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by Benjamin Grin, MD

Abstract

Opioid use disorder (OUD) represents a growing public health crisis in Missouri and nationwide. Reversing the trend of rising OUD-associated morbidity and mortality will require implementing evidence-based approaches grounded in public health principles. Key evidence-based interventions include medications for opioid use disorder, naloxone distribution, overdose education, and syringe services programs. The increasing presence of fentanyl and xylazine in the drug supply represent new challenges to the OUD crisis in Missouri. Optimal implementation of evidence-based interventions will require action at the individual physician, community, and state policy level.

Introduction

Opioid use disorder and its associated morbidity and mortality represent a growing public health crisis, both in Missouri and nationally. In Missouri in 2022, 2,178 individuals lost their lives to a drug overdose. Among those overdose deaths, 72% involved opioids and 67% specifically involved fentanyl. The number of deaths from opioid overdose has climbed each of the last 4 years in the state. At a national level, annual opioid overdose deaths now far exceed annual deaths from HIV at the peak of the AIDS epidemic in the mid-1990s.

Opioid use disorder is a pattern of opioid use that leads to physical, mental, social and legal problems. It is a treatable chronic medical condition characterized by episodes of remission and recurrence.

The recent history of the opioid epidemic in the United States can be described in four major phases, or waves. The first wave in the 1990s was largely driven by availability of prescription opioid medications in response to a push to increase prescribing of these medications for chronic pain. The dynamic of the epidemic shifted around 2010 at which time there were increasing rates of overdose from heroin. The third wave started soon thereafter in the mid-2010s, and was characterized by rising

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mortality from fentanyl, a highly potent synthetic opioid that has increasingly become part of the illicit heroin supply in the United States. We are now in the fourth wave of the epidemic. This most recent wave is characterized by increasing mortality from fentanyl, rising rates of polysubstance use including methamphetamine, and the addition of other constituents to the fentanyl supply including xylazine.6

An Evidence-Based, Public Health-Oriented Approach to Opioid Use Disorder

Reversing the trend of escalating morbidity and mortality related to OUD in Missouri will require optimal implementation of evidence-based approaches that have shown empirical success in reducing harm from opioid use. This includes medications for opioid use disorder (MOUD) like methadone and buprenorphine, along with harm reduction approaches such as naloxone and syringe services programs. This focus on evidence-based approaches with strong outcomes data should be combined with analysis of the problem through a public health lens. A public health approach to addressing the OUD crisis considers not only individual biomedical and psychosocial treatment approaches, but also what is needed to address this health challenge at a community and population level. Such an approach requires consideration of the broader socio-economic factors and policy landscape that may either accelerate or impede progress in addressing the OUD crisis.

Role of Medications for Opioid Use Disorder

The standard of care for treatment of patients with opioid use disorder is medication therapy. There are currently three FDA-approved medications to treat opioid use disorder: methadone, buprenorphine, and naltrexone. These medications have been shown to increase retention in treatment, reduce ongoing opioid use, and reduce the harms associated with opioid use disorder.7 Methadone and buprenorphine are considered first-line and have been associated with reductions in both all-cause and cause-specific mortality. A meta-analysis of 138,716 people treated for OUD with methadone or buprenorphine demonstrated reductions of all-cause mortality from 36.1 to 11.3 per 1,000 person/years with methadone and a reduction from 9.5 to 4.3 per 1,000 person/years with buprenorphine, compared with individuals with OUD not receiving these medications.8 In fact, the data to support medication treatment for opioid use disorder is as strong or stronger than many medications routinely prescribed in outpatient primary care. A recent cohort study showed that the number needed to treat (NNT) with buprenorphine to prevent one death in the year after an overdose was 52.6.9 By comparison, the NNT for statins used as primary prevention to prevent a composite of adverse cardiovascular outcomes in asymptomatic patients is 78.10

