Medications for Opioid Use Disorder: Evidence-based Science and Practice

Opioid use disorder (OUD) is an often-chronic neurobehavioral condition that is associated with changes in brain structure and function. The onset and continuation of OUD are strongly influenced by social, psychological, political, and legal factors. Chronic opioid use is associated with higher-than-usual levels of release of the neurotransmitter, dopamine, which can alter the brain's natural reward pathway and contribute to risk for continued use despite negative consequences as well as symptoms like intense craving and withdrawal upon discontinuation of use (Volkow et al., 2011; Volkow et al., 2016; SAMHSA TIP 63, 2021). Medications for opioid use disorder (MOUD) help to stabilize dysregulations in brain chemistry that can occur with chronic opioid use, relieve withdrawal symptoms when agonist MOUD is used, alleviate craving, and block or reduce the euphoric effects of other opioids (NIH, 2018; SAMHSA TIP 63, 2021). The three FDA-approved MOUD are buprenorphine (partial opioid agonist), methadone (full opioid agonist), and naltrexone (antagonist).

Potential objections to the use of MOUD, especially buprenorphine and methadone, include: 1) preferences for psychotherapy rather than medication to treat OUD, 2) concerns that patients are just substituting one drug addiction for another, 3) concerns about diversion of the medications for nonmedical use to another person, and 4) concerns about the risks of neonatal abstinence syndrome in babies born of mothers who are maintained on MOUD. The scientific evidence addressing each of these points is described below and policy implications are provided.

Psychotherapy is beneficial but MOUD is essential in the treatment of OUD

The available evidence is clear that MOUD is the most effective treatment for OUD. MOUD is more effective than psychotherapy alone, and should be considered "first-line" therapy (Mattick et al., 2014; Sofuoglu et al., 2018; Samples et al., 2022).

Practice guidelines from the American Society of Addiction Medicine (ASAM, 2020), National Academies of Sciences, Engineering, and Medicine (NASEM, 2019), the Substance Abuse and Mental Health Services Administration (SAMHSA, 2021), and the World Health Organization (WHO, 2009) converge on the need to prioritize MOUD as the first-line treatment for OUD, with behavioral health and psychotherapy as complementary but not primary treatments.

Among the 58.7 million American adults with any mental illness, approximately 20.4 million (35%) have a co-occurring substance use disorder (NSDUH, 2023). While psychiatric comorbidity in the context of OUD is significant and should be addressed with integrated care models (Moran et al., 2019), therapy or behavioral health in the absence of MOUD is not supported by available evidence.

MOUD is not "just substituting one drug for another"

Treatment with MOUD is associated with less drug use and fewer fatal overdoses, improvements in physical health, fewer acute care visits, and lower rates of criminal justice system involvement (Mattick et al., 2009; Farrell-MacDonald et al., 2014; Mattick et al., 2014; Murphy et al., 2017; Sordo et al., 2017; Tanum et al., 2017; Brinkley-Rubinstein et al., 2018; LaRochelle et al., 2018; Lee et al., 2018; Wakeman et al., 2020).

Those with OUD on MOUD are 38-80% less likely to experience a drug overdose than those with OUD who are not on medication. Studies show that:

- During the 12 months following a nonfatal overdose, patients on buprenorphine were 38% less likely and those on methadone were 59% less likely to have a subsequent fatal overdose compared to patients not on MOUD (LaRochelle et al., 2018).
- Individuals who were on MOUD after being withdrawn from opioids had an all-cause mortality rate that was 66% lower than those who received no additional treatment following withdrawal (Walley et al., 2021).
- Treatment with buprenorphine or methadone was associated with up to an 80% reduction in overdose (Krawczyk et al., 2023; Wakeman et al., 2020). Notably, no other treatment types (no treatment,

behavioral health treatment only, inpatient detoxification, etc.,) were associated with reductions in overdose rates.

- Data collected internationally are consistent with these findings (Brugal et al., 2005; Clausen et al., 2008; Degenhardt et al., 2009; Degenhardt et al., 2011; Sordo et al., 2017).

Diversion of MOUD (giving it to another person) is rare

"Diversion generally means the selling, trading, sharing, or giving away, either voluntarily or involuntarily (e.g., by way of theft), of a prescription medication to someone to whom it was not prescribed" (Krawczyk et al., 2023). Studies have shown that diversion of methadone and buprenorphine is rare, typically motivated by efforts to help others or to address barriers inherent in restrictive prescribing practices and decreases when access to the medications increases. More specifically, studies show that:

