Pharmacist Toolkit: Medication Management of Opioid Use Disorder

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This toolkit is intended to highlight both the evidence base available as well as strategies of clinical decision making used by expert clinicians. The content reflects the views and practice of the authors as substantiated with evidence-based facts as well as opinion and experience.

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Overview[1]

In 2017, about 57 million persons had access to at least one prescription for an opioid. There were approximately 191 million opioid prescriptions dispensed in 2017. Self-reported opioid misuse within the past year was documented in approximately 11.5 million people over the age of 12 who participated in the 2016 National Survey on Drug Use and Health. Over 2 million self-reported a diagnosis of opioid use disorder. It has been documented that approximately 1.8 million Americans have opioid use disorder related to opioid prescriptions. About 626,000 have heroin-related opioid use disorder.

The true incidence of opioid use disorder is unknown and is likely underestimated. Pharmacists can be advocates for the appropriate assessment of opioid use to screen for an opioid use disorder and make recommendations for most clinically appropriate medication management of Opioid Use Disorder (OUD).

Screening

The most commonly used, evidence-based, self-reported screening tool for future opioid misuse for adult patients who are prescribed opioids for chronic pain is the Opioid Risk Tool.[2] Scores of 0 to 3 are associated with low risk, 4 to 7 with moderate risk, and 8 or higher with high risk.

Opioid Risk Tool		
Mark each box that applies	**Female**	**Male**
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Prescription drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Prescription drugs	5	5
Age between 16-45	1	1
History of preadolescent sexual abuse	3	0
Psychological disease		
Attention Deficit Disorder, Obsessive Compulsive Disorder, Bipolar Disorder, Schizophrenia	2	2
Depression	1	1
Scoring totals		

Other screenings and measurement-based in a primary setting include the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) and Drug Abuse Screening Test (DAST-10).

The American College of Obstetricians and Gynecologists recommend the following for prenatal substance use screenings:[3]

The 4 Ps:

Parents	Did any of your parents have a problem with alcohol or other drug use?
Partner	Does your partner have a problem with alcohol or other drug use?
Past	In the past, have you had difficulties in your life because alcohol or other drugs, including prescription medications?
Present	In the past month have you drunk any alcohol or used other drugs?
Scoring: Any "yes" should indicate the need for further assessment.	

National Institute on Drug Abuse (NIDA) Drug Screening Tool

CRAFFT 2.1 behavioral health screening tool for use with children ages 12-21

Diagnosis[4]

DSM-5 Opioid Use Disorder Criteria

OUD is defined by the Diagnostic and Statistical Manual 5th Edition as two or more of the following symptoms in a 12-month period:

- Tolerance
- Withdrawal
- Using larger amounts over greater time than intended
- Difficulty cutting down
- Craving opioids
- Excessive time spent opioid seeking
- Reduction in other recreational activities
- Failure to fulfill obligations at work, school, or home
- Continued use despite social or interpersonal problems
- Use in physically hazardous situations
- Continued use despite knowledge of persistent physical or psychological problems

Specifiers

- Mild (presence of 2-3 symptoms)
- Moderate (presence of 4-5 symptoms)
- Severe (presence of 6+ symptoms)

Remission is categorized as:

- Early remission – criteria is no longer met for 3-12 months
- Sustained remission – criteria no longer met for 12 months or longer
- Patients may still meet criteria for remission if they continue to experience cravings for opioids. Additional specifiers include whether a patient is on maintenance therapy for OUD or if they are in a controlled environment where access to opioids is restricted

SBIRT Model: Screening, Brief Intervention, and Referral to Treatment

An evidenced-based intervention and universal approach to OUD in community settings can follow the SBIRT model which includes:

1. Screening - assessment for the existence of problematic opioid use
2. Brief Intervention - provide advice and guidance on the risks
3. Referral to treatment - refer the patient to brief therapy or appropriate treatment

More information and training modules can be found at: https://www.integration.samhsa.gov/clinical-practice/sbirt

Opioid Withdrawal[5]

While opioid withdrawal syndrome (OWS) is not inherently life-threatening, medical management is recommended over abrupt discontinuation of opioids, given risk of increased cravings and continued use. Most patients experiencing OWS can be safely managed in the outpatient setting. Patients should be managed in the inpatient setting because of safety concerns, pregnancy, risk of withdrawal from multiple substances, or medical/psychiatric instability. Withdrawal management is not recommended as a treatment for OUD; patients should be offered medication treatment (see section on Medication Treatment for OUD).