The goals of medication treatment for opioid use disorder include managing symptoms of withdrawal (sometimes referred to as “detoxification”), preventing complications of OUD, and helping people maintain long-term recovery from OUD.4 Given that OUD is a chronic medical condition characterized by periods of remission and recurrence, MOUD is intended to be utilized as an ongoing treatment aimed at reducing opioid use and its associated harms. Despite strong evidence supporting medication treatment beyond the period of opioid withdrawal, many addiction treatment facilities provide medications only during the period of opioid withdrawal (“detoxification”), or provide psychosocial treatments only. Studies of medications for opioid withdrawal management not followed by ongoing pharmacotherapy have shown that more than 80% of patients return to illicit or non-prescribed opioid use.7

Behavioral treatments such as counseling and peer support can be valuable adjuncts to medication therapy; however, these treatments have not demonstrated effectiveness as standalone treatments for OUD. A large comparative effectiveness study comparing six treatment pathways for OUD (no treatment, inpatient detoxification, intensive behavioral health, non-intensive behavioral health, buprenorphine or methadone, and naltrexone) showed that only methadone and buprenorphine were significantly
associated with reductions in overdose and opioid-related acute care.\textsuperscript{11}

Methadone is a long-acting full opioid agonist that reduces opioid withdrawal symptoms and cravings. Patients in opioid withdrawal can begin methadone immediately without any washout period.\textsuperscript{4} In the US, methadone can only be prescribed for OUD through federally-regulated opioid treatment programs (OTPs). These highly structured treatment programs require patients to present in-person up to six days a week for medication administration.\textsuperscript{12} Although this treatment structure may benefit some patients, it may present a barrier to care for others with OUD who are unable to access in-person care at this frequency. Furthermore, the requirement that methadone only be administered for OUD treatment at federally regulated OTPs may inequitably limit access in rural areas,\textsuperscript{13} a challenge that may significantly affect access in Missouri.

Buprenorphine is a partial mu-opioid receptor agonist that reduces opioid withdrawal symptoms and reduces cravings for opioids. As a partial agonist, it has a lower overdose risk given that its maximal effect is lower than full agonists like methadone. A unique feature of buprenorphine is that it may cause precipitated withdrawal from opioids, due to its strong affinity for the mu opioid receptor. For this reason, patients need to be in mild to moderate withdrawal at the time of buprenorphine initiation.\textsuperscript{4,6} One advantage of buprenorphine for patients with opioid use disorder has been its availability in office-based settings outside of highly structured OTPs. Until 2023, office-based buprenorphine treatment was limited by the Drug Addiction Treatment Act (DATA 2000), requiring physicians to obtain a special “X waiver” to their DEA license to prescribe buprenorphine outside of an OTP. The X waiver included a requirement for physicians to complete eight hours of training, additional documentation requirements for patients on buprenorphine, along with caps on the number of patients a prescriber could simultaneously treat with buprenorphine. Recent federal legislation eliminated the X waiver effective January 12, 2023, removing one important barrier to outpatient MOUD. With this change, any prescriber with a general DEA license to prescribe schedule III controlled substances can now also prescribe buprenorphine.\textsuperscript{14} This legislative change presents a valuable opportunity to increase patient access to MOUD in Missouri.

**Role of Harm Reduction**

Patients with opioid use disorder may present to health care settings at varied levels of readiness to make behavioral changes. For some, abstinence from all non-prescribed substances may be a realistic and attainable goal. For others, reducing use, preventing acquisition of HIV and/or Hepatitis C, and/or preventing fatal overdose may be the most appropriate immediate goals. This situation is similar with other chronic diseases like hypertension and diabetes. For example, although complete abstinence from all sugar-sweetened beverages be ideal for managing type 2 diabetes, this approach is not realistic for all patients. In spite of this reality, many addiction treatment programs continue to herald abstinence from all non-prescribed substances as the only appropriate treatment goal.\textsuperscript{15} A myopic focus on abstinence excludes many individuals who would greatly benefit from tailored addiction treatment, but for whom abstinence is not the most appropriate treatment goal.

