Buprenorphine MAT as an Imperfect Fix

Brian Mund and Kate Stith

Introduction

Medical experts have aggressively pushed for the use of medication-assisted treatment ("MAT") — coined as the "the gold standard" for opioid addiction care — to combat the opioid crisis.[1] And rightly so: employing MATs with opioids like methadone and buprenorphine can play a critical and even necessary role in the recovery of many individuals suffering from opioid abuse disorder.[2] In particular, MAT advocates have propelled buprenorphine treatment into the limelight, identifying buprenorphine as both the safest treatment option and easily self-administrated.[3] As articulated by its most outspoken advocates, the idea is that if we eliminate cumbersome prescription regulations and take proactive steps to get buprenorphine into the hands of opioid users, then we can treat those afflicted with opioid use disorder: problem solved.[4]

In this article, we argue for a more balanced approach to expanding buprenorphine access in the United States, through evidence-based decision-making that considers both the drug's potential dangers and its potential benefits.[5] Advocacy groups such as the National Alliance of Advocates for Buprenorphine Treatment officially recognize that "[b]uprenorphine is not a cure nor a miracle medication, but a new and effective tool in fighting opioid addiction"; however, these groups have not devoted appropriate attention to buprenorphine's downsides.[6] According to Dr. Eric Wish, Director of the Center for Substance Abuse Research at the University of Maryland, "This is the first drug that nobody seems to want to know about as a potential problem."[7] The Food and Drug Administration (FDA), even as it has adopted a pro-MAT position,[8] has been criticized for its more cautious approach to MAT proliferation and buprenorphine access.[9]

The vigorous advocacy for treatment expansion has effectively caricatured buprenorphine to the layperson as a miracle drug. Intended or not, this kind of advocacy can lead to simplified or even false perceptions. Former Senator Carl Levin, for instance, described buprenorphine "as a miracle drug, bringing addicts back from the brink and helping them lead normal lives when all else had failed."[10] Others are left with the misimpression that buprenorphine "can't be abused."[11]

Brian Mund, J.D., *received his B.A. from the University of Pennsylvania and his J.D. from Yale Law School.* **Kate Stith, J.D.,** *is the Lafayette S. Foster Professor of Law at Yale Law School. She received her B.A. from Dartmouth College, and her M.P.P. and J.D. from Harvard University.*

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291. © 2018 The Author(s)
DOI: 10.1177/1073110518782935
https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

Methadone As a Cautionary Tale

The current MAT advocacy story echoes an earlier one. Several decades ago, methadone was hailed as a wonder drug, the solution to heroin addiction, when Drs. Vincent Doe and Marie Nyswander "intimated that they had discovered the 'magic bullet' because methadone allegedly provided a blockade to the effects of heroin."[12] In the early 1960s, America had been in the throes of a heroin epidemic and was seeking a solution.[13] Researchers had demonstrated that methadone — originally invented by German scientists during WWII[14] — lasted longer than other opiate treatments and lacked the "severe highs and lows" characteristic of heroin addiction.[15] As a result, researchers concluded that "methadone could act as a replacement for heroin."[16] From 1967 to 1970, the FDA liberally issued Investigational New Drug applications for methadone research, and by 1969, "several thousand patients were enrolled in methadone maintenance treatment research programs."[17] By early 1973, there were 73,000 people with opioid addiction receiving methadone maintenance treatment.[18] However, as one 1972 *Atlantic* article put it, "[M]ethadone is turning out to be no 'magic bullet.'"[19] While methadone was intended as an oral treatment, it could easily be injected to achieve a concentrated euphoric effect akin to heroin. It quickly became clear that many addicts use heroin and methadone (and other opioids) interchangeably."[20] As a result, Methadone Maintenance Therapy led to street diversion and misuse, with many resulting deaths.[21]

Table 1

Drug Abuse Warning Network Reports of National Heroin and Methadone Deaths[22] September 1972–December 1972

	Heroin		Methadone	
	No. of reports	%	No. of reports	%
September	643	85.5	93	14.5
October	683	76.7	159	23.3
November	667	64.6	236	35.4
December	552	62.1	209	37.9

In the end, this cycle resulted in seriously diminished access to methadone. In 1972, new FDA regulations created a closed system for methadone whereby only approved clinics and hospital pharmacies could prescribe methadone for maintenance treatment purposes.[23] Furthermore, the Narcotic Addict Treatment Act of 1974 gave the Drug Enforcement Agency ("DEA") jurisdiction over the drugs used in addiction treatment and required all physicians approved for methadone prescription to register with the DEA each year.[24] In practice, these regulations have resulted in a system where methadone maintenance treatment remains largely limited to clinic-based treatment with daily visits. Federal policies allow for take-home (unregulated) methadone doses, but these practices are subject to highly restrictive criteria.[25] Even if one meets these criteria, further restrictions establish maximum take-home doses based on the time that a patient has been in treatment.[26] Methadone has also been plagued with a series of other side effects and problems that have prevented widespread adoption.[27] While symptoms vary in intensity, patients have reported methadone side effects of "weight gain, weight loss, amenorrhea, acne, hoarseness, sweating, constipation, leg cramps, muscle spasms, hair loss, bladder infections, nervousness, arthritis, anxiety, memory loss, body aches, emotionality, nonemotionality, and lethargy."[28] Some patients describe methadone's side effects, "as severely discomforting, disabling, numbing and tiring," leaving a broad dysphoric impact on quality of life.[29]

Nevertheless, methadone is still available as maintenance treatment — and continues to be abused.[30] In 2014, methadone accounted for only 1% of all opioid prescriptions yet was involved in 22.9% of all opioid-related deaths.[31] That is not to say that methadone maintenance is fully responsible for deadly diversion; methadone is less regulated when prescribed for pain.[32] To take Vermont as an example, most methadone involved in fatal overdoses was obtained through illegal diversion, but of the prescribed methadone leading to death, 68% had received pain prescriptions and only 8% were on methadone maintenance therapy.[33]

There are reasons to think that buprenorphine, too, may not live up to the vaunted representations made-about it. "Least dangerous" does not necessarily mean "safe."[34] By describing some of the imperfections of buprenorphine, this paper seeks to promote a more comprehensive perspective on the risks associated with widespread reliance on prescribing buprenorphine to the opioid-using population. Armed with a realistic depiction of this efficacious yet flawed treatment, policymakers and regulators will be better positioned to determine the appropriate target populations for buprenorphine treatment, the best avenues for accessing this substance, and the appropriate prescription and review mechanisms to reduce misuse and undesired outcomes.

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)

https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

Risks Associated With Buprenorphine

Buprenorphine has proliferated as an opioid treatment in two formulations: Subutex (buprenorphine hydrochloride) and Suboxone (buprenorphine hydrochloride and naloxone hydrochloride).[35] Both forms (and their generic counterparts) are approved by the Food and Drug Administration for opioid treatment, and each is classified as a Schedule III drug under the Controlled Substances Act.[36] The FDA has also approved Zubsolv, a tablet medication with the same buprenorphine-to-naloxone ratio as Suboxone but with higher bioavailability, which allows for smaller dosing options. However, these differences are largely cosmetic — a faster disolve time and a preferable aftertaste during sublingual administration.[37] At present, physicians must participate in an eight-hour training course to obtain a waiver to prescribe buprenorphine and are limited to a maximum of 275 patients.[38] Physicians first receive a waiver to prescribe buprenorphine for up to 30 patients, then can apply a year later for permission to increase their buprenorphine limit to 100 patients. After one year at the 100-patient limit, physicians may apply for the increase to 275 patients.[39] Additionally, nurse practitioners and physician assistants may qualify for buprenorphine prescription waivers for up to 30 patients after completing 24 hours of training.[40] These strict buprenorphine prescription regulations have led to some significant access problems, as detailed elsewhere in this issue.[41] Nevertheless, "there has been a steady increase in buprenorphine's diffusion, particularly in office-based practice."[42]

Buprenorphine operates as a partial μ-opioid receptor agonist. As is true of full agonists such as heroin and methadone, the use of buprenorphine produces a euphoric "high" and induces respiratory depression.[43] Unlike full μ-agonists, however, the effects of buprenorphine do not increase in proportion to the amount ingested; buprenorphine's chemical profile limits its euphoric effect to the equivalent to 60 mg of methadone.[44] That is to say, this substance has an effective "ceiling." This ceiling works as a safety factor compared with full agonists; individuals are unlikely to overdose on buprenorphine when taken as properly prescribed.[45] Moreover, those engaged in buprenorphine abuse alone are very unlikely to overdose fatally.[46] Therefore, when compared with the overdose havoc caused by abuse of methadone, buprenorphine provides a safer option.