Stages of Opioid Withdrawal Syndrome

- Early symptoms: anxiety, restlessness, rhinorrhea, tearing eyes, sweating, insomnia, dilated pupils
- Late symptoms: rhinorrhea, watery eyes, yawning, tremor, muscle aches, piloerection, nausea, vomiting, diarrhea, abdominal pain, chills

Opioid	Time course of acute opioid withdrawal symptoms following last dose		
	Start	Peak	Resolution
Short-acting	6-12 hours	72 hours	5-10 days
Long-acting	24-72 hours	4-6 days	14-21 days

Opioid Withdrawal Monitoring Scales

- Clinical Opiate Withdrawal Scale (COWS) is an 11-item clinician-administered tool to assess the severity of opioid withdrawal symptoms.[5] COWS is not intended to diagnose opioid withdrawal, since there may be significant symptomatic overlap with other substances and/or conditions. The COWS can be administered in either the inpatient or outpatient setting to monitor progress of OWS at initial presentation and subsequent follow-up. Scores ≥13 indicate moderate to severe withdrawal symptoms.
- Objective Opioid Withdrawal Scale (OOWS) is a 13-item clinician-administered tool assessing opioid withdrawal symptoms during a 5-minute observation period, with scores ranging from 0-13.[6] The higher the score, the more severe the withdrawal symptoms. The OOWS can be used during initial assessment of opioid withdrawal and for ongoing monitoring of symptoms.
- Subjective Opioid Withdrawal Scale (SOWS) is a 16-item self-administered tool assessing opioid withdrawal symptoms based on patient self-report.[6] Each item is scored with a range of 0-4, with total scores ranging from 0-64. Scores ≥11 indicate moderate to severe withdrawal symptoms.
- Clinic Institute Narcotic Assessment (CINA) Scale for Withdrawal Symptoms is an 11-item tool with clinician-observed and patient self-report components used to assess withdrawal severity and monitor clinical status over time.[7] The scores range from 0-31, with higher scores indicative of more severe symptoms.
- Finnegan Neonatal Abstinence Syndrome (NAS) Scoring System is a clinician-administered tool assessing and monitoring opioid withdrawal in infants.[8] Depending on the version, the scoring chart assesses 10-20 symptoms and can be adjusted for prematurity. The infant should initially be scored 2 hours after birth and then every 3-4 hours prior to a feeding. The scoring system has been modified a multitude of times, with most modified versions recommending treatment of NAS with 2 consecutive scores ≥12 or 3 consecutive scores ≥8.

Pharmacotherapy for Management of Opioid Withdrawal

Opioid and non-opioid medications may be provided to reduce symptoms of opioid withdrawal. First-line treatment for withdrawal includes buprenorphine products or methadone.[4,9] Both agents may be used for acute withdrawal management, during which the medications are tapered and discontinued, or may be initiated and continued following stabilization for treatment of OUD. Ongoing treatment with these agents is associated with improved outcomes compared with medically supervised withdrawal alone.[11]

Methadone

Methadone is recommended for use in the inpatient setting or in the outpatient setting through an opioid treatment program (OTP). Doses less than 40mg/day are typical for management of withdrawal symptoms. Higher doses are typically associated with cessation of opioid cravings.