Harm reduction is one evidence-based approach to addiction care that can help physicians provide care tailored to the needs of each individual patient. Harm reduction “refers to interventions aimed at reducing the negative health effects of behaviors without necessarily extinguishing the problematic behaviors entirely.”\textsuperscript{16} Harm reduction is grounded in principles of patient-centeredness and respect for persons. A harm reduction approach involves meeting patients where they are at, discussing substance use in an open, non-judgmental manner, and using motivational interviewing techniques to help patients develop shared goals around managing their addiction.\textsuperscript{16,17}

Naloxone—a rapid-acting opioid antagonist that can reverse opioid overdose—is one key evidence-based intervention grounded in principles of harm reduction. A Massachusetts–based study showed that community level opioid overdose education and naloxone distribution was associated with substantial reductions in mortality from
opioid overdose. There are opportunities for expanding naloxone distribution at the individual clinic level as well as the community level. Physicians can set up their electronic medical records (EMRs) to automate prescribing of naloxone whenever MOUD is prescribed, or whenever full opioid agonists are prescribed for chronic pain. At the community level, local public health departments can explore opportunities for direct naloxone distribution, ideally targeted to areas where opioid overdose rates are highest.

Syringe service programs (SSPs) are another important intervention based on harm reduction principles. SSPs were initially established with the goal of preventing HIV transmission through distribution of safe injection equipment. Their role has expanded to encompass other modalities of reducing harm associated with opioid use including testing for HIV and Hepatitis C, distribution of naloxone and fentanyl test strips to reduce risk of death from drug overdose, and linkage to medications for opioid use disorder. SSPs meet people with opioid use disorder where they are at and create a low–barrier, non–stigmatizing environment for patients to connect with treatment when they are ready. There is strong data supporting the efficacy of syringe services programs. SSPs are associated with about a 50% decrease in HIV and HCV incidence. Furthermore, people who inject drugs who utilize SSPs are more than five times as likely to enter into addiction treatment and about three times as likely to report reducing or stopping injection as those who have never utilized SSPs. In light of data supporting the effectiveness of SSPs, 31 states have legalized or reduced legal barriers to operating SSPs, including many southern, Midwestern and rural states who have changed these laws in the face of HIV/HCV outbreaks. Missouri law does not currently allow for the legal establishment of SSPs.

Beyond naloxone distribution and SSPs, harm reduction strategies can be incorporated into other components of treatment for opioid use disorder, including medication treatment for OUD. Many treatment programs create high barriers to entry and continuation in treatment. Such barriers include long wait lists for treatment, requirements for intensive counseling to remain in treatment, as well as cessation of treatment in patients who continue to use illicit opioids and/or other substances. These barriers limit the number of patients who are able to benefit from treatment and leave many vulnerable to overdose and death from OUD. “Low-threshold” or “low barrier” buprenorphine treatment represents one promising approach to remove barriers to evidence–based OUD treatment and expand treatment access. These programs offer features like same–day treatment access, flexibility, and availability in places where people with opioid use disorder go. Early data on these approaches indicates that low barrier OUD treatment clinics fill gaps in the care continuum for patients with OUD, help patients initiate treatment in non-traditional settings, and help link patients to long-term care for OUD.

Addressing Challenges Related to the Third and Fourth Waves of the OUD Epidemic

The shifting dynamics of the opioid epidemic—including rising mortality from fentanyl overdose and xylazine in the drug supply—will require innovative approaches to reduce morbidity and mortality from OUD in Missouri. In the last several years, illicitly manufactured fentanyl has overtaken heroin and prescription opioids as the most common drug involved in overdoses. Illicitly manufactured fentanyl is a highly potent synthetic opioid (up to 50 times more potent than heroin) often used as an additive by drug manufacturers to enhance the effect of other illicit substances. Powdered fentanyl is often mixed with drugs like heroin, cocaine and methamphetamine and manufactured into pills that look like other prescription opioids. People may be unaware that their drugs contain fentanyl. One valuable public health strategy to reduce harm from fentanyl in the drug supply is fentanyl test strips, which allow people who use drugs to determine if their drugs have been laced with fentanyl. People who use opioids and other drugs can also be counseled to “never
use alone” and carry naloxone with them to reduce the risk of death due to unintentional overdose. Given the increased overdose risk with fentanyl–containing products, naloxone distribution and overdose education has taken on increased importance as part of a comprehensive public health strategy to reduce OUD–related morbidity and mortality. Lastly, medications for opioid use disorder remain a valuable strategy for treatment of people with OUD who use fentanyl; however, there is emerging evidence that the increased potency and lipophilicity of fentanyl may require modifications of usual protocols to buprenorphine induction to avoid the challenge of precipitated withdrawal.25