However, "safer" does not mean "abuse-proof." While the latter term has been implied by some advocates,[47] such a characterization is simply inaccurate. As the DEA has noted, "buprenorphine is capable of producing significant euphoria. Data from other countries indicate that buprenorphine has been abused by various routes of administration (sublingual, intranasal and injection) and has gained popularity as a heroin substitute and as a primary drug of abuse."[48] While mass use of the drug is relatively new to the United States, many countries around the world have already grappled with the challenges posed by buprenorphine proliferation — buprenorphine has been available as treatment in some countries since 1999.[49] In 2014, Michelle Lofwall and Sharon Walsh published a thorough examination of buprenorphine diversion and misuse around the world and concluded that "buprenorphine diversion and misuse appear to be common behaviors of opioid addicted individuals."[50] Lofwall and Walsh report buprenorphine diversion and misuse experiences in diverse countries such as France, Germany, Australia, Finland, and Malaysia and regard these as cautionary tales of buprenorphine injection and illicit use.[51]

A Substitute for Heroin?

There are several avenues for buprenorphine misuse. For those without opioid dependence, ingestion of buprenorphine tablets or filmstrips can provide euphoria.[52] In addition, buprenorphine tablets can be crushed and then injected, resulting in opioid euphoria and eventual dependence if use continues.[53] Indeed, in Finland, injected buprenorphine replaced heroin as the primary used street drug in 2002.[54] Suboxone filmstrips may be misused through sublingual ingestion or can be mixed with water and snorted.[55]

Buprenorphine advocates — including Reckitt-Benckiser, the pharmaceutical company that produces Suboxone and Subutex — have acknowledged the risk of buprenorphine abuse through injection.[56] The company has advertised Suboxone as less subject to abuse than Subutex because it contains naloxone in addition to buprenorphine.[57] Naloxone is an opioid antagonist.[58] If taken orally, naloxone alone has no effect,[59] but the dominant narrative touts the claim that if injected, naloxone binds with opioid receptors to induce unpleasant withdrawal symptoms, thereby deterring misuse through injection.[60]

Unfortunately, this claim is only partially true. Diversion surveillance reports provide evidence that the buprenorphine/naloxone combination is still employed for misuse purposes.[61] It turns out that, while naloxone is an excellent medication for blocking heroin, it is not very good for blocking buprenorphine. Buprenorphine's chemical properties result in a stronger binding to the μ-opioid receptors than do heroin's, and naloxone is not strong enough to effec-

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)
https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

tively block this interaction.[62] Therefore, Suboxone's chemical composition does not effectively deter the injection abuse of buprenorphine — especially among those who have previously used buprenorphine (rather than heroin) as their primary drug.[63] In Malaysia, buprenorphine "spread like wildfire" between 2004 and 2006, overtaking the heroin market and leading to widespread abuse.[64] The introduction of the buprenorphine/naloxone (Suboxone) combination in Malaysia reduced but did not stop the misuse of the drug.[65]

In several countries, buprenorphine has arisen as a major substitute for heroin and other full μ-agonists. For example, buprenorphine remains "the most commonly used illicit opioid in Finland"[66] and is the "most frequently misused non-heroin opioid" in the Czech Republic.[67] In India, researchers found buprenorphine to be second to heroin as the most commonly injected drug in the country.[68] Moreover, once buprenorphine misuse takes hold, it can be difficult to eradicate. As Finnish researchers found, "restrictions on the access of mono-buprenorphine and the lower street price of buprenorphine/naloxone did not significantly alter the illicit use of this drug [buprenorphine] over several years of its availability on the street."[69] In part, this reflects naloxone's inability and hence irrelevance for preventing abuse of buprenorphine by those without heroin dependence, making it especially risky for young, "gateway" users who initiate opioid use through buprenorphine.

In some countries, widespread availability of buprenorphine (by prescription or through diversion) risks attracting new, younger users and new cases of opioid addiction. As one report noted, "From a medical point of view, buprenorphine is a[n] effective drug in the treatment of opiate dependents, but has simultaneously proven to be a deepening problem among abusers and especially so among young ones."

Attracting Youth Abuse

In some countries, widespread availability of buprenorphine (by prescription or through diversion) risks attracting new, younger users and new cases of opioid addiction. As one report noted, "From a medical point of view, buprenorphine is a[n] effective drug in the treatment of opiate dependents, but has simultaneously proven to be a deepening problem among abusers and especially so among young ones."[70] Europe as a whole, however, has not seen a shift to youth adoption of buprenorphine misuse.[71] The European Monitoring Centre for Drugs and Drug Addiction report indicates that "buprenorphine misusers seem to differ from other opiate users in several respects: they are reported to be younger, enter treatment earlier, start injecting sooner, and inject more often."[72] Additionally, "Younger people are reported to use [buprenorphine] often as the primary drug of choice, whereas older users more often use buprenorphine as 'self-medication.'"[73] This suggests that younger people are more likely to view buprenorphine as an available avenue for recreational misuse — in contrast to those seeking to "self-medicate," usually heroin users seeking to stave off withdrawal symptoms.[74] For such individuals, Suboxone and Subutex do not act as treatments but instead present additional avenues to "get high." India provides a particularly jarring example, where many teenagers buy a "set" of daily injections "consisting of an ampule of Buprenorphine (semi-synthetic opioid), an ampule of Diazepam (Valium), an ampule of Avil (an antihistamine) and two disposable syringes ... sold for 50 rupees — a little less than $1."[75] Additionally, a 2010 study in India found "a predominance of buprenorphine injection among younger injectors."[76]

Buprenorphine's abuse potential might help explain why the introduction of buprenorphine as a treatment led to "lucrative black markets" in countries including Germany, New Zealand, and the United Kingdom during the mid-2000s.[77] In France, studies have linked relaxed prescribing regulations for buprenorphine to a thriving black market.[78] However, increased prescription monitoring in France helped reduce diversion without reducing access to treatment.[79] In sum, it is vital that those considering the increased proliferation of buprenorphine availability also be cognizant that widespread buprenorphine access might concomitantly be associated with a greater number of people misusing the drug, including becoming addicted to opioids.

Deadly Risk

Buprenorphine use can also turn deadly. It is true that buprenorphine's partial-μ agonist composition greatly

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)

https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

reduces the likelihood that misuse will result in a fatal overdose. The drug's "ceiling effect" means that after reaching a certain dosage level, the opioid effects level off despite further dose increases.[80] Unfortunately, buprenorphine's "safety ceiling" is neither an absolute rule nor immutable principle. By mixing buprenorphine with a benzodiazepine (such as Xanax, Valium, or Tranxene), users can "lift the plateau" for buprenorphine's chemical ceiling.[81] This technique both allows a greater euphoric high and creates a potentially lethal combination. For example, in 2014, Finland reported 75 cases of fatal overdoses where the toxicology report included buprenorphine,[82] with many of these cases involving the concomitant use of benzodiazepines.[83]

Moreover, the specific chemical nature of buprenorphine exacerbates this overdose risk. The partial μ-agonist nature of Suboxone and Subutex results in diminishing utility for users who have developed tolerance. In fact, because of the ceiling, neither can effectively treat those individuals who, if treated with methadone, would require more than 60 mg of that substance.[84] This limitation is significant because "[f]or most patients, a stable dose [of methadone] ranges from 80–120 mg per day."[85] Additionally, those in provisionally long-term buprenorphine treatment will also develop tolerance and will over time need more buprenorphine to obtain the same effects.[86] Thus, many individuals who struggle with opioid use disorder eventually require significantly larger doses than buprenorphine can provide. While "[t]olerance, a loss of analgesic potency, is one of the common complications of opioid treatment, leading to ever-increasing dose requirements and decreasing effectiveness over time," buprenorphine's ceiling prevents indefinite dose escalation.[87]

If such individuals obtain buprenorphine as part of their treatment regime, they may be unable to achieve the semblance of "feeling normal." Likewise, individuals who obtain illicit buprenorphine may find that it is inadequate, in whatever dose, to feel "normal," much less to achieve any desired "high." In both situations, the addicted individual may undertake a concerted effort to combine buprenorphine with benzodiazepines. The evidence shows that individuals caught in the throes of their opioid addiction pursue dangerous behavior in the quest to achieve the desired level of euphoria.[88] This same dangerous motivation has been attributed to the rise in fentanyl and even carfentanil-related deaths by (non-buprenorphine) opioid abusers seeking a more cost-effective and satisfying high.[89] The concern is that if buprenorphine availability becomes widespread, this may lead high-tolerance drug users to shift to the dangerous mix of buprenorphine and benzodiazepines or to street drugs such as heroin.