Buprenorphine

Buprenorphine products may be used in the inpatient, outpatient, or OTP settings; prescriber requirements and laws vary depending on the setting of withdrawal management. Use in individuals who are physically dependent on opioids should not be initiated until signs and symptoms of mild to moderate opioid withdrawal have begun in effort to avoid precipitated opioid withdrawal resulting from differences in receptor activity. Initiation should be delayed until 12-18 hours following the last dose of short-acting opioids (heroin, oxycodone) or 24-48 hours following the last dose of long-acting opioids (morphine extended release or methadone, respectively).

Monoproduct buprenorphine (without naloxone) may be used for hospital-based withdrawal management. However, in the outpatient setting, the combination product (buprenorphine/naloxone) is preferred because of an increased risk of misuse through intravenous or intranasal administration with the monoproduct.

If there are no resources available to coordinate the use of buprenorphine or methadone for withdrawal management, clonidine (off-label) or lofexadine (FDA approved), may be used, but are not as effective in managing withdrawal symptoms. Low doses of oral naltrexone in addition to buprenorphine with intention to accelerate the initiation of extended-release naltrexone has been used but is not commonly recommended.

Supportive therapy should be provided during opioid withdrawal for symptoms including anxiety or irritability (hydroxyzine or clonidine), diarrhea (loperamide), pain (acetaminophen or non-steroidal anti-inflammatory agents), nausea (ondansetron or metoclopramide), and insomnia (diphenhydramine or trazodone).

Legislation[3,12,13,14]

In accordance with the code of federal regulations (21 CFR 1306.07), patients with OUD admitted to the inpatient or emergency department setting may require provision of opioid therapy to alleviate or prevent withdrawal symptoms. Providers are legally permitted to order and administer, but not prescribe, opioids if the patient is admitted for a primary diagnosis other than OUD, even if they are not waivered or the facility is not registered as an opioid treatment program (OTP). If a patient is currently on opioid agonist therapy, it is recommended that providers contact the patient's outpatient prescriber or OTP to confirm the patient's current dose, how many doses they were last prescribed or permitted to take home, and the last date of administration or office visit.

For patients who are admitted to the inpatient or emergency department setting with a primary diagnosis of OUD, if there is no waivered prescriber or the facility is not registered as an OTP, a provider may order and administer opioids for maintenance or withdrawal for up to 72 hours while referral to a waivered provider or OTP is being coordinated. No more than one day supply of medication may be administered to the patient at one time and the 72-hour period may not be extended or renewed. A provider may not prescribe opioids upon discharge for OUD, with the exception of buprenorphine when written by a waivered prescriber.

It is recommended that pharmacists familiarize themselves not only with federal regulations related to medication treatment for OUD, but also state regulations as laws do vary state to state. An outline of legislations, regulations, and guidelines for OTPs and medication treatment for OUD can be found at: https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/legislation-regulations-guidelines.

Medications for Treatment of Opioid Use Disorder[4]

Ongoing medications for the treatment of OUD should be considered for all patients with OUD, as it has been proven to be superior to non-medication-assisted, abstinence-based treatment in retaining patients in treatment and reducing illicit opioid use.[10] Medications for OUD should be offered along with medical management and psychosocial treatment, when deemed necessary by the provider and wanted by the patient to support recovery. There are three medications approved by the US Food and Drug Administration for OUD: methadone, buprenorphine (both buprenorphine and buprenorphine/naloxone), and naltrexone.

The optimal duration of treatment should largely be directed by the patient's stability in recovery, not necessarily after a certain amount of time has elapsed; it is reasonable to maintain patients on medications treatment for OUD for decades or even a lifetime.

Some evidence suggests that relapse risk is high in the months following discontinuation, further supporting long-term use of medications treatment for OUD. It has been documented that approximately 13% of patients taper off methadone successfully (no reentry into treatment, death, or opioid-related hospitalization) based on outcomes within the first 18 months following discontinuation. The addition of psychotherapy during tapers has not been shown to improve outcomes or success rates.

Routine monitoring includes regular urine drug testing and review of the prescription drug monitoring database programs (PDMPs). Abnormal results or aberrant behaviors may indicate a need for higher level of care, not necessarily a need for discontinuation of therapy.

