MEDICATIONS USED TO MANAGE OPIOID USE DISORDER

Also known as Medication-Assisted Treatment

While opioid analgesics have a place in the treatment of severe and uncontrolled pain, their use can result in abuse and addiction, also known as opioid use disorder (OUD). The following medications may be used to help manage OUD through medication-assisted treatment (MAT). The FDA is advising prescribers to discuss the use of naloxone with patients being treated with medications for OUD to help reduce opioid overdose.

Methadone (long-acting opioid agonist)

Medications	Uses	Available dosages
Methadone (Dolophine®, Methadose®)	• Opioid dependence • Opioid withdrawal • Moderate pain • Severe pain	• Oral solution: Methadose®; methadone 5 mg/5 ml; 10 mg/ml; 10 mg/5 ml • Solution for injection: methadone 10 mg/ml • Oral Tablet: Dolophine®, Methadose®; methadone 5 mg; 10 mg • Tablet for oral suspension: Methadose®; methadone 40 mg dispersible tablets and diskettes* *40 mg Dispersible Tablets and Diskettes are only available through an approved detoxification and maintenance of an opioid addiction treatment program

Advantages	Disadvantages	Important considerations
• Methadone is a long-acting opioid that binds tightly to the opioid receptor. The long duration of action allows methadone to occupy opioid receptors and displace the other opioid agonists (both medications and heroin), thereby suppressing cravings and minimizing opioid withdrawal symptoms • Methadone has a long history of use for opioid dependence and withdrawal as part of an opioid treatment program and under close supervision of a licensed practitioner • At regular dosing intervals, methadone may be a cost effective therapy to suppress opioid craving and withdrawal • Methadone may be a useful option for patients with opioid dependence or withdrawal and co-occurring pain, or after treatment failure with buprenorphine	**Medication interactions (select):** Antiarrhythmic; antiretrovirals; antibiotics – not all inclusive (consult a healthcare professional) **Adverse effects (select):** Respiratory depression (breathing); irregular heartbeat (cardiac risks); sedation; constipation; death • Methadone has a very long and unpredictable half-life; the drug accumulation in the body may result in serious adverse effects, including respiratory depression, sedation and death • Close and careful monitoring required for signs of sedation and respiratory depression especially during initiation and dosage changes • Difficult to transition to buprenorphine/naloxone • Methadone has a potential for addiction, abuse and misuse: DEA Schedule II class drug	• Extreme caution is recommended as the use of methadone involves a high-level risk of adverse events and drug interactions which may lead to overdose or death • Methadone carries a black box warning for respiratory depression and death; extreme caution is advised for use in patients who have never used opioids before (opioid-naïve) • Caution is advised for patients with sleep apnea (shallow breaths while sleeping); respiratory problems; older adults; renal (kidney) or hepatic (liver) insufficiency; mental health disorders; patients with alcohol or other substance abuse disorders • Use of methadone is recommended for treatment under the direct observation of pain and/or addiction specialists experienced in the prescribing of methadone • Methadone for opioid agonist dependence or withdrawal is restricted to a certified opioid treatment program as outlined by Substance Abuse and Mental Health Services Administration (SAMHSA)

MEDICATIONS USED TO MANAGE OPIOID USE DISORDER

Also known as Medication-Assisted Treatment

Buprenorphine (long-acting mixed opioid agonist-antagonist)

Medications	Uses	Available dosages
Buprenorphine sublingual tablet (Subutex®)	• Opioid dependence • Opioid withdrawal	• Sublingual tablet: Buprenorphine 2 mg; 8 mg* • Sublingual tablet is placed under the tongue *Brand Subutex® sublingual tablet is off U.S. market
Buprenorphine injection, extended-release (Sublocade™)	Opioid dependence Maintenance in patients who have initiated treatment with an oral buprenorphine-containing product, followed by dose adjustment for a minimum of seven days	Prefilled syringe: Sublocade™ 100 mg/0.5 mL; 300 mg/1.5 mL Prefilled syringe is injected below the skin (subcutaneously) by a licensed healthcare professional