Alcohol use is also contra-indicated for buprenorphine users. While co-use of alcohol — also a CNS suppressant — does not pose the same degree of danger as co-use of benzodiazepines, it still significantly increases the risk of overdose morbidity and mortality.[90] Indeed, it has been reported that mixing alcohol with buprenorphine can lead to death even if a patient does not exceed the medically prescribed buprenorphine dosage.[91] Like other forms of misuse or abuse, the dangers from co-use of alcohol are not a problem specific to buprenorphine; polydrug users in general face an increased risk of death.[92]

Nevertheless, such a risk is especially relevant given the particular context of buprenorphine's benefits. One of the lauded advantages of buprenorphine over methadone is the ease and anonymity that buprenorphine medication allows.[93] Instead of being indefinitely on a regime of regular visits to a methadone clinic to receive treatment, buprenorphine is a "take-home" medication that patients pick up from a local pharmacy and self-administer.[94] In addition, because buprenorphine does not require regular trips to an opioid clinic, it also provides for greater privacy.[95] An individual can live a normal life while privately medicating with buprenorphine.[96] Within this context, alcohol creates complications. First, buprenorphine can prove a much less effective form of MAT for those suffering from alcoholism, which poses a significant problem given the frequent coexistence of alcoholism and opiate dependence.[97] Second, the contra-indication of alcohol use may pose a significant constraint in many social contexts. Additionally, prescription warnings for Subutex and Suboxone suggest that this constraint goes beyond mere social discomfort. The danger of alcohol is sufficiently extreme to warrant the need for individuals to check their food and medicine labels to ensure that their products do not contain alcohol.[98] Even small amounts of alcohol consumption alongside buprenorphine can result in impairment of judgment, extreme lethargy, and unconsciousness.[99]

Serious Side Effects

Even when used properly, buprenorphine brings a multitude of side effects that may deter widespread patient adoption of this evidence-based treatment. As with other opioids, common side effects include nausea, vomiting, constipation, muscle aches and cramps, cravings, the inability to sleep, distress and irritability, and fever.[100] Buprenorphine treatments very commonly bring the risk of psychiatric side effects,[101] including rare but severe cases of psychosis.[102] While these risks are not unique to buprenorphine, the exceptionally high rate of concurrent mental health disorders among opioid abusers means that

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)
https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

treatment in the form of opioid maintenance imposes added pressures on an already vulnerable population.[103] Buprenorphine can also have adverse effects on motor skills and liver function, though to a lesser degree than methadone.[104] Respiratory depression is likewise a concern.[105]

We must also consider that buprenorphine, even as medication, carries the risk of addiction.[106] While the benefits of treating severe opioid abuse certainly outweigh the costs of medication-assisted treatment, long-term buprenorphine users will go into withdrawal if, for whatever reason, they find themselves without access to the drug. Such withdrawal would encourage patients to seek buprenorphine, methadone, or heroin through illicit channels in an attempt to self-medicate.

Growing youth adoption is a particularly poignant concern should buprenorphine proliferate in the United States. The experience in Finland shows that buprenorphine can serve as a gateway opioid. A ubiquitous buprenorphine presence could well present American teenagers with a readily accessible, euphoria-inducing substance.

Buprenorphine, like other opioids, may be especially contraindicated for pregnant women, because it can affect fetal development and its withdrawal leads to significant distress for newborn infants.[107]

Remarkably, however, the National Alliance of Advocates for Buprenorphine Treatment (the major advocacy group funded by producers of the substance) lists only headache, constipation, and dry mouth as common side effects; the many downsides discussed above remain largely absent.[108] Such a picture elides the evidence that buprenorphine may not present the right treatment option, or deliver better results than methadone treatment, for many users. In one comparison of methadone and buprenorphine, the trials showed that "[b]uprenorphine did not differ from methadone in its ability to suppress heroin use, but retained approximately 10% fewer patients."[109] In sum, buprenorphine treatment provides an effective weapon for combating the opioid epidemic, but optimal utilization requires risk management based on a clear-eyed understanding of buprenorphine's boons and banes.

Policy Considerations for the United States

The Risk of Large-Scale Diversion

Increasing access also increases the likelihood of diversion. Many of the problems with buprenorphine in Europe and Malaysia would be amplified with large-scale prescription availability in the United States. As experts repeatedly reminded the authors, the United States is very different from most other countries in the causes, nature, and severity of its opioid crisis. America's size and intolerance for pain makes this national crisis *sui generis*. An estimated 80 percent of the world's opioid supply is consumed in the United States.[110] The United States also already has the highest global percentage of opioid abuse,[111] the highest percentage of deaths from opioid abuse,[112] and by far the largest stock of opioid substance users under treatment.[113] Twenty percent of Americans (61.8 million Americans) legally obtained at least one opioid prescription, for pain or opioid maintenance, in 2016.[114] To concretize the scale of this epidemic: SAMHSA estimates 626,000 Americans have experienced heroin dependence or abuse in 2016 alone.[115] Eleven and a half million Americans misused prescription pain relievers.[116] Of those, at least 1.8 million Americans have a diagnosed pain reliever use disorder.[117] Undeniably, an effort to use buprenorphine to treat all those with substance use disorders would require the proliferation of millions of pills.

Growing youth adoption is a particularly poignant concern should buprenorphine proliferate in the United States. The experience in Finland shows that buprenorphine can serve as a gateway opioid. A ubiquitous buprenorphine presence could well present American teenagers with a readily accessible, euphoria-inducing substance. In York Beach, Maine, one convicted Suboxone dealer noted that "Every kid on the beach was looking for [Suboxone], ... The high lasts all day."[118] Given buprenorphine's addictive nature, these "kids" could quickly find it impossible to stop. And once buprenorphine addiction takes hold, withdrawing its supply jeopardizes recreating the OxyContin pathway: from prescription painkiller to heroin.[119] Moreover, buprenorphine users may not appreciate the risks of misuse. As one user reflected on the death of his friend: "I didn't know you could overdose on Suboxone ... We were just a bunch of friends getting high and hanging out, doing what 20-year-olds do. Then we went to sleep, and Miles never woke up."[120]

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)

https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

Downplaying the medication's limitations and its diversion and misuse potential is counterproductive to shaping a thoughtful, informed discussion over the appropriate buprenorphine policy for the United States. To reduce the risk of a significant growth in the opioid dependent population and other adverse consequences, any increase in buprenorphine distribution should be carefully administered and continuously evaluated.