Methadone[14,15,16]

Methadone is a full mu-agonist, synthetic opioid which has the most literature available regarding efficacy for treatment of OUD. The goals of treatment include reduction in illicit opioid use, reduction of psychosocial and medical morbidity and mortality, improvement of in overall health, reduction in criminal activity, and improvement of in social function.

This medication can be administered through OTPs with a combination of nonpharmacologic services. Doses above 40mg/day are typically required for maintenance to avoid opioid cravings.

Methadone is contraindicated in patients with an allergy to methadone and other instances which opioids are contraindicated including acute or severe chronic asthma, abnormally high carbon dioxide blood levels from significant respiratory depression (i.e. pulmonary disease or sleep apnea), or known or suspected paralytic ileus.

When verifying if a patient is currently on methadone treatment, PDMPs should not be used for confirmation as OTP treatment is not done through outpatient prescriptions and therefore not reported to PDMPs. This provision is aligned with the federal confidentiality law, 42 CFR Part 2.

Urine drug tests (UDTs) for opioids do not routinely screen for methadone. Additional specialized testing for methadone and inactive metabolites such as 2-ethylidene-1,5dimethyl-3,3-diphenylpyrrolidene (EDDP), is typically used for evaluation of this medication in the urine which may be detected for approximately 2 to 11 days. Each facility's laboratory specificity and sensitivity should be reviewed in effort to accurately interpret UDTs.

Buprenorphine[17]

Buprenorphine is a semi-synthetic opioid with partial agonist activity at the mu-opioid receptor. It has several unique properties advantageous for the treatment of OUD including:

- High affinity for the mu-opioid receptor
  - Prevents opioids with lower affinity from binding (i.e. heroin, oxycodone, etc.)
  - Results in blunting or blockade of opioid effects, including euphoria

- Partial agonist activity with ceiling effect
  - Less opioid effect than full agonist opioids, including respiratory depression and euphoria
  - Once moderate dose is reached, effects no longer increase even if dose increases

Both of these properties explain the risk of precipitated withdrawal during initiation of buprenorphine in someone who is physically dependent on opioids; buprenorphine will displace a full agonist opioid from the mu-opioid receptor and precipitate opioid withdrawal symptoms given the stronger receptor affinity and weaker opioid activity. Buprenorphine should be initiated after someone has started to experience opioid withdrawal symptoms to minimize risk of precipitated withdrawal. Buprenorphine induction can be completed in clinic or at home. Home induction may be most suitable, if the patient and prescriber have experience with using buprenorphine. Buprenorphine can be initiated in patients not currently physically dependent on opioids without risk of precipitated withdrawal, but is typically initiated at lower doses and titrated more slowly in these cases.

Several dosage forms exist, including sublingual and buccal tablets and films, as well as newer formulations including subcutaneous long-acting injection and subdermal implant. Some transmucosal buprenorphine products also contain naloxone as an abuse deterrent, given naloxone will only produce an effect if the medication is injected or snorted. Transdermal and low-dose transmucosal buprenorphine products should not be used as maintenance therapy for OUD because of lack of efficacy and FDA approval for this indication.

Drug Addiction Treatment Act of 2000 (DATA 2000) allows waivered physicians, nurse practitioners, and physician assistants to prescribe buprenorphine for the treatment of OUD in a community setting and for the prescription to be filled at any pharmacy. OTPs may administer or dispense buprenorphine through OTP physician order without a waiver.

