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Methadone Versus Buprenorphine for Treatment of Opioid Use Disorder

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Both methadone and buprenorphine are considered first-line medications for opioid use disorder (MOUD) with a demonstrated reduction in morbidity and mortality associated with opioid use disorder (OUD). Despite similar benefits, there may be instances where one form of MOUD is clinically preferred over another. Methadone and buprenorphine differ in accessibility due to the regulations surrounding the provision of methadone for OUD, impacting the ability to access this life-saving treatment.

MOUD Pharmacology and Efficacy

Conceptualize opioid receptors like a dimmable light switch.

Methadone

Full Opioid Receptor Agonist

- Turns on the opioid receptor light switch fully and at maximum brightness. This allows for methadone to be initiated without regard to when another opioid was last used.
- There is no established maximum dose. It may be titrated to effect based on response.
- Similar risk profile compared to other prescribed opioids.

Buprenorphine

Partial Opioid Receptor Agonist

- Turns on the opioid receptor light switch part way; light is on and functional but dimmed. This requires that you must consider when another opioid was last used and wait for moderately-rated withdrawal symptoms. Initiating buprenorphine too early should be avoided as that can precipitate an unpredictable degree of opioid withdrawal.
- FDA labeling (and some state-specific legislation) limits maximum daily doses.
- Lower risk of certain side effects, like respiratory depression.

Both suppress withdrawal and cravings for opioids and reduce morbidity and mortality associated with OUD, though some evidence suggests that methadone may be superior to buprenorphine in regard to treatment retention.

Regulatory Factors Impacting Accessibility and Utilization

Methadone	Buprenorphine
• Restricted to use in licensed opioid treatment programs (OTP) that must adhere to stringent legal and regulatory requirements.* • OTPs are particularly difficult for rural Americans to access, with 80% of counties (pop. 77.5 million) lacking an OTP as of 2018. • Requires frequent, often times daily, travel to the OTP for methadone dispensing and administration with limited ability to dispense “take home” doses. • Less flexibility in how the daily dose is administered due to OTP dispensing requirements.	• May be prescribed in an office-based setting by any provider with a valid Drug Enforcement Administration (DEA) registration. • Clinicians may prescribe up to 6 months supply via telemedicine visit (audio-only allowed), thereafter an in-person visit is required to continue prescribing. • May be filled at any outpatient pharmacy. • Schedule III controlled substance → may be prescribed for a 30-day supply with an additional 5 refills. • Flexibility in how the daily dose is administered (i.e. once daily vs. multiple divided doses per day).

*Note that these restrictions do not apply to methadone prescribed for pain, which can be prescribed by any Drug Enforcement Administration (DEA)-registered provider and filled at any outpatient pharmacy

Additional Factors Impacting Access to Buprenorphine

Buprenorphine is available in various formulations (e.g. sublingual/under the tongue tablets, sublingual films, extended-release injection, buccal/between cheek and gum films, transdermal patch). While this provides opportunities to individualize OUD treatment, access to these formulations may be limited by factors such as varying FDA-approved indications (pain vs. OUD), formulary restrictions, and other state-specific laws governing buprenorphine prescribing.

Historically, high buprenorphine utilization and dispensing rates have been flagged as potential red flags by the DEA and wholesale distributors, categorizing buprenorphine used for OUD treatment similarly to full agonist opioids used for pain management. This has led to drug wholesalers setting limits on the amount of buprenorphine pharmacies may purchase and pharmacies fearing legal repercussions for dispensing larger volumes of buprenorphine, thus limiting the number of patients on buprenorphine a pharmacy may serve. While the DEA has taken steps to encourage wholesalers to evaluate MOUD quantities separately from other opioid medications, guidance remains limited.

Reasons to Consider Methadone for OUD Treatment Over Buprenorphine

- Lack of response to buprenorphine: There may be patients for whom previous buprenorphine treatment has been unsuccessful, whether due to inability to successfully initiate the medication due to withdrawal or lack of treatment response after initiation (e.g., continued use of non-prescribed opioids, ongoing cravings, etc.). In these instances, methadone would present a preferable alternative for MOUD.
- Buprenorphine intolerability or allergy: Some patients may experience an allergy or intolerable side effect to buprenorphine, leaving only methadone or naltrexone as viable options. While naltrexone is another FDA-approved medication for OUD, there is less demonstrated morbidity and mortality benefit, and the initiation can pose a prohibitive barrier as patients must undergo full withdrawal from opioids prior to initiation.
- Fentanyl/fentanyl analogs: While there are limited data establishing to what extent the use of high-potency fentanyl or fentanyl analogs impacts the success of buprenorphine treatment, buprenorphine initiations may be more difficult to complete given their unique pharmacokinetic properties and buprenorphine's activity as a *partial* opioid receptor agonist. Fentanyl collects in fat, resulting in persistent release from fatty tissues, delayed clearance from the body, and prolonged opioid withdrawal. When treating patients who use fentanyl, clinicians must wait longer to give buprenorphine, which can lead to difficulties in managing cravings, precipitated withdrawal, and treatment failure. Patients using illicit fentanyl are at substantial risk for opioid-related overdose and would benefit from initiation of MOUD as soon as is practicable.
- Well Studied: Methadone is the most well-studied pharmacotherapy for OUD, with the longest track record. Methadone is safe and effective for patients when indicated, dispensed, and consumed.

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