Current Buprenorphine Misuse in the United States

Preliminary reports show that even with strict buprenorphine regulation, the United States has already seen some buprenorphine misuse. A 2011 report of buprenorphine use leading to drug-related emergency department visits shows relatively modest misuse compared to heroin and other opioids such as methadone, oxycodone, and morphine.[121] Still, misused buprenorphine grew explosively (2,242%) from 2004 through 2009.[122] SAMHSA estimated that 712,000 buprenorphine products (defined as "Suboxone, generic buprenorphine, generic buprenorphine plus naloxone, or other similar products") were misused in 2016.[123] Many anecdotes confirm that the American public has experienced buprenorphine misuse. In 2013, the New York Times reported "a seemingly unstoppable flow of Suboxone onto the streets" of Portland, Maine.[124] In Southwest Kansas, treatment providers found themselves disenchanted with buprenorphine as "a vast number of patients attempt[ed] to abuse the medication like they would a traditional opiate."[125] In Vermont, locals report, "You can buy buprenorphine outside Rite Aid."[126] Of even greater concern, reports suggest that some users have employed buprenorphine in a potentially lethal combination with benzodiazepines.[127]

Buprenorphine has also emerged as a drug of choice in many United States prisons.[128] One former New York State prisoner reports, "[T]he prison yards of America are now full of inmates high on [buprenorphine]."[129] Illustrative of its powerful euphoric effect, a single strip or pill of buprenorphine is "way too much for a prisoner" with a relatively "clean" system.[130] Instead, prisoners will use one-eighth of a pill or strip for euphoria.[131] This misuse has become so pervasive that the New York Department of Corrections needed to add an additional urinalysis test for buprenorphine.[132] In Vermont, buprenorphine accounted for half of all illicit substances in the state's correctional facilities in 2012.[133] In Maryland, the "staggering" number of intercepted Suboxone doses (over 2,300 "hits" in six months) led the state to remove Suboxone from Maryland's list of preferred drugs.[134]

Buprenorphine MAT May Facilitate Addiction But Not Indefinite Treatment

An important outstanding question surrounds the goal of buprenorphine MAT. Some see buprenorphine MAT as an interim phase, with the strategy of tapering the dose to a goal of eventual abstinence.[135] There has been some clinical evidence published on the efficacy of this abstinence-oriented approach. One study finds that tapering over four weeks works more effectively than shorter tapering durations,[136] while another suggests that many experience opioid recovery without the use of any FDA-approved medications.[137] However, many experts see buprenorphine MAT as an indefinite treatment[138] and advise against tapering with a goal of detoxification.[139] "There is a high risk for relapse, even if maintenance has been stable for a while, when medication assisted treatment is discontinued."[140] In other words, tapering buprenorphine doses to eventual abstinence may not be an advisable option. One study goes so far as to argue that tapering with buprenorphine — whether initially or after a period of substantial improvement — leads to nearly universal relapse in people dependent on prescription opioids.[141] One educational website funded by the National Institute on Drug Abuse suggests that physicians should frame buprenorphine MAT treatment as "parallel to medication for a chronic condition" in order to explain the need for indefinite maintenance.[142] Such an approach compares opioid use disorder to conditions such as hypertension or diabetes. This analogy may be incomplete. Buprenorphine's tolerance and ceiling effect, explored previously in this article, at least complicate — and may vitiate — its use as a long-term option.

Of course, the right treatment approach will depend on the specific case. For many individuals, complete abstinence may be the ideal outcome, but abstinence can be an unreasonable goal for long-term opioid abusers. One former opioid user with whom one of us spoke, who does not want to be identified, was offered the opportunity of MAT treatment and declined it. He explained (paraphrasing), "I had only been using for a year or so and had consciously tried to avoid becoming too tolerant. I hoped my brain wasn't completely hard-wired. And I just didn't want to be dependent on opioids for the rest of my life. There are so many downsides." In short, buprenorphine MAT does not provide the clear best-treatment option in every circumstance.

Self-Treatment or Misuse?

Policymakers must also consider the extent to which increasing prescriptions for buprenorphine may lead to an increase in misuse or abuse of the drug. Even under current regulations, some patients use their MAT-prescriptions to barter for heroin: "Suboxone is

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)
https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

plentiful because it is prescribed, so [drug addicts] get their monthly allotment of several dozen doses, pay with a Medicaid card, and sell it off at five dollars a pill or strip to buy a real bag of dope."[143]

With buprenorphine, moreover, the distinction between treatment and enabling can often blur. Many buprenorphine advocates downplay the risk of buprenorphine misuse by claiming that when buprenorphine is purchased on the street, it is used for self-medication, not euphoria. For example, a recent piece in *Health Affairs* contends that "most people addicted to opiates appear to be purchasing illicit, 'street' buprenorphine not for a euphoric effect, but instead as a form of self-treatment."[144] As the argument goes, the reason for this illegal self-care is because the buprenorphine restrictions prevent those with opioid use disorder from receiving medical treatment: "Most [people] who take "street bupe" aren't after a high, they are tired of chasing pills or heroin, and they are self-medicating with illegally obtained bupe because they can't get medical care."[145]

The reality is more complicated, however, because self-treatment and euphoria-seeking use are not mutually exclusive. As Lofwall and Walsh report,

> Much attention has been given to misuse for reasons that mimic the medical reasons for which the medication is prescribed. These latter reasons should not be used to legitimize IV misuse of diverted medication because many persons addicted to illicit substances (e.g., heroin) will similarly report use of heroin to prevent or treat their withdrawal/to feel "normal," and there is clear morbidity and mortality associated with IVDU. There are no data showing that IV self-medication with buprenorphine is effective treatment. [146]

Fortunately, recent developments offer the possibility of technological solutions to some of the diversion and misuse concerns. In 2016, the FDA approved Probuphine, a subdermal six-month surgical implant.[147] In November 2017, the FDA approved the much less invasive Sublocade.[148] Sublocade consists of a monthly injection. Careful administration of these newer formulations might greatly reduce the risk of buprenorphine diversion and misuse.[149]

Buprenorphine MAT Requires More Than Buprenorphine

Finally, policymakers considering measures to increase access to prescribed buprenorphine must act with the understanding that, in order to be an effective treatment, MAT needs to be accompanied by additional interventions — which may well be more costly than is the provision of buprenorphine itself. Just as successful diabetes treatment requires behavior changes as well as medicine,[150] so does MAT for opioid use disorder. Dispensing buprenorphine unaccompanied by behavioral or psycho-social therapies would be unfair, even cruel, to those patients who, due to increased tolerance and the limitations of the medication itself, are at risk of relapse to illicitly obtained opioids.[151]

Conclusion: Moving Forward With Informed Policies

Current buprenorphine restrictions might not provide the optimal balance. But the dangers of buprenorphine expansion militate in favor of well thought-out, measured steps to increase access as well as ongoing evidence-based evaluation of the consequences of each stage of increased access. On the basis of what we now know about buprenorphine, we do not see the case for abandoning all prescription limitations and physician training. Our concerns include but also extend beyond the risks of diversion and abuse. Without careful physician training, negligent provision will assuredly lead some users to combine their prescriptions with benzodiazepines or alcohol, leading to fatalities among the very population that the doctors are trying to help. In a recent policy statement, FDA Commissioner Scott Gottlieb candidly addressed the balance between access and control: "[T]he [FDA] is also reinforcing that MAT should not necessarily be denied to patients taking [benzodiazepines]. The dangers associated with failing to treat an opioid use disorder can outweigh the risks of co-prescribing buprenorphine MAT and benzodiazepines. Instead, careful management of the patient and coordination of care is recommended."[152] In other words, there are circumstances where the patient's need for buprenorphine provision outweighs associated risks. These circumstances include buprenorphine use in short-term tapering and treating less severe cases. However, smart decisions require drug policies based on a thorough understanding of the reality of this medicine, not the miracle substance we all wish we had.

Note

The authors have no conflicts to disclose

Acknowledgements

The authors thank Dr. Marek Chawarski, Associate Professor of Psychiatry and of Emergency Medicine at the Yale School of Medicine; Dr. Alessandro Pirona, Principal Scientific Analyst at the European Monitoring Centre for Drugs and Drug Addiction; and Dr. Elina Kotovirta, Ministerial Adviser at the Government of

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)

https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

Finland's Ministry of Social Affairs and Health, for lending their thoughtful insights and scientific expertise to this project.