Naltrexone

Naltrexone is a mu-opioid receptor antagonist, blocking the effects of exogenously administered full agonist opioids. Both the oral and injectable extended-release (XR-NTX) formulations are available. However, the oral formulation is not commonly used because of high rates of nonadherence and, subsequent lack of efficacy.[4,18] A Cochrane Review of 13 trials comparing treatment of patients with OUD with or without oral naltrexone in addition to counseling concluded that oral naltrexone was not superior to placebo in reducing illicit opioid use and treatment retention.[19] XR-NTX has been shown to be superior to placebo in reducing illicit opioid use.[20] Several studies have demonstrated that once initial barriers to XR-NTX induction are overcome, treatment outcomes are similar between buprenorphine and XR-NTX.[21,22] Patients must be abstinent from opioids for 7-10 days prior to initiating naltrexone to minimize risk of precipitated withdrawal. Patients may need to be abstinent for longer if transitioning from methadone to naltrexone. If the risk of precipitated withdrawal is uncertain, it is possible to perform a naloxone challenge test by administering low doses of naloxone intranasally, intravenously, subcutaneously, or intramuscularly. It is important to note that a negative naloxone challenge test does not provide assurance that a patient will not experience precipitated withdrawal, if naltrexone is administered.[23]

Pharmacotherapy for Maintenance Treatment of Opioid Use Disorder

Medication/Dosing	Side Effects	Monitoring	Comments
Methadone Day 1: First dose maximum: 30mg *5-10mg with no or low opioid tolerance Day 1 maximum: 40mg Typical Target: 60mg/day or higher associated with greater retention 80-120mg/day (some patients require higher doses)	Common: constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating Rare: ECG abnormalities, psychosis, pruritis, sexual dysfunction or decreased libido, amenorrhea, weight gain, edema, seizures, hypotension	Liver function tests (LFTs), EKG (QTc), pregnancy test, serum concentrations (interpretation varies- should consider duration of therapy and delayed reflection of dose adjustments in serum; peak 2-4 hours post-dosing)	• Formulation for OUD: liquid, powder to be dissolved in water, or dispersible tablets to be dissolved in water (tablets typically used for pain) management outside of OTPs) • Daily doses for OUD maintenance are higher than those used for pain management • Dose adjustments should not be made daily; titrations to be done slowly • Dose stabilization expected to take weeks • Take-home methadone cannot be considered in most states until day 90 of treatment • Many interactions with prescription and over-the-counter medications: inhibitors of CYP3A4 and 2C9, inducers of CYP3A4 • Evaluate for risk factors for QTc prolongation at baseline and as changes occur throughout treatment; do not initiate if baseline QTc ≥ 500 milliseconds • Concomitant use of other opioids or CNS depressants should be carefully reviewed and benefits and risks should be clearly discussed when determining ongoing treatment
Buccal or sublingual (SL) buprenorphine (including buprenorphine/ naloxone)[17,24,25] Initiation: 2 – 8mg total on induction day Target: 8 – 16mg/day Maximum: 24mg/day *Doses up to 32mg/day have been studied but have not been demonstrated to provide any clinical advantage	Common: Sedation, constipation, nausea, headache, hyperhidrosis, oral hypoesthesia, glossodynia, oral mucosal erythema Rare: Hepatitis, respiratory depression, serotonin syndrome	LFTs	• Risk Evaluation and Mitigation Strategy (REMS) program to educate on and mitigate risks of accidental overdose, misuse, and abuse • Newer formulations with greater bioavailability of buprenorphine have been developed, achieving the same effect as original formulations with lower doses (i.e. Bunavail® 4.2mg/0.7mg and Zubsolv® 5.7mg/1.4mg are equivalent to 8mg/2mg Suboxone®) • Doses ≥16mg/day confer 80-95% mu-opioid receptor occupancy
Subcutaneous (SC) Buprenorphine[26] 300mg SC monthly x 2 months, then 100mg SC monthly; may increase to 300mg SC monthly	Common: constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain Rare: Hepatitis, respiratory depression, serotonin syndrome	LFTs, Signs of patient attempted removal	• REMS program because of risk of serious complications if administered incorrectly • Must NOT be dispensed directly to patient because of risk of embolus, if administered intravenously • Must be stabilized on SL buprenorphine ≥7 days prior to initiation