- Increased flexibility in methadone prescribing and take-home dosages since the COVID pandemic have ***not*** been associated with significant diversion, increased rates of methadone overdose or mortality, poorer treatment outcomes, or increased healthcare utilization costs (Knopf et al., 2020; Panwala et al., 2023).
- Increased flexibility in prescribing during the COVID pandemic raised concerns about increased diversion, but this did not occur (Brothers et al., 2021; Treitler et al., 2022; Krawczyk et al., 2023).
- Across studies, rates of methadone diversion are low, varying from 5-24%. The vast majority of patients report that medication diversion is motivated by an effort to help individuals who may not have access to methadone, to help alleviate withdrawal symptoms in another person with OUD, or to save up for time away from a program (e.g. a vacation; Duffy et al., 2014; Johnson et al., 2014; Johnson, 2015; Figatt et al., 2021). Similarly, among those endorsing use of diverted methadone, a missed methadone pickup was the most common motivator, highlighting the ways in which restrictive methadone prescribing may contribute to diversion when it does occur (Duffy et al., 2014).
- Though estimates vary, rates of buprenorphine diversion among those in treatment for OUD are thought to be very low and estimated at 4.8% (Rubel et al., 2024).
- Increased availability of buprenorphine is associated with lower rates of diversion (Cicero et al., 2007; Lofwall and Walsh, 2014).

Precautions have been implemented to address concerns about diversion. For example, sustained-release injectable formulations of buprenorphine that last for 1 week to 1 month are now available (e.g., Brixadi, Sublocade). Sublingual buprenorphine/naloxone combination products were also developed to mitigate risks of buprenorphine misuse (namely injection). These products remain the most commonly prescribed formulation in the United States (Nyugen et al., 2022; Braun et al., 2024) and are indeed less likely to be misused or diverted compared to the buprenorphine monoproduct (Lavonas et al., 2014). In the United States, methadone can only be provided in federally designated Opioid Treatment Programs which require observed ingestion initially until some clinical stability is achieved.

During pregnancy, MOUD plays a critical role in protecting both the mother and baby

Opioid use during pregnancy confers a risk of neonatal abstinence syndrome (NAS), also referred to as neonatal opioid withdrawal syndrome (NOWS). NAS occurs when opioids pass through the placenta to the fetus during pregnancy, which contributes to physical dependence on opioids in the newborn baby. Opioid withdrawal signs following birth include excess crying, increased temperature, irritability, seizures, slow weight gain, tremors, diarrhea, and vomiting (NIDA, 2011).

Research on NAS suggests:

- Buprenorphine may be related to less severe signs of NAS compared with methadone, but treatment retention was higher among those on methadone. This highlights the importance of individualized decision making between patients and their healthcare providers (Minozzi et al., 2013).

- Among pregnant women, longer duration of MOUD (buprenorphine or methadone) is associated with significantly lower rates of overdose, preterm birth, and low birth rate, and significantly higher rates of medication continuation post-partum (Krans et al., 2021).
- There is no evidence to support lower rates of NAS in pregnant women with OUD who are not on MOUD (buprenorphine or methadone) compared to those who are, because those not on medication are likely to continue using opioids and other drugs (Krans et al., 2021).
- Compared to those not on buprenorphine or methadone, pregnant women on medication have significantly lower rates of nonfatal overdose, and longer duration of treatment is associated with the greatest benefit (Jarlenski et al., 2022).
- Comprehensive programs offering combined MOUD (buprenorphine or methadone), obstetric care, and counseling have been associated with reduced rates of substance use during pregnancy (Ordean et al., 2013), greater compliance with prenatal visits, better outcomes for neonates, and greater likelihood of infants being discharged home (Ordean & Kahan, 2011).

While NAS is a potential outcome among pregnant women with OUD, MOUD (buprenorphine or methadone) can provide opportunities for careful monitoring, referrals, and appropriate treatment for both the mother and neonate (CDC, 2024). NAS is considered a treatable condition (ACOG, 2017). Current clinical guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2017) and SAMHSA (SAMHSA, 2018) also support use of buprenorphine or methadone during pregnancy over supervised withdrawal or sudden discontinuation of opioid use. Quickly stopping opioids during pregnancy is associated with increased risks of miscarriage, preterm labor, and fetal distress (CDC, 2024).

Summary and Policy Implications

MOUD is an essential component in the treatment of OUD. It reduces the risk of opioid overdose, allows patients to resume gainful employment and reestablish fractured relationships with friends and family, and protects the mother and baby during the perinatal period. Although the clinical benefits of MOUD are clear, it remains underutilized in many treatment facilities and settings.

The Substance Abuse and Mental Health Services Administration (SAMHSA) recommends the following policy changes (https://www.samhsa.gov/sites/default/files/samhsa-fy-2025-cj.pdf) to increase access to MOUD:

- Implementing grant programs and initiatives, such as the State Opioid Response program,
- Easing regulations at Opioid Treatment Programs,
- Implementing programs that emphasize prevention at the community level, such as programs that describe the risks of opioid use and discuss early intervention strategies,
- Partnering with programs, such as syringe service programs, that focus on reducing the risks associated with drug use (such as HIV and hepatitis C), and
- Increasing the clinician workforce capacity to treat addictions through enhancement of training programs for addiction specialists and primary care providers, as well as through telehealth provision of MOUD.