References

1. G. Lopez, "There's a Highly Successful Treatment for Opioid Addiction. But Stigma is Holding it Back," *Vox*, July 20, 2017, *available at* <https://www.vox.com/science-and-health/2017/7/20/15937896/medication-assisted-treatment-methadone-buprenorphine-naltrexone> (last visited April 13, 2018).
2. M. Pierce et al. "Impact of Treatment for Opioid Dependence on Fatal Drug-Related Poisoning: A National Cohort Study in England," *Addiction* 111, no. 2 (2016): 298–308.
3. *See* Lopez, *supra* note 1.
4. *See e.g.* "It's Time for the U.S. to Decriminalize Drug Use and Possession," *Drug Policy Alliance* 2017): 1-38, at 12, *available at* <http://www.drugpolicy.org/sites/default/files/documents/Drug-Policy-Alliance-Time-to-Decriminalize-Report-July-2017.pdf> (last visited April 13, 2018).
5. *See e.g.* F. Schulte and D. Donovan, "The 'Bupe' Fix," *Baltimore Sun*, December 16, 2007, *available at* <http://www.baltimoresun.com/bal-te.bupe16dec16-story.html> (last visited April 13, 2018) ("Though he described Suboxone as a 'good drug' for treating addicts, [RADARS executive director Richard] Dart said that buprenorphine enthusiasts tend to minimize abuse.")
6. "About Us," *The National Alliance of Advocates for Buprenorphine Treatment*, *available at* <https://www.naabt.org/about_us.cfm> (last visited April 13, 2018).
7. D. Sontag, "Addiction Treatment With a Dark Side," *New York Times*, November 16, 2013, *available at* <http://www.nytimes.com/2013/11/17/health/in-demand-in-clinics-and-on-the-street-bupe-can-be-savior-or-menace.html> (last visited April 13, 2018).
8. "Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's Continued Efforts to Promote the Safe Adoption of Medication-Assisted Treatment for Opioid addiction," *U.S. Food and Drug Administration*, September, 20, 2017, at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm576752.htm> (last visited April 13, 2018) (committing to "promoting more widespread, safe adoption of MAT as a way to help more people overcome addiction.")
9. *See e.g.* M. Szalavitz, "*What Trump's National Opioid Emergency Should Look Like*," *Vice*, August 14, 2017, at <https://www.vice.com/en_us/article/qvv8nw/what-trumps-national-opioid-emergency-should-look-like> (last visited April 13, 2018); M. Rigg, "FDA Commissioner Scott Gottlieb Goes to Bat For Evidence-Based Opioid Policies," *Reason: Hit & Run Blog*, October 27, 2017, *available at* <http://reason.com/blog/2017/10/27/fda-commissioner-scott-gottlieb-goes-to> (last visited April 13, 2018).
10. Senator Levin, speaking on S231, 109th Congress, 1st Session, *Congressional Record* 151 (Jan. 24, 2005): S231-S232; *see also* Sontag, *supra* note 7.
11. *See e.g.* "Fighting Back: The Way Out," *Highlands Current*, October 13, 2017, *available at* <http://highlandscurrent.com/2017/10/13/fighting-back-the-way-out> (last visited April 13, 2018).
12. H. Abadinsky, *Drug Use and Abuse: A Comprehensive Introduction* (Boston: Cengage Learning, 2017): at 205.
13. J. H. Jaffe and C. O'Keeffe, "From Morphine Clinics to Buprenorphine: Regulating opioid agonist treatment of addiction in the United States," *Drug and Alcohol Dependence* 70, no. 2 supplement (2003): S3-S11, at S4; H. Joseph, S. Stancliff, and J. Langrod, "Methadone Maintenance Treatment (MMT): A Review of Historical and Clinical Issues," *Mount Sinai Journal of Medicine* 67, no. 5-6 (2000): 347-365, at 348.
14. S. Quinones, *Dreamland: The True Tale of America's Opiate Epidemic* (New York: Bloomsbury Books, 2015): at 63.
15. *Id.* at 78.
16. *Id.*
17. Jaffe and O'Keefe, *supra* note 13 at S4.
18. Adabinsky, *supra* note 12.
19. J. Vorenberg, "The War on Crime: The First Five Years," *Atlantic*, May 1972, *available at* <https://www.theatlantic.com/past/docs/politics/crime/crimewar.htm> (last visited April 13, 2018). *See also* Adabinsky, *supra* note 12.
20. Vorenberg *supra* note 19.
21. Institute of Medicine, *Federal Regulation of Methadone Treatment*, (Washington, DC: The National Academies Press, 1995): at 95, *available at* <https://doi.org/10.17226/4899> (last visited April 13, 2018).
22. *Id.*
23. Jaffe and O'Keefe *supra* note 13 at S5.
24. *Id.*
25. *See* Center for Substance Abuse Treatment, *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs*, (Rockville, MD), Substance Abuse and Mental Health Services Administration (US), (2005): at 78, *available at* <https://www.ncbi.nlm.nih.gov/books/NBK64152> (last visited April 13, 2018).
26. *Id.* See also 42 C.F.R., § 8.12 (2015).
27. *See e.g.* M. Rosenbaum and S. Murphy, "Not the Picture of Health: Women on Methadone," *Journal of Psychoactive Drugs* 19, no. 2 (1987): 217-226, at 217.
28. *Id.*
29. B. Fischer, J. Rehm, G. Kim, and M. Kirst, "Eyes Wide Shut? – A Conceptual and Empirical Critique of Methadone Maintenance Treatment," *European Addiction Research* 11, no. 1 (2005): 1-14, at 4.
30. See L. Manchikanti, "Prescription Drug Abuse: What is Being Done to Address this New Drug Epidemic? Testimony Before the Subcommittee on Criminal Justice, Drug Policy and Human Resources," *Health Policy Review* 9, no. 4 (2006): 287-321, at 287, 300; *see also* M. Madden and S. Shapiro, "The Methadone Epidemic: Methadone-Related Deaths on the Rise in Vermont," *American Journal of Forensic Medicine* 32, no. 2 (2011): 131-135, at 134.
31. M. Faul, M. Bohm, and C. Alexander, "Methadone Prescribing and Overdose and the Association with Medicaid Preferred Drug List Policies — United States, 2007–2014," *Morbidity and Mortality Weekly Report 2017* 66, no. 12 (2017): 320–323, *available at* <http://dx.doi.org/10.15585/mmwr.mm6612a2> (last visited April 13, 2018).
32. Institute of Medicine, *supra* note 21 at 10.
33. Madden and Shapiro, *supra* note 30.
34. See I. K. Khanna and S. Pillarisetti, "Buprenorphine – an Attractive Opioid with Underutilized Potential in Treatment of Chronic Pain," *Journal of Pain Research* 8 (2015): 859–870, 864, *available at* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4675640> (last visited April 13, 2018).
35. "Buprenorphine Drug Label," *U.S. Food & Drug Admin.* (2002), *available at* <https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM191529.pdf> (last visited April 13, 2018).
36. *Id.*
37. K. A. Lyseng-Williamson, "Buprenorphine/Naloxone Sublingual Tablet (Zubsolv®): A Guide to its use in the Maintenance Treatment of Opioid Dependence in the USA," *Drugs & Therapy Perspectives* 29, no. 11 (2013): 336-341.
38. "Buprenorphine Training for Physicians," *Substance Abuse and Mental Health Services Administration*, July 7, 2016, *available at* <https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training> (last visited April 13, 2018).
39. *Id.*
40. 21 U.S.C. § 823 (2018); *Qualify for Nurse Practitioners (NPs) and Physician Assistants (PAs) Waiver*, Substance Abuse and Mental Health Services Administration, January 18, 2018, *available at* <https://www.samhsa.gov/programs-campaigns/