			• Dosing is equivalent to 8-24mg SL buprenorphine • Emergency surgical excision within 14 days of administration is possible
Subdermal Buprenorphine Implant[27] 4 implants inserted subdermally into upper arm for 6 months (must be removed by end of the sixth month). After initial 6 months, 4 implants may be inserted into upper arm on opposite side for 6 months	Common: Implant site pain, pruritus, erythema, headache, constipation, nausea, vomiting Rare: Complications from improper insertion or removal (nerve damage, migration, embolism, and death), spontaneous expulsion, protrusion, local migration	LFTs Signs of patient attempted removal Examine insertion site 1 week after insertion	• REMS program because of risk of serious complications with insertion and removal • Maximum duration of use is 12 months; if buprenorphine treatment still indicated, must convert back to SL formulation • Must be stable on SL doses ≤8mg/day for ≥3 months prior to initiation • Each implant contains 74.2mg buprenorphine (equivalent to 80mg buprenorphine SL) • Monthly follow-up recommended for counseling and psychosocial treatment • Limited utility given maximum duration of 12 months, low equivalent SL daily dose, and invasive procedure
Naltrexone[18] 50mg/day oral 380mg monthly injection	Common: Nausea, vomiting, headache, low energy, anxiety, depression, rash, decreased alertness, injection site reactions Rare: Hepatotoxicity	LFTs	• Hepatotoxicity is idiosyncratic and dose-dependent • Avoid in patients with acute hepatitis or liver failure • Must be abstinent from most opioids for 7-10 days and longer for methadone • Opioids will not be as effective for emergency management of pain • Patients should carry wallet card or wear medical alert bracelet noting use in case of emergency requiring analgesia

Non-Pharmacologic

Strong evidence for psychotherapy in opioid use disorder is not currently available. Psychotherapies or techniques for intervention which have been studied include motivational interviewing, cognitive behavioral therapy for substance use disorders, contingency management and relapse prevention techniques.[14] Twelve-step or other mutual-help groups, such as Narcotics Anonymous, are encouraged at a minimum for those in opioid treatment programs.[28]

Opioid Overdose Prevention Education and Treatment

Use of opioids at any dose places an individual at risk for opioid overdose. Naloxone education and access should be offered and coordinated for all patients using opioids illicitly or prescribed. Those with an opioid use disorder are considered to be in the highest risk category for opioid overdose therefore coordination of care is a priority. Detailed guidance can be found at: https://cpnp.org/guideline/naloxone

In effort to reduce unintentional exposure and potential overdoses, lockboxes should be used for storage of methadone take home doses or other opioids.

Special Populations

Hepatic Impairment

- Buprenorphine
  - Buprenorphine is primarily metabolized hepatically.
  - Patients with moderate to severe hepatic impairment have been shown to have increased exposure to both buprenorphine and naloxone because of decreased clearance.
  - There have been case reports of hepatitis and liver failure, however, most patients had risk factors at baseline.
  - Mild impairment (Child-Pugh score of 5–6): No dose adjustment needed.
  - Moderate impairment (Child-Pugh score of 7–9): Combination products with naloxone are not recommended.
    - Naloxone in combination products may precipitate withdrawal or interfere with buprenorphine's efficacy.
    - Monitor for signs and symptoms of toxicity or overdose caused by increased buprenorphine levels.
    - Use combination products cautiously for maintenance treatment in patients who were inducted with a monoproduct.
  - Severe impairment (Child-Pugh score of 10–15): Do not use combination products with naloxone.
    - Consider decreasing buprenorphine initiation and titration doses by 50%.
    - Monitor for signs and symptoms of toxicity or overdose caused by increased buprenorphine levels.
- Methadone
  - Lower starting doses should be considered with slower than typical titrations, if hepatic impairment due to hepatic metabolism; extensive guidance not available.
- Naltrexone
  - Generally, should not be used if hepatic enzymes are greater than 5 times the upper limit of normal.
  - Preexisting liver abnormalities increase the risk of acute hepatitis.
  - LFT elevations are not expected with use in the absence of other risk factors for liver dysfunction.
    - May be used in patients with severe comorbidities such as hepatitis C and HIV without expected increase in LFTs.
  - No case reports have definitely associated naltrexone use with hepatoxicity; some experts indicate that baseline and repeat monitoring of LFTs is not necessary.[29,30]

