	Methadone (dolophine, methadose)	Buprenorphine±naloxone (Subutex buprenorphine sublingual tablets; Suboxone buprenorphine/naloxone sublingual film for sublingual or buccal use)	Naltrexone (ReVia tablets, Vivitrol injection)
Mu-opioid receptor activity	► Synthetic, full agonist	► Buprenorphine: partial agonist with high-affinity binding ► Naloxone: non-selective and competitive opioid receptor antagonist with the high affinity for the mu receptors	► Pure, full competitive opioid antagonist with the highest affinity for the mu receptors
Other receptor considerations	► Some agonist action at the kappa receptor ► Weak antagonist action at N-methyl-D-aspartate receptor ► Possible antagonist action at the delta receptor	► Buprenorphine: partial kappa receptor agonist or functional antagonist (possibly with antidepressant effects) ► Weak delta antagonist	► Modifies the hypothalamic-pituitary-adrenal axis to suppress alcohol consumption
Clinical considerations	► Stimulation of the mu receptor causes euphoria, analgesia, constipation, and respiratory depression	► Due to buprenorphine being a partial agonist, there is a ceiling effect for the binding of mu receptors, which causes decreased euphoric feelings and respiratory depression ► Due to high-affinity binding, buprenorphine can displace full agonists from the mu receptor and cause withdrawal symptoms ► The addition of naloxone to buprenorphine is to help decrease injection misuse. Buprenorphine monotherapy is reserved for patients who are pregnant or have a documented severe reaction to naloxone	► Due to naltrexone being a high-affinity opioid antagonist, it blocks the euphoric effects if other opioids are used
FDA-approved formulations	► Oral solution, dissolvable tablet	► Transmucosal buprenorphine/naloxone (Suboxone, Bunavail, Zubsolv) ► Injectable buprenorphine (Sublocade)	► Oral tablets ► Extended-release intramuscular injection (Vivitrol)
Dosing	► Oral: 10–30 mg/day; titrated up to 80–100 mg/day as tolerated	► Transmucosal: 8–16 mg (or equivalent) once daily (or in divided doses) ► Sublocade (for patients maintained on ≤8 mg/day): 300 mg subcutaneous injection monthly for two doses, then 100 mg/month	► Oral: 25 mg on day 1, then 50 mg/day ► Vivitrol: 380 mg intramuscular every 4 weeks ► Patient needs to be opioid free for a minimum of 7–10 days to avoid withdrawal symptoms
Setting	► Licensed outpatient treatment program	► Any medical setting; x-waiver required if prescribing outside the inpatient setting	► Any medical setting
Additional benefits	► Use in comorbid pain, high potency, high structure of delivery setting; low risk of precipitating withdrawal symptoms	► Safety compared with methadone, use in comorbid pain, dosing flexibility, less structured treatment setting ► Displaces opioid→precipitated withdrawal	► Low diversion, not an opioid, compliance ► No physical dependence, verifiable dosing, less stigma, fewer drug-drug interactions, FDA approved for both alcohol and OUD
Adverse effects	► Respiratory depression ► Constipation ► QTc prolongation ► Hypoglycemia ► Hypotension	► Headache ► Insomnia ► Diaphoresis ► Nausea/Vomiting ► Constipation ► Abdominal pain ► Infection with the implant ► Sedation, especially when combined with alcohol and benzodiazepines	► Headache ► Insomnia ► Unintended precipitation of opioid withdrawal ► Accidental opioid overdose ► Depression ► Suicidality ► Nausea/Vomiting/Diarrhea ► Hepatic enzyme abnormalities ► Nasopharyngitis ► Injection-site reactions
Contraindications	► Significant respiratory depression ► Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ► GI obstruction including paralytic ileus ► Caution in patients with hepatic impairment due to drug accumulation	► Buccal film, intramuscular injection, transdermal patch ► Significant respiratory depression ► Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ► GI obstruction including paralytic ileus	► Current physiological opioid dependence or current use of opioid analgesics (including partial opioid agonists) ► Acute opioid withdrawal ► Failure to pass naloxone challenge ► Positive urine screen for opioids ► Acute hepatitis or hepatic failure
Warnings and precautions	► CNS depression ► QTc prolongation ► Respiratory depression ► Serotonin syndrome	► CNS depression ► Respiratory depression ► Hepatotoxicity ► QTc prolongation ► Hypotension	► Hepatotoxicity ► Accidental opioid overdose ► Acute opioid withdrawal ► Eosinophilic pneumonia ► Hypersensitivity reaction ► Suicidal ideation/Depression
Pharmacokinetics	► Oral bioavailability: 36%–100% ► Onset of action: – Oral: 0.5–1 hours – Intravenous: 10–20 min – Metabolized in the liver by CYP2B6 (major), CYP3A4 (major), CYP2D6 (minor), CYP2C19 (minor), and CYP2C9 (minor) ► Half-life: – Children: 19.2+13.6 hours – Adults: 8–59 hours ► Excreted as metabolites by the kidneys and in the bile	► Bioavailability ► Buccal film: 46%–65% ► Intramuscular: 70% ► SL tablet: 29% ► Transdermal patch: 15% ► Onset of action: intramuscular >15 min ► Metabolized in the liver by CYP3A4 to norbuprenorphine (active metabolite), which then undergoes glucuronidation by UGT1A3 or to a lesser extent is metabolized by glucuronidation by UGT1A1 and UGT2B7 to buprenorphine-3-glucuronide ► Half-life adults – Buccal film: 27.6+11.2 hours – SL tablet: 37 hours – Transdermal patch: 26 hours ► Excreted in the feces and urine	► Oral bioavailability: 5%–40% ► Duration of action: – Oral 50 mg: 24 hours – Oral 100 mg: 48 hours – Oral 150 mg: 72 hours – Intramuscular: 4 weeks ► Metabolized by non-cytochrome-mediated dehydrogenase conversion to 6-beta-naltrexol (primary metabolite) and minor metabolites and glucuronide conjugates ► Half-life adults: – Oral: 4 hours – Intramuscular: 5–10 days ► Excreted in the urine

CNS, central nervous system; FDA, Food and Drug Administration; GI, gastrointestinal; SL, sublingual.