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)

https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

medication-assisted-treatment/training-materials-resources/qualify-np-pa-waivers> (last visited April 13, 2018).
41. See N. Guevremont, M. Barnes, and C. Haupt, "Physician Autonomy and the Opioid Crisis," *The Journal of Law, Medicine & Ethics* 46, no. 2 (2018): 203-219.
42. H. K. Knudsen, J. R. Havens, M. R. Lofwall, J. L. Studts, and S. L. Walsh, "Buprenorphine Physician Supply: Relationship with State-Level Prescription Opioid Mortality," *Drug and Alcohol Dependence* 173 (2017): S55-S64, at S56, *available at* <https://doi.org/10.1016/j.drugalcdep.2016.08.642> (last visited April 13, 2018).
43. "Buprenorphine," *Substance Abuse and Mental Health Services Administration*, May 31, 2016, *available at* <https://www.samhsa.gov/medication-assisted-treatment/treatment/buprenorphine> (last visited April 13, 2018).
44. S. L. Walsh, K. L. Preston, M. L. Stitzer, E. J. Cone, and G. E. Bigelow, "Clinical Pharmacology of Buprenorphine: Ceiling Effects at High Doses." *Clinical Pharmacology & Therapeutics* 55**,** no. 5 (1994): 569–580, at 579.
45. "The Facts About Buprenorphine for Treatment of Opioid Addiction," *Substance Abuse and Mental Health Services Administration* (2011), *available at* <https://store.samhsa.gov/shin/content/SMA09-4442/SMA09-4442.pdf> (last visited April 17, 2018).
46. "Buprenorphine," *Substance Abuse and Mental Health Services Administration*, May 31, 2016, *available at* <https://www.samhsa.gov/medication-assisted-treatment/treatment/buprenorphine> (last visited April 17, 2018); *see also* "Annual Report 2005," *European Monitoring Centre for Drugs and Drug Addiction* (2005), at 42, *available at* <http://www.emcdda.europa.eu/system/files/publications/365/sel2005_3-en_69710.pdf_en> (last visited April 17, 2018).
47. See *supra* notes 4-9.
48. "Buprenorphine," *U.S. Drug Enforcement Administration* (2013) *available at* <https://www.deadiversion.usdoj.gov/drug_chem_info/buprenorphine.pdf> (last visited April 17, 2018).
49. "United Kingdom: Country Report 2017," *European Monitoring Centre for Drugs and Drug Addiction* (2017), at 13 *available at* <http://www.emcdda.europa.eu/system/files/publications/4529/TD0116925ENN.pdf_en>(last visited April 17, 2018).
50. M.R. Lofwall and S. Walsh, "A Review of Buprenorphine Diversion and Misuse: The Current Evidence Base and Experiences from Around the World," *Journal of Addictive Medicine* 8**,** no. 5 (2014): 315-326, at 322.
51. *Id*. *See also* J. Ahmadi, K. Ahmadi, and J. Ohaeri, "Controlled, Randomized Trial in Maintenance Treatment of Intravenous Buprenorphine Dependence with Naltrexone, Methadone or Buprenorphine: A Novel Study," *European Journal of Clinical Investigation* 33**,** no. 9 (2003): 824–829, at 825.
52. See Sontag, *supra* note 7.
53. A. Nigam et al., "Naloxone-Induced Withdrawal in Patients with Buprenorphine Dependence," *Addiction* 89**,** no. 3 (1994): 317-320, at 317-318; Ahmadi, Ahmadi and Ohaeri, *supra* note 51, at 824; *Substance Abuse and Mental Health Services Administration*, *supra* note 45.
54. H. Uosukainen et al., "Twelve-Year Trend in Treatment Seeking for Buprenorphine Abuse in Finland," *Drug and Alcohol Dependence* 127**,** no. 1-3 (2013) 207-214, at 210-211.
55. D. Genis, "This Anti-Heroin Drug Is Now King of the Jailhouse Drug Trade," *Daily Beast*, July 17, 2014, *available at* <https://www.thedailybeast.com/this-anti-heroin-drug-is-now-king-of-the-jailhouse-drug-trade> (last visited April 17, 2018).
56. Reckitt Benckiser Pharmaceuticals Inc., "Safety Concerns Regarding Buprenorphine For Opioid Dependence," September 25, 2012, at 5 *available at* <https://www.naabt.org/documents/Reckitt_Benckiser_Pharmaceuticals_Inc_2012_FDA_Citizen_Petition.pdf> (last visited April 17, 2018).
57. Food and Drug Administration, "Sublingual Tablets, Equivalent 2 Milligrams Base and Equivalent 8 Milligrams Base, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness," 80 Federal Register 8088 (2015), *available at* <https://www.federalregister.gov/documents/2015/02/13/2015-03001/determination-that-subutex-buprenorphine-hydrochloride-sublingual-tablets-equivalent-2-milligrams>; see also Reckitt Benckiser, *supra* note 56.
58. "Naloxone," *Substance Abuse and Mental Health Services Administration*, March 3, 2016, *available at* <https://www.samhsa.gov/medication-assisted-treatment/treatment/naloxone> (last visited April 17, 2018).
59. See *Substance Abuse and Mental Health Services Administration, supra* note 46.
60. *Id*. *See also* K. Simojoki, H. Vorma, and H. Alho, "A Retrospective Evaluation of Patients Switched from Buprenorphine (Subutex) to the Buprenorphine/Naloxone Combination (Suboxone)," *Substance Abuse Treatment, Prevention & Policy* (2008): 3-16, at 3; "Suboxone — INN Buprenorphine/Naloxone," *European Medicines Agency* (2011) at 4, *available at* <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000697/WC500058505.pdf> (last visited April 17, 2018); *Substance Abuse and Mental Health Services Administration*, *supra* note 45, at 4; D. Jacobs, "I'm a Doctor who wants to Treat Addiction, but the Rules won't Let Me," *Washington Post*, January 14, 2017, *available at* <https://www.washingtonpost.com/national/health-science/im-a-doctor-who-wants-to-treat-addiction-but-the-rules-wont-let-me/2017/01/13/faaa6ee4-d2b0-11e6-9cb0-54ab630851e8_story.html> (last visited April 17, 2018).
61. Lofwall and Walsh, *supra* note 50.
62. *See* B. Vicknasingam, M. Mazlanb, R. S. Schottenfeld, and M.C. Chawarski, "Injection of Buprenorphine and Buprenorphine/Naloxone Tablets in Malaysia," *Drug and Alcohol Dependence* 111**,** no. 1-2 (2010): 44–49; at 45; H. Alho, D. Sinclair, E. Vuori, and A. Holopainen, "Abuse Liability of Buprenorphine–Naloxone Tablets in Untreated IV Drug Users," *Drug and Alcohol Dependence* 88**,** no. 1 (2007): 75–78, at 77.
63. *See* Vicknasingam, Mazlanb, Schottenfeld, and Chawarski *supra* note 62.
64. Dr. Marek Chawarski (Associate Professor of Psychiatry and of Emergency Medicine, Yale School of Medicine), interview with author**,** October 26, 2017; *Id* at 44.
65. *See* Vicknasingam, Mazlanb, Schottenfeld, and Chawarski *supra* note 62.
66. K. Simojoki and H. Alho, "A Five-Year Follow-up of Buprenorphine Abuse Potential," *Journal of Alcohol and Drug Dependence* 1**,** no. 2 (2013): 1-6, at 1, *available at* <https://www.omicsonline.org/open-access/a-five-year-follow-up-of-buprenorphine-abuse-potential-2329-6488.1000111.php?aid=11701> (last visited May 25, 2018).
67. "European Drug Report: Trends and Developments," *European Monitoring Centre for Drugs and Drug Addiction* (2016), at 49 *available at* <http://www.emcdda.europa.eu/system/files/publications/2637/TDAT16001ENN.pdf> (last visited April 17, 2018).
68. M. A. Yokell, N. D. Zaller, T. C. Green, and J. D. Rich, "Buprenorphine and Buprenorphine/Naloxone Diversion, Misuse, and Illicit Use: An International Review," *Current Drug Abuse Reviews* 4**,** no. 1 (2011): 28–41, at 33 *available at* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3154701> (last visited April 17, 2018).
69. Simojoki and Alho, *supra* note 66.