Renal Impairment

- Methadone
  - Lower starting doses should be considered, if renal impairment, however, extensive guidance for dose adjustments in renal insufficiency are not available.
  - Methadone has been used in patients undergoing hemodialysis without need for dose adjustments.[31,32]
- Naltrexone
  - Extensive renal elimination of parent drug and active metabolite, 6-beta naltrexol.
  - Use with caution in moderate to severe impairment.

Adolescents[4,28]

- Substance use disorders in adolescents are common in those with co-morbid psychiatric illness and/or who experience peer or family pressures or exposure.
- A comprehensive care plan including thorough assessment, case management, family therapy (i.e. Family Behavior Therapy, Multidimensional Family Therapy, Brief Strategic Family Therapy, Functional Family Therapy, etc.) which consider culture and gender are critical for adolescent substance use care.
- Therapy in group settings should be conducted by trained counselors or therapists as some group members may reinforce drug use and distract from the purpose of the therapy.
- Buprenorphine is FDA approved for those 18 and older but has been studied and is suggested to be efficacious in individuals as young as 16.
- Methadone treatment can be provided to patients younger than 18, if they have parent or legal guardian informed consent following at least two documented unsuccessful, medically supervised withdrawals or treatments without OUD medication in a 12-month period.

Older Adults

- Buprenorphine
  - Use with caution and titrate slowly because of increased risk of adverse drug reactions
- Methadone
  - Use of low doses is recommended with close monitoring of respiratory and central nervous system depression[16]

Pregnancy/Lactation[3,4,33]

Females with child-bearing potential should be educated about risks with pregnancy and counseled on treatment recommendations, if pregnancy were to occur. Abrupt discontinuation of opioids or medically supervised withdrawal in pregnancy increases the risk of overdose death and harm to the fetus secondary to relapse. Medication assisted therapy with an opioid agonist is recommended for pregnant women. Methadone has previously been the agonist treatment of choice for pregnant women, however, emerging evidence supporting use of buprenorphine has become available. Birth defects and neurodevelopmental consequences to infants have not been associated with methadone or buprenorphine use during pregnancy.

- Buprenorphine
  - Experts are unable to reach consensus on whether buprenorphine monoproduct or combination product is preferred in treating pregnant women. Emerging data show that the combination product is likely safe, however, carries the risk of precipitated withdrawal in the fetus, if it is injected or snorted.
  - Limited data are available regarding use of buprenorphine implants or injection during pregnancy.
  - Buprenorphine passes into breastmilk. Advise breastfeeding women taking buprenorphine to monitor the infant for signs of excessive drowsiness or breathing disturbances.
- Methadone
  - Patients stable on methadone at the time of pregnancy should not have their medication changed or discontinued.
  - Dose adjustments during pregnancy may be required, especially during the third-trimester. Methadone serum concentrations can be monitored to guide adjustments in additional to clinical presentation.
- Naltrexone
  - Naltrexone is not recommended to be initiated during pregnancy due to the risk of precipitating opioid withdrawal. Patients currently on naltrexone who become pregnant are recommended to continue this medication through pregnancy with consideration of the unknown harm to the fetus and potential benefit for controlled opioid use disorder during pregnancy. If naltrexone is discontinued during pregnancy, buprenorphine or methadone should be considered versus reinitiating of naltrexone.
  - Neonatal abstinence syndrome (NAS) is not expected to occur with naltrexone.
  - If naltrexone is recommended to be continued, breastfeeding is encouraged as it is minimally excreted into the breastmilk.

During delivery, medications such as butorphanol, nalbuphine, and pentazocine should be avoided in patients on opioid agonist therapy, as they may induce precipitated withdrawal during labor. If opioid agonists are used during pregnancy, upon delivery, newborns may experience neonatal abstinence syndrome (NAS), which may occur for weeks following delivery pending the duration of exposure and the type of opioid the fetus was exposed to in utero. These babies are also at higher risk for low birth weight and respiratory complications.

