Pharmacotherapy for Opioid Use Disorder

	Methadone	Buprenorphine/Naloxone or Buprenorphine	Naltrexone
Indications	– DSM diagnosis of OUD and patient meets Federal OTP Standards (42 CFR 8.12(e)). More information at http://store.samhsa.gov/shin/content/PEP15-FEDGUIDEOTP/PEP15-FEDGUIDEOTP.pdf	– DSM diagnosis of OUD – Willingness and stability to receive, store, and administer weekly medication	**DSM diagnosis of OUD with:** – Prevention of relapse to opioid dependence/use following detoxification – Treatment for alcohol use disorder – Willingness and stability to receive monthly injections
Contraindications	– Hypersensitivity	– Hypersensitivity – Chronic pain that requires opioid treatment beyond buprenorphine	– Hypersensitivity – Receiving opioid agonists – Physiologic opioid dependence – Failed naloxone challenge or naltrexone challenge test – Positive urine opioid screen – Acute hepatitis or liver failure – Advanced psychiatric disease, active suicidal ideation – Breastfeeding
Warnings/ Precautions	– Concurrent enrollment in another OTP – Prolonged QTc interval – Use caution in patients with respiratory, liver, or renal insufficiency – Concurrent benzodiazepines or other CNS depressants including opioids and active AUD (potential respiratory depression) – Use of opioid antagonists (including parenteral naloxone, oral or parenteral nalmefene, naltrexone) – Pregnancy category C	– Buprenorphine/naloxone may precipitate withdrawal in patients on full agonist opioids – Use caution in patients with respiratory, liver, or renal insufficiency – Current benzodiazepines or other CNS depressants, including opioids and active AUD (potential respiratory depression, overdose) – Use of opioid antagonists (eg, parenteral naloxone, oral or parenteral nalmefene, naltrexone) – Pregnancy category C	– Active liver disease, cirrhosis – Moderate to severe renal insufficiency; unknown effects – Thrombocytopenia or coagulation disorders – Chronic and/or acute pain must be managed with non-opioids – Large body habitus – Vulnerability for fatal opioid overdose in case of relapse to opioids – Pregnancy category C
Baseline Evaluation	– Consider electrocardiogram and physical examination for patients at risk of QT prolongation or arrhythmias – Toxicology screen	– Liver transaminases – Urine beta-HCG for females – Toxicology screen	– Liver transaminase levels < 5x upper limit of normal – CrCl (estimated or measured) 50 mL/min or greater – Ensure patient has adequate muscle mass for injection – Urine beta-HCG for women – Toxicology screen

Pharmacotherapy for Opioid Use Disorder *(continued)*

	Methadone	Buprenorphine/Naloxone or Buprenorphine	Naltrexone
Dosage and Administration	– **Initial dose:** 15-20 mg single dose, maximum 30 mg – **Daily dose:** Maximum 40 mg/day on first day – **Usual dosage range for optimal effects:** 60-120 mg/day – Titrate carefully, consider methadone's delayed cumulative effects – Administer orally in single dose – Individualize dosing regimens – Daily visits at MAT clinic, may receive take-home doses per clinic protocol	**Sublingual dosing:** – **Induction:** Patient presents in mild-moderate withdrawal – **Induction dose:** 2-4 mg initial dose, titrate per prescription instructions and/or until withdrawal symptoms subside – Typical Day 1 dose = 8 mg – **Days 2-7:** Patient takes total dose equivalent from Day 1 upon awakening. Check in with clinical team. May titrate up to 16 mg. – **Stabilization/maintenance:** Target dose = 8-16 mg (max 24 mg daily) may be taken in QD or BID dosing regimen – Weekly visits/prescriptions until stable, then biweekly and eventually monthly or random call-back basis	– To be administered after negative urine toxicology screen and/or successful naltrexone/naloxone challenge – **Oral:** 25-50 mg by mouth daily – **ER injectable:** 380 mg every 28 days by deep intramuscular gluteal injection – Alternate injection sites – Weekly visits until stable, then biweekly, may progress to clinic visits every 28 days occurring on the date of patient's extended-release naltrexone injection
Alternative Dosing Schedules	– Give in divided doses based on peak and trough levels that document rapid metabolism that justifies divided doses	– Divided dosing helpful for patients with chronic pain for dual effectiveness and avoidance of narcotic medications – Residential programs may require specific Sig	– For patients with coagulation disorders, thrombocytopenia, or large body habitus, consider remaining on oral formulation
Adverse Effects	– **Major:** Respiratory depression, shock, cardiac arrest, prolongation of QTc interval on electrocardiogram and torsades de pointes ventricular tachycardia – **Common:** Lightheadedness, dizziness, sedation, nausea, vomiting, sweating, constipation, edema – **Less common:** Sexual dysfunction	– **Major:** Hepatitis, hepatic failure, respiratory depression (usually when misused intravenously or if combined with other CNS depressants) – **Common:** Headache, pain, abdominal pain, insomnia, nausea, vomiting, sweating, constipation – **Sublingual buprenorphine/naloxone film:** Oral hypoesthesia, glossodynia, oral mucosal erythema	– **Major:** Eosinophilic pneumonia, depression, suicidality – **Common:** Injection-site reaction, tenderness, induration, nausea, abdominal pain, anorexia, headache, asthenia

Pharmacotherapy for Opioid Use Disorder *(continued)*

	Methadone	Buprenorphine/Naloxone or Buprenorphine	Naltrexone
Drug Interactions	– **Drugs that reduce serum methadone levels:** Ascorbic acid, barbiturates, carbamazepine, ethanol (chronic use), interferon, phenytoin, rifampin, efavirenz, nevirapine, other antiretrovirals with CYP3A4 activity – **Drugs that increase serum methadone level:** Amitriptyline, atazanavir, atazanavir/ritonavir, cimetidine, delavirdine, diazepam, fluconazole, fluvoxamine, ketoconazole, voriconazole – Opioid antagonists may precipitate withdrawal	– Metabolized in the liver by cytochrome P450 3A4 system – **Drugs that reduce serum buprenorphine level:** Ascorbic acid, barbiturates, interferon, carbamazepine, ethanol (chronic use), phenytoin, rifampin, efavirenz, nevirapine, other antiretrovirals with CYP3A4 activity – **Drugs that increase serum buprenorphine level:** Amitriptyline, atazanavir, atazanavir/ritonavir, cimetidine, delavirdine, diazepam, fluconazole, fluvoxamine, ketoconazole, voriconazole – **Opioid partial agonist:** Buprenorphine/naloxone or buprenorphine may precipitate opioid withdrawal – Opioid antagonists may precipitate withdrawal	– Opioid-containing medications, including over the counter preparations – Thioridazine (increased lethargy and somnolence)
Monitoring	– Signs of respiratory and CNS depression – Frequent toxicology screening	– Liver function tests prior to initiation and during therapy as needed – Frequent toxicology screening	– Repeat liver transaminase levels at 6 and 12 months and then every 12 months thereafter – Increase hepatic monitoring in cases of mild to moderate elevation (1-5x upper limit of normal – Frequent toxicology screening

Abbreviations: OUD: opioid use disorder; UTS: urine toxicology screening; Cmax: maximum concentration; CNS: central nervous system; CrCl: creatinine clearance; DSM: Diagnostic and Statistical Manual of Mental Disorders; HCG: human chorionic gonadotropin; m: meter(s); mg: milligram(s); min: minute(s); mL: milliliter(s)

Adapted from Department of Veteran Affairs. The Management of Substance Use Disorders Work Group. (December 2015). *VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.* Version 3.0-2015.