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)

https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

70. A. Partanen and J. Mäki, "Buprenorphine More Common as a Problem Drug in Finland," *Nordisk Alkohol- & Narkotikatidskrift* 21 (2004): 156-161, at 159, *available at* <http://journals.sagepub.com/doi/pdf/10.1177/14550725040210 1s17> (last visited May 25, 2018).
71. A. Pirona, B. Guarita, L. Montanari, and A. Noor, "Ageing and Addiction: Challenges for Treatment Systems," *European Monitoring Centre for Drugs and Drug Addiction*, *available at* <http://www.emcdda.europa.eu/system/files/publications/3435/05_LXAddictions_AP_ageing_FINAL.pdf> (last accessed Jan. 14, 2018).
72. See *European Monitoring Centre for Drugs and Drug Addiction, supra* note 46.
73. *Id.*
74. S. T. Williams, "What's it Really like to Withdraw from Heroin and Painkillers?" *MinnPost*, February 14, 2014, *available at* <https://www.minnpost.com/mental-health-addiction/2014/02/whats-it-really-withdraw-heroin-and-painkillers> (last visited April 18, 2018).
75. J. Fite, "Musings: 'India's New Drug Subculture,'" *National Geographic*, November, 18, 2013, *available at* <http://proof.nationalgeographic.com/2013/11/18/musings-indias-new-drug-subculture> (last visited April 18, 2018).
76. See S. S. Solomon et al., "The Profile of Injection Drug Users in Chennai, India: Identification of Risk Behaviours and Implications for Interventions," *Substance Use & Misuse* 45, no. 3 (2010): 354–367, *available at* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924430> (last visited April 18, 2018).
77. "Intelligence Bulletin: Buprenorphine: Potential for Abuse," *National Drug Intelligence Center* September 2004, *available at* <https://www.justice.gov/archive/ndic/pubs10/10123/index.htm> (last visited April 18, 2018).
78. A. Casati, R. Sedefov, and T. Pfeiffer-Gerschel, "Misuse of Medicines in the European Union: A Systematic Review of the Literature," *European Addiction Research* 18 (2012): 228–245, at 241.
79. *Id.*
80. See *Substance Abuse and Mental Health Services Administration, supra* note 46
81. Vicknasingam, Mazlanb, Schottenfeld, and Chawarski *supra* note 62 at 47.
82. See *European Monitoring Centre for Drugs and Drug Addiction, supra* note 67, at 67.
83. *European Monitoring Centre for Drugs and Drug Addiction*, *supra* note 46, at 42-43.
84. Walsh, Preston, Stitzer, Cone, and Bigelow, *supra* note 44 at 579.
85. A. J. Saxon, H. Yih-Ing, G. Woody, and W. Ling, "Medication-Assisted Treatment for Opioid Addiction: Methadone and Buprenorphine," *Journal Food Drug Analysis* 2, no. 4 (2014): S69–S72, at S70.
86. T. R. Kosten and T. P. George, "The Neurobiology of Opioid Dependence: Implications for Treatment," *Science & Practice Perspectives* 1, no. 1 (2002): 13–20, at 15, *available at* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2851054> (last visited April 18, 2018).
87. *See e.g.* R. Benyamin, A. M. Trescot, and S. Datta, "Opioid Complications and Side Effects," *Pain Physician* 11, no. 2, supp (2008): S105-S120, at S115, *available at* <http://www.thblack.com/links/RSD/PainPhysician2008_11_S105_complications%26side-effects.pdf> (last visited April 18, 2018).
88. K. Q. Seelye, "Heroin Epidemic Is Yielding to a Deadlier Cousin: Fentanyl," *New York Times*, March 25, 2016, *available at* <https://www.nytimes.com/2016/03/26/us/heroin-fentanyl.html> (last visited April 18, 2018); *see also* S. Birr, "Heroin Addicts Are Seeking Out Fatal Batches To Score The 'Most Potent Dose,'" *Daily Caller*, April 5, 2017, *available at* <http://dailycaller.com/2017/04/05/heroin-addicts-are-seeking-out-fatal-batches-to-score-the-most-potent-dose> (last visited April 18, 2018).
89. Seelye, *supra* note 88.
90. *European Monitoring Centre for Drugs and Drug Addiction*, *supra* note 46, at 48.
91. O. Ferrant et al., "Fatal Poisoning Due to Snorting Buprenorphine and Alcohol Consumption," *Forensic Science International* 204, no. 1-3 (2011): e8-e11, at e10.
92. R. L. Collins, P. L. Ellickson, and R. M. Bell, "Simultaneous Polydrug Use Among Teens: Prevalence And Predictors," *Journal of Substance Abuse* 10, no. 3 (1999): 233-253, at 233-234.
93. J. Cherkis, "Dying To Be Free," *Huffington Post*, January 28, 2015, *available at* <http://projects.huffingtonpost.com/dying-to-be-free-heroin-treatment> (last visited April 18, 2018).
94. *Id.*
95. S. Harris, "To Be Free and Normal: Addiction, Governance, and the Therapeutics of Buprenorphine," *Medical Anthropology Quarterly* 29, no. 4 (2015): 512–530, at 521.
96. *Id.*, see also Genis, *supra* note 55.
97. P. Cushman, Jr., "Alcohol and Opioids: Possible Interactions of Clinical Importance," *Advances Alcohol & Substance Abuse* 6, no. 3 (1987): 33-46, at 41.
98. "Suboxone Label," *U.S. Food and Drug Administration*, (December 2011) at 19, *available at* <https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020733s007s008lbl.pdf> (last visited April 18, 2018).
99. *Id.* at 4.
100. *Substance Abuse and Mental Health Services Administration*, *supra* note 46.
101. "Suboxone (buprenorphine HCl and naloxone HCl dehydrate sublingual tablets) and Subutex (buprenorphine HCl sublingual tablets)," *US Food and Drug Administration, available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM191529.pdf> (last visited April 18, 2018).
102. S. Varma, S. Balachander, and D. Basu, "Buprenorphine-Induced Psychotic Symptoms: A Case Report," *The Primary Care Companion for CNS Disorders* 15, no. 4 (2013).
103. *See* "Co-occurring Disorders," *Substance Abuse and Mental Health Services Administration*, March 8, 2016, *available at* <https://www.samhsa.gov/disorders/co-occurring> (last visited April 18, 2018), Center for Substance Abuse Treatment, *supra* note 25 at Chapter 12; R. K. Brooner, V. L. King, M. Kidorf, C. W. Schmidt, and G. E. Bigelow, "Psychiatric and Substance Use Comorbidity Among Treatment-Seeking Opioid Abusers," *Archives of General Psychiatry* 54, no. 1 (1997): 71–80, at 71.
104. *European Monitoring Centre for Drugs and Drug Addiction*, *supra* note 46, at 38; M. Soyka, B. Hock, S. Kagerer et al., "Less Impairment on one Portion of a Driving-Relevant Psychomotor Battery in Buprenorphine-Maintained than in Methadone Maintained Patients," *Journal of Clinical Psychopharmacology* 25, no. 5 (2005): 490-493, at 493.
105. *See e.g.* Benyamin, Trescot, and Datta, *supra* note 87 at S115.
106. *See* discussion *supra* at note 53.
107. J. D. Allen, M. J. Casavant, H. A. Spiller et al., "Prescription Opioid Exposures Among Children and Adolescents in the United States: 2000–2015," *Pediatrics* 139, no. 4 (2017): 1-10, *available at* <http://pediatrics.aappublications.org/content/early/2017/03/16/peds.2016-3382> (last visited April 18, 2018); C. Konijnenberg and A. Melinder, "Prenatal Exposure to Methadone and Buprenorphine: A Review of the Potential Effects on Cognitive Development," *Child Neuropsychology* 17, no. 5 (2011): 495–519.
108. "Common Buprenorphine Side Effects," *The National Alliance of Advocates for Buprenorphine Treatment*, *available*

