physician response is more common is part of fully evaluating the effects of opioid prescribing reduction policies.

Finally, in thinking about iatrogenic effects, it is critical to distinguish impact on the stock (people already addicted to prescription opioids) and the

flow (people who could become addicted to prescription opioids in the future). Modelling work suggests that restrictions on opioids may cause some currently addicted individuals to switch from prescription opioids to heroin, which is more dangerous (Pitt et al. 2018). In the short term, this can mean that such policies do not save lives. But that should not be taken as a last word on such policies because with each passing year as more and more people who would have become addicted to prescription opioids don't actually do so, the number of lives saved can far exceed those lost in the early years of the policy's implementation (Pitt et al., 2018). This is also an argument for multi-modal policies, i.e., coupling restrictions on prescribing with expansions of addiction treatment that provide an option to prescription opioid addicted individuals other than transitioning to heroin use.

Where are the biggest policy research opportunities? There are clearly health care systems policies that can promote safer opioid prescribing and thereby reduce the prevalence of damage caused by overprescribing and risky prescribing. The evidence base just reviewed suggests different areas to prioritize for policy research in this area, with different potential impacts.

The impact of some potentially quite important policies (e.g., insurers limiting first fills of opioids for acute pain to a maximum three or seven day supply) has not been evaluated at all. This creates an opportunity to be a first mover, which is appealing because often the first study done of a new policy has an unusually high level of impact.

A different type of opportunity concerns intriguing findings from a single study, for example the trials showing that informing prescribers of a patient death reduce subsequent opioid prescribing, that extremely prolific prescribers can be identified and cut off from pharmacy access, and that peri-operative gabapentin reduces patient demand for opioids after surgery. These are tantalizing findings, but in the health and social sciences many tantalizing findings have not survived replication. The research opportunity is therefore conducting such replications to see which interventions are ready to be taken to the policy level and which are not.

Other policies have some evidence of effectiveness but there is a crucial piece missing from what research has learned about them to date. For example what are the critical elements of system change efforts regarding prescribing, what is the cost-effectiveness case for reimbursing pharmacists for counselling, and what financial incentives would be needed to increase the utilization of prescription drug take back programs? Supporting research on these "missing links" can help translate interventions with promising scientific evidence into compelling policy proposals ready for adoption.

Finally, there are other policies, for example using nudges in the electronic medical record, implementing self-tapering and consultation programs, and more broadly employing treatment contracts, that have been

validated in multiple settings by multiple teams and are "ready for prime time". The opportunity here is to mount them on a policy scale and evaluate their impact. In many cases, this will involve partnerships with outside organizations (e.g., pharmacy chains, electronic medical records system developers, hospitals), but such collaborations should be easily formed given the widespread concern in the country about the opioid epidemic.

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