OPIOID USE DISORDER PHARMACOTHERAPY

FDA-approved medications for opioid use disorder (OUD) treatment are safe and effective and should be considered for all patients with OUD.[1,2] This resource provides links to evidence-based treatment guidelines as well as an overview of pharmacologic agents used for the treatment of OUD and overdose reversal. Ideally, medications for OUD should be used as part of a comprehensive treatment plan that includes psychosocial treatment.[18]

Table 1: Available Pharmacologic Agents for the Treatment of Opioid Use Disorder [1,2,3]

Agent	Mechanism of Action	Pharmacokinetics	Dosing	Drug Interactions/ Toxicities	Special Considerations
Methadone	Mu-opioid receptor full agonist	Oral [3-5] Onset: 30-60 min Peak: 1-2 h (3-5 days with continued dosing) Half-life: 15-60 h Duration: 3-6 h (8-12 h with continued dosing) Bioavailability: 36-100% Metabolism: hepatic (N-demethylation) by CYP3A4, CYP2B6, CYP2C19, CYP2C9, CYP2D6	Oral Initial: Generally 10-30 mg; observe patients for 2-4 hours before considering a second dose of 5 mg if withdrawal persists. After waiting 2-4 hours, consider a third dose of 5 mg if the patient is not showing signs of sedation, and withdrawal symptoms persist. Take caution when exceeding a total first day's dose above 40mg. See also 42 CFR 4.12(h)(3) Titration: Increase in 5-10 mg increments every 7 or more days Maintenance: Average daily dose is 60-120 mg[14]	Use with caution in liver dysfunction, respiratory insufficiency May prolong QT interval; use with caution with other QT prolonging drugs; EKG recommended at baseline, 1 month, and then annually after initiation Avoid concomitant use of other CNS depressants Monitor for P450 based drug interactions	Consider Federal regulations: 42 CFR 8.12 which outlines Federal Opioid Treatment Program Standards. When used for OUD, methadone must be provided in a federally licensed opioid treatment program. Methadone may not be included in a prescription drug monitoring program Due to risk of misuse, requires monitored administration until non-monitored dosing is appropriate Complicated pharmacokinetics due to large volume of distribution, accumulation in tissues, and complex metabolism Can switch to buprenorphine if on low doses (30-40 mg); can switch to naltrexone once completely withdrawn
Naltrexone	Opioid receptor antagonist Prevents relapse	Oral [8,9] Half-life: 4-10 h Duration: 24-72 h Bioavailability: 5-40% Metabolism: hepatic (non-cytochrome) by dehydrogenases	Oral Typically, 50 mg once daily. Alternatively, a total weekly dose of 350 mg is an option where the first two doses are 100 mg and the third is 150 mg. Research concluded oral naltrexone was not superior to placebo or to no medication in treatment retention of illicit opioid use reduction.[15]	Monitor for hepatic injury; discontinue if hepatitis observed Monitor for suicidal thoughts and/or depression Do not administer concomitant peripheral opioid antagonists (methylnaltrexone, naloxegol, etc.)	Can be stopped at any time; duration determined on an individual basis The injection is often provided after oral use to ensure there are no intolerable adverse effects Can switch to methadone or buprenorphine 24 hours after oral dose or 30 days after intramuscular dose; begin with low dose of agonist Due to the half-life of the formulation, extra care support may be warranted during the final week of a given dose
		IM Depot [9,10] Half-life: 5-10 days Duration: 4 weeks Metabolism: hepatic (non-cytochrome) by dehydrogenases	IM Depot Give 380 mg by gluteal intramuscular injection every 4 weeks		

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Table 1: Available Pharmacologic Agents for the Treatment of Opioid Use Disorder [1,2,3] *(continued)*