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)
https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

at <https://www.naabt.org/buprenorphine-side-effects.cfm> (last visited Jan. 12, 2018).
109. R. P. Mattick, R. Ali, and J. M. White, "Buprenorphine versus Methadone Maintenance Therapy: A Randomized Double-Blind Trial with 405 Opioid-Dependent Patients," *Addiction* 98, no. 4 (2003): 441–452, at 441.
110. D. Gusovsky, "Americans Consume Vast Majority of the World's Opioids," *CNBC*, April 27, 2016, *available at* <https://www.cnbc.com/2016/04/27/americans-consume-almost-all-of-the-global-opioid-supply.html> (last visited April 18, 2018); G. Lopez, "America Leads the World in Drug Overdose Deaths—by a Lot," *Vox*, June 28, 2017, *available at* <https://www.vox.com/policy-and-politics/2017/6/28/15881246/drug-overdose-deaths-world> (last visited April 18, 2018).
111. "World Drug Report 2016," *United Nations Office on Drugs and Crime*, 2016, *available at* <https://www.unodc.org/wdr2016/interactive-map.html> (last visited April 18, 2018).
112. J. Katz, "Short Answers to Hard Questions About the Opioid Crisis," *New York Times*, August 10, 2017, *available at* <https://www.nytimes.com/interactive/2017/08/03/upshot/opioid-drug-overdose-epidemic.html> (last visited April 18, 2018); Lopez, *supra* note 110.
113. United Nations Office on Drugs and Crime, *Word Drug Report*, (United Nations publication, Sales No. E.16.XI.7), at 8, *available at* <https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf> (last visited April 18, 2018).
114. CDC, "Rate of Patients with at Least one Opioid Prescription in the U.S. 2014 to 2016 (per 100 persons)," *Statista - The Statistics Portal*, *available at* <https://www.statista.com/statistics/752053/total-patient-rate-with-at-least-one-opioid-prescription-in-us> (last accessed January 22, 2018); CDC, "Number of patients with at least one opioid prescription in the U.S. 2016, by age," *Statistica*, *available at* <https://www.statista.com/statistics/753093/total-patient-number-with-at-least-one-opioid-prescription-in-us-by-age> (accessed Jan. 22, 2018).
115. SAMHSA, "Number of Individuals with a Heroin Dependence or Abuse During the Past Year in the United States from 2002 to 2016 (in 1,000)," *Statistica*, *available at* <https://www.statista.com/statistics/476276/number-of-individulas-with-a-heroin-dependence-us> (accessed Jan. 16, 2018).
116. P. Tice, "Key Substance Use and Mental Health Indicators in the United States: Results from the 2016 National Survey on Drug Use and Health," *Substance Abuse and Mental Health Administration*, September 2017, at 21, *available at* <https://store.samhsa.gov/shin/content/SMA17-5044/SMA17-5044.pdf> (last visited April 18, 2018).
117. *Id* at 29.
118. Sontag, *supra* at note 7.
119. *See e.g.* R. A. Pollini et al., "Problematic Use of Prescription-Type Opioids prior to Heroin Use among Young Heroin Injectors," *Substance Abuse and Rehabilitation* 2, no. 1 (2011): 173–180, at 174, *available at* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3536052> (last visited April 18, 2018); *See also* D. Leinwand Leger, "OxyContin a Gateway to Heroin for Upper-Income Addicts," *USA Today*, April 15, 2016, *available at* <https://www.usatoday.com/story/news/nation/2013/04/15/heroin-crackdown-oxycodone-hydrocodone/1963123> (last visited April 18, 2018).
120. Sontag, *supra* at note 7.
121. J. C. Maxwell, "The Prescription Drug Epidemic in the United States: A Perfect Storm." *Drug & Alcohol Review* 30, no. 3 (2011): 264-270, at 267.
122. *Id.*
123. Tice, *supra* note 116 at 31.
124. Sontag, *supra* at note 7.
125. M. Minton, "Southwest Kansas treatment providers targeting opioid addiction," *Garden City Telegram*, October 29, 2017, *available at* <http://www.gctelegram.com/news/20171029/southwest-kansas-treatment-providers-targeting-opioid-addiction> (last visited April 18, 2018).
126. L. Kranz, "Special Report: State Spends Millions on Addiction-Fighting Drug that is Diverted for Street Sale," *VT Digger*, February 11, 2014, *available at* <https://vtdigger.org/2014/02/11/special-report-state-spends-millions-addiction-fighting-drug-diverted-street-sale> (last visited April 18, 2018).
127. *Id.*
128. See J. A. Moleski, "Jeanette Ann Moleski, D.O.: Options matter in the Opioid Crisis," *Akron Beacon Journal*, November 8, 2017, *available at* <https://www.ohio.com/akron/editorial/commentary/jeanette-ann-moleski-d-o-options-matter-in-the-opioid-crisis> (last visited Apri l18, 2018).
129. Genis *supra* note 55.
130. *Id.*
131. *Id.*
132. *Id.*
133. Kranz, *supra* note 126.
134. A. Kodjak, "Maryland Switches Opioid Treatments, And Some Patients Cry Foul," *NPR*, July 19, 2016, *available at* <https://www.npr.org/sections/health-shots/2016/07/19/486419277/maryland-switches-opioid-treatments-and-some-patients-cry-foul> (last visited April 18, 2018).
135. W. Ling et al., "Buprenorphine Tapering Schedule and Illicit Opioid Use," *Addiction* 104, no. 2 (2009): 256–265, at 257.
136. S. C. Sigmon et al., "A Randomized, Double-Blind Evaluation of Buprenorphine Taper Duration in Primary Prescription Opioid Abusers," *JAMA Psychiatry* 70, no. 12 (2013): 1347–1354, at 1351.
137. J. F. Kelly et al., "Prevalence and Pathways of Recovery from Drug and Alcohol Problems in the United States Population: Implications for Practice, Research, and Policy," *Drug and Alcohol Dependence* 181 (2017): 162-169, at 168, *available at* <https://doi.org/10.1016/j.drugalcdep.2017.09.028> (last visited April 18, 2018).
138. D. A. Fiellin, J. A. Renner Jr., "Tapering Buprenorphine in Patients with Opioid Use Disorders," *PCSS-O*, September 15, 2015, *available at* <https://pcss-o.org/event/tapering-buprenorphine-in-patients-with-opioid-use-disorders> (last accessed Feb. 6, 2018).
139. *Id;* "Tapering and Discontinuation of Patients from Buprenorphine," *Buppractice*, *available at* <https://www.buppractice.com/node/12121> (last accessed Jan. 15, 2018); see also R. D. Blondell et al., "A Clinical Trial Comparing Tapering Doses of Buprenorphine With Steady Doses for Chronic Pain and Coexistent Opioid Addiction," *Journal of Addictive Medicine* 4, no. 3 (2010): 140-146, at 140.
140. *Buppractice, supra* note 139. *See also* P. P. Cassadonte, "Transfer from Methadone to Buprenorphine," *PCSS*, August 9, 2006, at 3, *available at* <http://naabt.org/documents/PCSS_Meth-bupe-transfer.pdf> (last visited April 18, 2018).
141. "Publications and Research," *Substance Abuse and Mental Health Services Administration*, September 25, 2015, *available at* <https://www.samhsa.gov/medication-assisted-treatment/training-resources/publications> (last visited April 18, 2018).
142. *Buppractice, supra* note 139.
143. Genis *supra* note 55.
144. *See e.g.*, K. Chaiyachati, and J. Hom, "Let's Put Opioids For Treating Addiction On Equal Footing With Prescribing Opioids For Pain," *Health Affairs*, May 10, 2016, *available at* <http://www.healthaffairs.org/do/10.1377/hblog20160510.054813/full> (last visited April 18, 2018).
145. See Kranz, *supra* note 126.
146. Lofwall and Walsh, *supra* note 50 at 318.
147. "FDA Approves First Buprenorphine Implant for Treatment of Opioid Dependence," *U.S. Food and Drug Administration*, May 26, 2016, *available at* <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503719.htm> (last visited April 18, 2018).
148. "FDA Approves First Once-Monthly Buprenorphine Injection, a Medication-Assisted Treatment Option for Opioid use Disorder," *U.S. Food and Drug Administration*, November 30, 2017, *available at* <https://www.fda.gov/NewsEvents/News-

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)

https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press

room/PressAnnouncements/ucm587312.htm> (last visited April 18, 2018).
149. *Id.*
150. "Physical Activity is Important," *American Diabetes Association*, December 27, 2016, *available at* <http://www.diabetes.org/food-and-fitness/fitness/physical-activity-is-important.html> (last visited April 18, 2018).
151. Interview with Dr. Chawarski, *supra* note 64; *see also* A. I. Leshner, "Science-Based Views of Drug Addiction and Its Treatment," *JAMA* 282, no. 14 (1999): 1314-1316, at 1316. But see K. M. Carroll and R. Weiss, "The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review," *American Journal of Psychiatry* 174, no. 8 (2017): 738-747, at 745, available at <https://www.ncbi.nlm.nih.gov/pubmed/27978771> (last visited April 18, 2018).
152. "Statement from FDA Commissioner Scott Gottlieb," *supra* note 8.

The Journal of Law, Medicine & Ethics, 46 (2018): 279-291 © 2018 The Author(s)
https://doi.org/10.1177/1073110518782935 Published online by Cambridge University Press