<table>
<thead>
<tr>
<th>Methadone</th>
<th>Buprenorphine-naloxone</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Dolaphine, methadone)</td>
<td>(Subutex buprenorphine sublingual tablets; Suboxone buprenorphine/naloxone sublingual film for sublingual or buccal use)</td>
<td>(ReVia tablets, Vivitrol injection)</td>
</tr>
</tbody>
</table>

### Mu-opioid receptor activity
- Synthetic, full agonist
- Some agonist action at the kappa receptor
- Weak antagonist action at N-methyl-D-aspartate receptor
- Possible antagonist action at the delta receptor

### Other receptor considerations
- Buprenorphine: partial agonist with high-affinity binding
- Naloxone: non-selective and competitive opioid receptor antagonist with the highest affinity for the mu receptors
- Buprenorphine: partial kappa receptor agonist or functional antagonist (possibly with antidepressant effects)
- Weak delta antagonist

### Clinical considerations
- Stimulates 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
- Sublocade (for patients maintained on 80 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-raying required if prescribing outside the inpatient setting
- Any medical setting

### Additional benefits
- Use in oropharyngeal pain, high potency, high structure of delivery setting, low risk of precipitating withdrawal symptoms
- Safety compared with methadone, use in oropharyngeal pain, dosing flexibility, less structured treatment setting
- Displaces opioid—precipitated withdrawal

### 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

### Contraindications
- Significant respiratory depression
- Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment
- GI obstruction including paralytic ileus
- CNS depression
- QTc prolongation
- Respiratory depression
- Serotonin syndrome
- Current physiological opioid dependence or current use of opioid analgesics (including partial opioid agonists)

### Warnings and precautions
- Acute opioid withdrawal
- Failure to pass naloxone challenge
- Positive urine screen for opioids
- Acute hepatitis or hepatic failure
- 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 (minor), CYP2D6 (minor), CYP2E1 (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
  - Buccal film: 0.7–2.6 hours
  - Sublingual tablet: 1.9 hours
  - Transdermal patch: 1.5 hours
- Excreted in the urine

- Oral bioavailability: 46%–65%
- Intramuscular: 70%
- SL tablet: 29%
- Transdermal patch: 15%
- 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:
    - Buccal film: 27.6–11.2 hours
    - SL tablet: 37 hours
    - Transdermal patch: 26 hours
    - Excreted in the urine

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