Agent	Mechanism of Action	Pharmacokinetics	Dosing	Drug Interactions/ Toxicities	Special Considerations
Buprenorphine	Buprenorphine hydrochloride: Mu-opioid receptor partial agonist/ kappa-opioid receptor antagonist Naloxone hydrochloride: Opioid receptor antagonist	Buprenorphine/naloxone sublingual films: Half-life: 35-37 hours (buprenorphine) Metabolism: hepatic by CYP3A4	Buprenorphine/naloxone sublingual films: Maintenance Target: 16 mg/4 mg Maintenance Range: 4 mg/1 mg – 24 mg/6 mg	Use with caution in liver dysfunction Causes hypotension; use with caution in hypovolemia, cardiovascular disease, with other hypotension drugs Potential interactions with agents that affect CYP3A4 activity	Can switch to methadone at any time; or can switch to naltrexone 7-14 days after last dose of buprenorphine Sublingual films: Dosages above 24 mg/6 mg buprenorphine/naloxone per day have shown no clinical advantage
		Buprenorphine/naloxone sublingual tablet (generic): Half-life: 24-42 hours Metabolism: hepatic by CYP3A4	Buprenorphine/naloxone sublingual tablet (generic): Maintenance Target: 16 mg/4 mg Maintenance Range: 4 mg/1 mg – 24 mg/6 mg		Dosages above 24 mg/6 mg per day have shown no clinical advantage
		Buprenorphine/naloxone Buccal films: Half-life: 24-42 hours Metabolism: hepatic by CYP3A4	Buprenorphine/naloxone Buccal films: Maintenance Target: 8.4 mg/1.4 mg Maintenance Range: 2.1 mg/0.3 mg - 12.6 mg/2.1 mg		
		Buprenorphine/naloxone sublingual tablet (brand) Half-life: 24-42 hours Metabolism: hepatic by CYP3A4	Buprenorphine/naloxone sublingual tablet (Brand) Maintenance Target: 11.4 mg/2.9 mg Maintenance Range: 2.9 mg/0.71 mg to 17.2 mg/4.2 mg		
		Buprenorphine (monoproduct) Half-life: 31-35 hours Metabolism: hepatic by CYP3A4	Buprenorphine monoproduct sublingual tablet (brand) Maintenance Target: 16 mg Maintenance Range: 4 mg to 24 mg		Dosages above 24 mg buprenorphine per day have shown no clinical advantage
		Buprenorphine implants Half-life: 24-48 hours Metabolism: hepatic by CYP3A4	Buprenorphine implants are a set of 4 rods; each rod contains the equivalent of 80 mg of buprenorphine hydrochloride		FDA approved for OUD maintenance treatment in patients who have achieved sustained clinical stability (e.g., periods of abstinence, minimal or no desire to use illicit opioids, stable house, social support) while taking no more than 8 mg daily of buprenorphine monoproduct or buprenorphine/naloxone equivalents. Implants must be removed after 6 months
		Buprenorphine extended-release injection Half-life: 43-60 days Metabolism: hepatic by CYP3A4	Buprenorphine extended-release injection (Prefilled syringes administered by subcutaneous injection in the abdomen): First two monthly doses recommended are 300 mg each followed by a 100 mg monthly maintenance dose		For moderate-severe opioid use disorder treatment among patients who have initiated treatment with transmucosal buprenorphine, followed by at least 7 days of dose adjustment. Store in the refrigerator in prefilled syringes. The product can be stored outside of the refrigerator in the original packaging at room temperature for up to 7 days prior to administration, but should be discarded if kept at room temperature beyond 7 days.

Note: For oral formulations, observed induction is recommended, but home induction may be considered; weekly visits recommended until patients are stable. [17]

Table 2: Agents used for overdose reversal

Agent	Mechanism of Action	Pharmacokinetics	Dosing	Special Considerations
Naloxone	Opioid receptor antagonist Reverses overdose	Intramuscular Injection[11,12] Onset: 2-5 min Half-life: 1-2 h Duration: 30-120 min Metabolism: hepatic (glucuronidation) Intranasal[11,12] Onset: 8-10 min Bioavailability: 50% Metabolism: see above	Intramuscular Injection Give 0.4-2 mg; may repeat dose in 2-3 min if no response Intranasal Give 4 mg; may repeat dose every 5-7 min if no response	Patients being treated for opioid use disorder should be prescribed naloxone; patients and family/friends should be trained in its use

CITATIONS:

1. ASAM Guidelines for MAT Involving Opioid Use: https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf
2. Tip 63 SAMHSA: https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document-Including-Executive-Summary-and-Parts-1-5-/SMA18-5063FULLDOC
3. 42 CFR 4.12
4. Meresaar U, Nilsson MI, Holmstrand J, Anggård E. Single dose pharmacokinetics and bioavailability of methadone in man studied with a stable isotope method. Eur J Clin Pharmacol. 1981;20(6):473-8.
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13. Ryan SA, Dunne RB. Pharmacokinetic properties of intranasal and injectable formulations of naloxone for community use: a systematic review. Pain Manag. 2018;8(3):231-245.
14. Clinical Guidelines for Withdrawal Management and Treatment of Drug Dependence in Closed Settings: https://www.ncbi.nlm.nih.gov/books/NBK310658/
15. Minozzi, S., Amato, L., Vecchi, S., Davoli, M., Kirchmayer, U., & Verster, A. (2011). Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database of Systematic Reviews, 2011(2), 1–45. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001333.pub4/information
16. Tip 63, Chapter 3B, SAMHSA: https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document-Including-Executive-Summary-and-Parts-1-5-/SMA18-5063FULLDOC
17. A Patient's Guide to Starting Buprenorphine at Home available at: https://www.asam.org/docs/default-source/education-docs/unobserved-home-induction-patient-guide.pdf?sfvrsn=16224bc2_0
18. VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders: https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf

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