Advantages	Disadvantages	Important considerations
• Buprenorphine is a long-acting mixed opioid agonist-antagonist; produces pain relief and allows opioid dependent patients to discontinue use of opioids without experiencing withdrawal effects • Has a greater safety profile over methadone; buprenorphine is less likely to cause respiratory depression than methadone due to limits also known as the "ceiling effect;" (opioid effects increase with each dose until at moderate doses they level off, even with further dose increases) • More accessible for the treatment of opioid dependence and withdrawal than methadone, as treatment may occur in an office-based setting by qualified prescribers • Fewer serious drug interactions than methadone • Subcutaneous injection may be beneficial for patients who may have problems with non-adherence, diversion or non-medical use • Buprenorphine-containing products may be a useful option for patients with opioid dependence or withdrawal and co-occurring pain	**Drug interactions (select):** Antifungals; antiarrhythmics (heart rhythm); antiretrovirals – not all inclusive (consult a healthcare professional) **Adverse effects (select):** Nausea; vomiting; constipation; dizziness; headache **Sublingual tablet:** May require close patient monitoring for potential signs of misuse or abuse; sublingual tablets may be abused by crushing and snorting or by injection **Subcutaneous injection (Sublocade™):** • Patients must initiate treatment with an oral buprenorphine-containing product, followed by dose adjustment for a minimum of seven days • Subcutaneous injection lasts approximately one month	• Prescribers of buprenorphine products for opioid withdrawal or opioid agonist dependence must comply with certain waiver qualifications approved under the Drug Addiction Treatment Act of 2000 (DATA 2000) outside of an Opioid Treatment Program • Buprenorphine-containing products carry a risk for respiratory depression; close clinical monitoring may be necessary • Buprenorphine-containing products have a potential for addiction, abuse and misuse: DEA Schedule III class drug • Subcutaneous injection is administered in abdomen region monthly by the healthcare provider; there is no maximum recommended duration of treatment

Note: This chart does not include those buprenorphine products indicated for pain, including Buprenex®, Belbuca®, and Butrans®

Buprenorphine/Naloxone (long-acting mixed opioid agonist-antagonist)

Medications	Uses	Available dosages
Buprenorphine/naloxone sublingual tablet; sublingual film (Suboxone®)	Opioid dependence	• Sublingual tablet: Buprenorphine/ Naloxone 2 mg-0.5 mg; 8 mg-2 mg* • Sublingual Film: Suboxone® 2 mg-0.5 mg; 4 mg-1 mg; 8 mg-2 mg; 12 mg-3 mg *Brand Suboxone® Sublingual Tablet is off U.S. market
Buprenorphine/naloxone sublingual tablet (Zubsolv®)	Opioid dependence	Sublingual tablet: Zubsolv® .7 mg-0.18 mg; 1.4 mg-0.36 mg; 2.9 mg-0.71 mg; 5.7 mg-1.4 mg; 8.6 mg-2.1 mg;11.4 mg-2.9 mg
Buprenorphine/naloxone buccal film (Bunavail®)	Opioid dependence	Buccal film: Bunavail® 2.1 mg-0.3 mg; 4.2 mg-0.7 mg; 6.3 mg-1 mg

Advantages	Disadvantages	Important considerations
• Buprenorphine/Naloxone is a mixed opioid agonist-antagonist; produces pain relief and allows opioid dependent patients to discontinue use of opioids without experiencing withdrawal effects • Buprenorphine/naloxone recommended for most patients over plain buprenorphine; naloxone becomes active if dissolved and injected intravenously, thereby blocking or limiting the effects of buprenorphine • Has a greater safety profile over methadone; buprenorphine is less likely to cause respiratory depression than methadone due to limits known as the "ceiling effect" (opioid effects increase with each dose until at moderate doses they level off, even with further dose increases) • More accessible for the treatment of opioid dependence and withdrawal than methadone, as treatment may occur in an office-based setting by qualified prescribers • Fewer serious drug interactions than methadone • Buprenorphine-containing products may be a useful option for patients with opioid dependence or withdrawal and co-occurring pain with opioid dependence or withdrawal and co-occurring pain • May require less frequent dosing and easier to discontinue than methadone	**Drug interactions (select):** Antifungals; antiarrhythmics (heart rhythm); antiretrovirals – not all inclusive (consult a healthcare professional) **Adverse effects (select):** Nausea; vomiting; constipation; dizziness; headache **Sublingual tablet and Buccal film:** • May require close patient monitoring for potential signs of misuse or abuse; sublingual tablet and buccal film may be abused by crushing and snorting or by injection • Buprenorphine-containing products have a potential for addiction, abuse and misuse: DEA Schedule III class drug • May precipitate withdrawal if started too soon after use of an opioid analgesic; thus, patients should be in withdrawal to receive first dose	• Prescribers of Buprenorphine/Naloxone • products for opioid withdrawal or opioid agonist dependence must comply with certain waiver qualifications approved under the Drug Addiction Treatment Act of 2000 (DATA 2000) outside of an opioid treatment program • Buprenorphine-containing products carry a risk for respiratory depression; close clinical monitoring may be necessary • There is no evidence that one product may be more effective than another • It is important to understand the difference in dose-equivalencies among the products. This information may be found in the prescribing information for each product. For example: - One Zubsolv 1.4 mg/0.36 mg tablet provides the same amount of buprenorphine as one generic 2 mg/0.5 mg sublingual tablet - One Bunavail 4.2 mg/0.7 mg buccal film provides the same amount of bupenorphine as one generic 8 mg/2 mg sublinqual tablet