Xylazine is a rapidly emerging public health threat in the US that is also increasingly being found in illicitly manufactured fentanyl products. Xylazine is a centrally acting alpha-2 agonist approved by the FDA as a veterinary sedative that is not approved for use in humans. It is increasingly being found in the illicit drug supply as an additive to fentanyl and is thought to enhance the euphoria induced by fentanyl due to its longer duration of action. Xylazine intoxication can cause central nervous system depression, bradycardia, and hypotension. Although naloxone can reverse opioid–induced respiratory depression, it cannot reverse the effects of xylazine. Beyond its acute effects, xylazine has also been associated with severe necrotic skin ulcerations. More research is needed to develop a comprehensive medical and public health approach to addressing the presence of xylazine in the drug supply. Some initial steps that may prove helpful include accelerating development and distribution of point-of-care tests for xylazine. This should include biologic specimen testing that can be used by physicians as well as drug product testing that can be utilized by public health authorities as well as consumers.26

**Future of Care for People with OUD in Missouri**

Among the 2.4 million Americans with opioid use disorder, only about 20% receive any treatment for their disorder in a given year.27 To reduce OUD–associated morbidity and mortality, we need to reach more people with OUD with health care tailored to their specific needs. This means meeting people with OUD wherever they are and providing them holistic, non–judgmental, non–stigmatizing care.

Improving our public health response to the OUD crisis will require action at the individual physician, community, and policy level. At the physician level, the removal of the X waiver for buprenorphine prescriber presents one valuable opportunity to increase MOUD access; however, more work is needed to increase access to MOUD for patients in Missouri. More physicians need training on opioid use disorder and MOUD, including trainees in medical schools, residencies and independent practice. Physicians need practice-level and institutional support to be able to provide effective OUD care, including adequate supports from administrative staff, nursing and behavioral health providers. Stigma is another major barrier to delivery of high quality, evidence-based OUD care at the physician level. Education for physicians and other health care providers should emphasize that opioid use disorder is a chronic medical illness characterized by periods of recurrence and remission, and is not a “moral failing.” Training on OUD should also debunk the myth that MOUD is simply substituting one drug for another.28

At the community level, local health departments and community clinics should work to expand access to naloxone and overdose training, particularly in areas with a high prevalence of opioid overdose. Communities should also work to address the social determinants or drivers of health, in light of evidence that social challenges may exacerbate substance use disorders, and vice versa. Homelessness and substance use disorder often co-exist and may reinforce one another. “Housing first” models of addressing homelessness focus on addressing housing needs first, understanding that housing stability is necessary for individuals to effectively engage with substance use treatment programs.28

At the policy level, advocates should support city- and state-level policies that have demonstrated success in reducing opioid overdose morbidity.
and mortality. Many Midwestern and rural states have reduced legal barriers to syringe services programs (SSP) in light of strong evidence that these programs can reduce infectious disease transmission and increase linkage to addiction treatment, yet SSPs are not legally permitted by Missouri state law.

**Conclusion**

By considering opioid use disorder from a public health perspective, Missouri physicians can work towards building a health care system that reduces OUD-associated morbidity and mortality and allows more patients with OUD to access high quality, evidence-based treatments. Key interventions include low barrier access to medications for opioid use disorder, increased availability of naloxone and overdose education, and access to syringe services programs. These interventions should be coupled with ongoing work to destigmatize substance use disorders and reframe OUD as a chronic medical condition—like hypertension or diabetes—that generalist physicians can effectively manage.

**References**


**Disclosure**

None reported. Artificial intelligence was not used in the study, research, preparation, or writing of this manuscript.

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