Breastfeeding while mothers are continued on methadone or buprenorphine is encouraged as it may decrease symptoms of NAS as well as provide clinical benefits of breastfeeding overall. Breastfeeding is not recommended if the mother has Human Immunodeficiency Virus (HIV), has relapsed, or other contraindications are identified.

Methadone or morphine are commonly used to decrease withdrawal symptoms in newborns experiencing NAS.

Co-Occurring Disorders

Mental Illness[14,34]

- In 2016, 43.3% of adults with a substance use disorder (SUD) suffered from co-occurring mental illness compared with 16.1% in those without a SUD; 18.5% of adults with any mental illness also met criteria for a SUD compared with 5.4% of adults without a co-occurring mental illness.
- Almost 50% of adults with co-occurring mental illness and SUD received specialty substance use or mental health treatment in 2016.
- Drug-drug interactions exist between both methadone and buprenorphine and many psychotropic medications.
- Naltrexone carries rare risk of depression; however, it is not considered clinically significant.

HIV

- OUD is associated with HIV risk behaviors including sharing needles for intravenous use and risky sexual behaviors.[35]
- Patients with OUD should be screened for HIV, especially if they have risk factors for infection (i.e., injection drug use, high risk sexual behaviors).
- Several national HIV and infectious disease organizations have recommended increasing federal funding for monitoring and responding to OUD-related infectious disease epidemics, including HIV, as well as expanding access to syringe-exchange and safe injection or consumption programs.[36]
- Methadone and buprenorphine have been shown to reduce rates of HIV risk behavior.[4]
- Methadone and buprenorphine interact with many antiretroviral agents.[37]

Hepatitis C[38]

- Shared use of needles or intranasal drug equipment increases the risk of hepatitis C infection. As hepatitis progresses, cirrhosis and liver cancer may occur. Hepatitis C should not delay treatment of opioid use disorder.
- Methadone and buprenorphine may be used in individuals with hepatitis C. If liver enzymes trend to five times the upper limit of normal, it is reasonable to evaluate the need for dose adjustments due to hepatic dysfunction (see Special Populations: Hepatic Impairment).
- Naltrexone has been associated with hepatitis in the presence of liver disease secondary to alcohol, viral hepatitis, or other preexisting liver abnormalities. Liver function tests should be monitored during treatment. If acute hepatitis or severe liver disease occurs, naltrexone should be discontinued and hepatitis should be treated.

Co-Occurring Substance Use Disorders[4]

- Concomitant alcohol and benzodiazepine use (prescribed or illicit) are common among those with OUD. The FDA recommends acknowledgement of increased risk of adverse reactions and overdose death, however, evidence-based treatment of OUD with opioid agonist treatment should not be denied to these patients due to combined use alone. Methods for reducing risk per the FDA can be found at https://www.fda.gov/downloads/Drugs/DrugSafety/UCM576377.pdf.
- Individuals with opioid and alcohol use disorders may benefit from naltrexone therapy for those not taking opioid agonist treatment. If opioid agonist treatment is used for opioids use disorder, medication such as disulfiram, acamprosate, or topiramate (off-label) can be considered for alcohol use disorder.
- If risky polysubstance use is present, behavioral treatment with contingency management should be offered in addition to pharmacologic treatment to reduce other substance use and to improve medication adherence.

Harm Reduction Strategies

Harm reduction strategies should be reviewed for all individuals with opioid use disorder in effort to decrease morbidity and mortality. Additional guidance can be found at CPNP's Harm Reduction Strategies for People Who Inject Drugs: Considerations for Pharmacists.

Other Resources

TIP 63: Medications for Opioid Use Disorder – Full Document (Including Executive Summary and Parts 1-5)

ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use

ASHP's The Pharmacist's Guide to Opioid Use Disorders

References

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