Note: This chart does not include those buprenorphine products indicated for pain, including Buprenex®, Belbuca®, and Butrans®

Naltrexone (opioid antagonist)

Medications	Uses	Available dosages
Naltrexone tablet (ReVia®)	• Opioid dependence • Ethanol (alcohol) dependence	• Oral tablet: ReVia®; naltrexone 50 mg
Naltrexone powder for injection (Vivitrol®)	• Opioid dependence • Ethanol (alcohol) dependence	Powder for suspension, injection: Vivitrol® 380 mg

Advantages	Disadvantages	Important considerations
• Non-opioid medication with no potential for addiction, abuse or misuse • Binds to opioid receptors and blocks other opioid analgesics (or heroin) to reduce cravings • No physical dependence; can be stopped abruptly with no risk of withdrawal symptoms • Naltrexone is not limited to certain prescribers or clinics like methadone or buprenorphine/naloxone • Vivitrol® is administered as an injection on a monthly basis by a licensed prescriber • May be a good choice for highly motivated patients and those who have already been detoxified	**Drug interactions:** All opioid analgesics, including (but not limited to), oxycodone, hydrocodone, tramadol, codeine, methadone, oxymorphone, fentanyl and illicit opioids such as heroin **Potential side effects:** • Headache; dizziness; nervousness; insomnia; anxiety; fatigue • Should not be used in patients that require an opioid analgesic for pain due to risk of fatal opioid overdose • Use may increase the risk for serious adverse effect of hepatotoxicity (liver damage) • Injection site reactions may be a concern with use of Vivitrol® injection	• The use of naltrexone in patients also taking opioid analgesics may cause opioid withdrawal and is not recommended • Naltrexone should only be reserved for patients that are not actively taking opioid analgesics • Treatment with naltrexone may be an acceptable option for preventing relapse in patients with opioid use disorder and for highly motivated patients

Note: This chart does not include those buprenorphine products indicated for pain, including Buprenex®, Belbuca®, and Butrans®

Key definitions:

Agonists: A medication (or molecule) that occupies and activates a receptor. This activity usually involves full activation of the receptor in the body.
Antagonists: A medication (or molecule) that occupies a receptor, but blocks its activation rather than eliciting a response.
Agonist-Antagonists: A medication that may behave under certain conditions as both an agonist and an antagonist. Agonist-antagonists produce some, but not full activation.

References:

1. Clinical Resource, Management of Opioid Use Disorder. Pharmacist's Letter/Prescriber's Letter. October 2020
2. Clinical Pharmacology. [Internet]. Tampa, FL: Elsiver Gold Standard, Inc.
3. Substance Abuse and Mental Health Services Administration. Medication-Assisted Treatment (MAT). Available at: https://www.samhsa.gov/medication-assisted-treatment
4. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain-United States, 2016. MMWR Recomm. Rep 2016;65:1-49.
5. Substance Abuse and Mental Health Services Administration (2015). SAMHSA Detoxification and Substance Abuse Treatment Tip 45. HHS Publication No. (SMA) 15-4131. Available at: https://store.samhsa.gov/system/files/sma15-4131.pdf
6. U.S. Food and Drug Administration (FDA). News Release. FDA requiring labeling changes for opioid pain medicines, opioid use disorder medicines regarding naloxone. July 23, 2020. Available at: https://www.fda.gov/news-events/press-announcements/fda-requiring-labeling-changes-opioid-pain-medicines-opioid-use-disorder-medicines-regarding