Medications for opioid use disorder

Buprenorphine, methadone, and naltrexone side by side. Where overdose reversal fits and how induction works. Reviewed against current guidelines as of June 8, 2026.

Three medications have FDA approval for OUD: buprenorphine, methadone, and extended-release naltrexone. All three reduce overdose deaths and improve retention. Buprenorphine and methadone (opioid agonists) have stronger evidence for retention and mortality reduction than naltrexone. Naloxone should be co-prescribed for anyone at overdose risk. Companion to the full guide at psychiatryrx.org/guides/medications-for-opioid-use-disorder/.

First-line options

Drug	Class	Notes
Buprenorphine (Suboxone, Subutex)	Partial mu agonist	8 to 24 mg SL a day. X-waiver eliminated (MAT Act 2023). Ceiling on respiratory depression. High receptor affinity blocks other opioids.
Buprenorphine ER (Sublocade, Brixadi)	Partial mu agonist LAI	Sublocade monthly SC. Brixadi weekly or monthly. Removes daily dosing and diversion.
Methadone	Full mu agonist	60 to 120 mg a day, sometimes higher. OTP-only in the US. QT concern above 100 to 120 mg. Complex CYP interactions.
Extended-release naltrexone (Vivitrol)	Full mu antagonist	380 mg IM monthly. No physical dependence. Requires 7 to 14 days opioid-free before first dose. Overdose risk after discontinuation because tolerance is lost.
Naloxone (Narcan OTC, Kloxxado, Zimhi)	Overdose reversal	OTC as Narcan nasal spray since 2023. Co-prescribe for every OUD patient and for anyone at overdose risk. Fentanyl overdoses may need multiple doses.

Second-line, adjuncts, and comorbidity

Drug	Class	When to consider
Lofexidine (Lucemyra)	Alpha-2A agonist	Withdrawal symptom management. Approved for that role. Doesn't cover craving as well as agonists.
Clonidine (off-label)	Alpha-2 agonist	Withdrawal symptoms at lower cost than lofexidine. More sedating and orthostatic.
Oral naltrexone	Full mu antagonist	Approved but much lower retention than injectable. Rarely first choice.
Sertraline, escitalopram, duloxetine	SSRI or SNRI	Comorbid depression or anxiety. Duloxetine covers depression plus pain.
Trazodone, DORAs, ramelteon	Sleep	Insomnia in OUD. Avoid benzodiazepines and z-drugs when possible.
Prazosin, sertraline, paroxetine, venlafaxine	PTSD	PTSD comorbid with OUD. Trauma-focused therapy alongside.
Symptomatic: loperamide, ondansetron, NSAIDs, hydroxyzine	Withdrawal support	Diarrhea, nausea, muscle aches, insomnia. Watch loperamide cardiac at high doses.

Special considerations

- Precipitated withdrawal is the main risk at buprenorphine induction. Wait for moderate withdrawal (COWS 8 or higher) or use microdosing (Bernese method) or extended-wait protocols, especially in the fentanyl era.
- Benzodiazepine plus buprenorphine: 2016 FDA guidance clarified this is not an absolute contraindication. Withholding buprenorphine because of concurrent benzodiazepines is often worse than the combination. Coordinated tapering when possible.
- Pregnancy: buprenorphine and methadone are both first-line for OUD in pregnancy. Do not discontinue if stable. Buprenorphine has slightly less NAS severity in some studies. Methadone has the longest track record.
- Chronic pain plus OUD: buprenorphine at split doses (BID or TID) covers both. Patients on stable maintenance can receive additional opioid analgesia for acute pain, coordinated with the addiction team.
- Adolescents: buprenorphine is FDA-approved for OUD in patients 16 and older.
- HCV and HIV: treatment is compatible with OUD medications. Methadone has some antiretroviral interactions.
- Incarceration transitions: initiating buprenorphine or methadone before release, plus naloxone, reduces overdose mortality substantially.

What tips the choice

Newly diagnosed OUD with active use: buprenorphine is the practical default in office-based settings. Methadone via OTP for patients preferring or requiring higher-intensity structure. Highly motivated and opioid-free for 7 to 10 days, prefers non-agonist: extended-release naltrexone. Prior buprenorphine failure: methadone. Adherence problems or diversion concerns: extended-release buprenorphine (Sublocade, Brixadi) or extended-release naltrexone. Pregnancy: buprenorphine or methadone, and don't discontinue if stable. Fentanyl use with difficult induction: microdosing or extended-wait. Chronic pain plus OUD: buprenorphine split dosing. Recent release from incarceration or residential treatment: initiate medication immediately, plus naloxone. Overdose history: buprenorphine or methadone (strongest mortality reduction).

Watchouts

- Precipitated withdrawal at buprenorphine induction: more common with fentanyl. If it happens, the answer is more buprenorphine, not less, plus symptomatic management.
- Overdose risk after abstinence (post-release, post-naltrexone discontinuation, post-residential): tolerance drops fast. Naloxone matters more here.
- Buprenorphine plus benzodiazepines or alcohol raises overdose risk but is not an absolute contraindication.
- Methadone QT: baseline ECG. Serial ECG at higher doses or with other QT-prolonging drugs.
- Return to use during treatment doesn't mean failure. Continue medication, address the trigger, adjust the dose.
- Mandating therapy as a condition of medication access is not evidence-based and worsens outcomes.
- Every patient should carry naloxone. Family and support people should know how to use it.

Reviewed against current guidelines as of June 8, 2026. Educational reference, not medical advice.