### Pharmacotherapy for Opioid Use Disorder

**Methadone**

- DSM diagnosis of OUD and patient meets Federal OTP Standards (42 CFR 8.12(e)).

**Buprenorphine/Naloxone or Buprenorphine**

- DSM diagnosis of OUD
- Willingness and stability to receive, store, and administer weekly medication

**Naltrexone**

- 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

### Indications

- Hypersensitivity
- Chronic pain that requires opioid treatment beyond buprenorphine

### Contraindications

- 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

### Warnings/Precautions

- Concurrent enrollment in another OTP
- Prolonged QTc interval
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- Pregnancy category C

### Baseline Evaluation

- Consider electrocardiogram and physical examination for patients at risk of QT prolongation or arrhythmias
- Toxicology screen

### Liver Transaminases

- 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

- 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
### Methadone

- **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, may progress to clinic visits every 28 days occurring on the date of patient’s extended-release naltrexone injection

### Buprenorphine/Naloxone or Buprenorphine

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### Naltrexone

- **Dosage and Administration**
  - 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

### Adverse Effects

- **Methadone**
  - **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

- **Buprenorphine/Naloxone or Buprenorphine**
  - **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

- **Naltrexone**
  - **Major:** Eosinophilic pneumonia, depression, suicidality
  - **Common:** Injection-site reaction, tenderness, induration, nausea, abdominal pain, anorexia, headache, asthenia

- For patients with coagulation disorders, thrombocytopenia, or large body habitus, consider remaining on oral formulation
### Methadone
- **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

### Buprenorphine/Naloxone or Buprenorphine
- 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

### Naltrexone
- 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

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