

# Opioid Use Disorder: Medical Treatment Options

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Opioid use disorder is highly prevalent and can be fatal. At least 2.1 million Americans 12 years and older had opioid use disorder in 2016, and approximately 47,000 Americans died from opioid overdoses in 2017. Opioid use disorder is a chronic relapsing condition, the treatment of which falls within the scope of practice of family physicians. With appropriate medication-assisted treatment, patients are more likely to enter full recovery. Methadone and buprenorphine are opioid agonists that reduce mortality, opioid use, and HIV and hepatitis C virus transmission while increasing treatment retention. Intramuscular naltrexone is not as well studied and is harder to initiate than opioid agonists because of the need to abstain for approximately one week before the first dose. However, among those who start naltrexone, it can reduce opioid use and craving. Choosing the correct medication for a given patient depends on patient preference, local availability of opioid treatment programs, anticipated effectiveness, and adverse effects. Discontinuation of pharmacotherapy increases the risk of relapse; therefore, patients should be encouraged to continue treatment indefinitely. Many patients with opioid use disorder are treated in primary care, where effective addiction treatment can be provided. Family physicians are ideally positioned to diagnose opioid use disorder, provide evidence-based treatment with buprenorphine or naltrexone, refer patients for methadone as appropriate, and lead the response to the current opioid crisis. (*Am Fam Physician*. 2019;100(7):416-425. Copyright © 2019 American Academy of Family Physicians.)

**Opioid use disorder** has reached epidemic proportions in the United States. At least 2.1 million Americans 12 years and older had opioid use disorder in 2016,<sup>1</sup> and approximately 47,000 Americans died from opioid overdoses in 2017.<sup>2</sup> People with opioid use disorder experience a loss of control over their use that can lead to physical disease and psychosocial disruptions, including unemployment, family disruption, and incarceration. Opioid use disorder can be fatal, with mortality rates 10-fold higher than in the general

population.<sup>3</sup> Death can occur from overdose, cardiovascular disease, or infectious diseases such as hepatitis C virus, HIV, and sepsis.

Opioid use disorder should be treated as a chronic condition with longitudinal, team-based, patient-centered care. Similar to type 2 diabetes mellitus or hypertension, opioid use disorder has genetic, environmental, and behavioral causes; the disorder responds best to long-term treatment with medication supplemented by behavior therapies. The American Academy of Family Physicians position paper on chronic pain and opioid misuse supports integrated chronic care with medication-assisted treatment, also known as medication addiction treatment, as part of a comprehensive primary care practice.<sup>4</sup>

Despite strong evidence that opioid use disorder is a chronic disease that responds to effective medical treatment, stigma against people who use illicit drugs can limit access to care. Furthermore, racial biases amplify negative consequences of substance use. For example, drug arrests are more likely to lead to treatment in white people

See related editorial on page 396.

**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 398.

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**Patient information:** Handouts on this topic are available at <https://www.aafp.org/afp/2018/0301/p313-s1.html> and <https://familydoctor.org/condition/opioid-addiction/>.

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
All adult patients should be screened for opioid use disorder in primary care. <sup>11</sup>	C	Expert opinion found in some clinical guidelines
Patients with opioid use disorder should be offered maintenance treatment with pharmacotherapy. <sup>11,15-17,19,20,32</sup>	A	Multiple clinical trials showing reduced opioid use and mortality
Pharmacotherapy for opioid use disorder should be continued for as long as it helps the patient; patients should not be required to discontinue according to preset timelines. <sup>11,31</sup>	A	Consistent results showing reduced mortality
Participation in behavior therapies may be helpful for some patients with opioid use disorder, but studies are equivocal; it should not be a prerequisite for buprenorphine treatment. <sup>11,33,34</sup>	B	Limited clinical trials
Naloxone should be prescribed to all patients with opioid use disorder or high-risk prescription opioid use or who use any illicit drugs to prevent overdose. <sup>55-57</sup>	C	Expert opinion and consensus guidelines

**A** = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <https://www.aafp.org/afpsort>.

and to incarceration in black people.<sup>5</sup> To mitigate stigma, family physicians can emphasize the chronic disease model of addiction; avoid language such as abuser, dirty, and junkie; and participate in unconscious bias training.<sup>6,7</sup>

### Risk Factors and Screening

Patients who have a history of trauma, adverse childhood events, and mental illness are at increased risk of opioid use disorder. Heritability of substance use disorder is estimated to be greater than 50%,<sup>8</sup> and family history is a strong predictor of disease.

In 2008, the U.S. Preventive Services Task Force found insufficient evidence to assess the balance of benefits and harms of screening adolescents and adults for illicit drug use<sup>9</sup>; however, the task force recently announced a draft guideline that recommends screening all adults older than 18 years for illicit drug use.<sup>10</sup> Some experts have also recommended screening all adults in primary care for opioid use disorder.<sup>11</sup> Screening can be accomplished with a single question: How many times in the past year have you used an illegal drug or prescription medication for nonmedical reasons?<sup>12</sup> A response of “at least once” is a positive screen

and should prompt further assessment. Criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., should then be used to make a diagnosis (Table 1).<sup>13</sup>

### Medications for Opioid Use Disorder

With appropriate medications, patients are more likely to enter full recovery, which includes the ability to make self-directed choices, to contribute to family and community, and to reach one’s full potential.<sup>14</sup>

Multiple medications are approved by the U.S. Food and Drug Administration for opioid use disorder (Table 2).<sup>15-21</sup> Oral methadone, sublingual buprenorphine/naloxone (Suboxone), sublingual buprenorphine (Subutex), buprenorphine implants (Probuphine), intramuscular long-acting buprenorphine (Sublocade), and intramuscular long-acting naltrexone (Vivitrol) are effective treatments for opioid use disorder. Buprenorphine is approved by the U.S. Food and Drug Administration for patients 16 years and older, and methadone and naltrex-

one are approved for patients who are at least 18 years of age<sup>22</sup> (Table 3).<sup>11,21-30</sup>

Buprenorphine and methadone are safe and effective for use in pregnancy. They improve maternal and neonatal outcomes and are first-line treatments for opioid use disorder in pregnancy<sup>25</sup> (Table 3).<sup>11,21-30</sup> Family physicians can help stabilize families by integrating buprenorphine therapy with prenatal and postpartum care.

Medication selection should involve shared decision-making with patients and depends on effectiveness, adverse effects, patient preference, and availability (Table 2).<sup>15-21</sup> Buprenorphine, methadone, and naltrexone work by reducing cravings and preventing intoxication if the patient resumes opioid use. Additionally, buprenorphine and methadone treat and prevent withdrawal and can help treat pain.

Medically assisted withdrawal, or detoxification, has high relapse rates, with more than 90% of patients returning to use within one month.<sup>31</sup> Medications for addiction are most effective when prescribed as long-term, often lifelong, therapy. Patients should be discouraged from tapering off medication without a compelling cause.<sup>11</sup>

**TABLE 1****DSM-5 Diagnostic Criteria for Opioid Use Disorder**

A. A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
  - a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
  - b. A markedly diminished effect with continued use of the same amount of an opioid.

**Note:** This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

11. Withdrawal, as manifested by either of the following:

- a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal, pp. 547-548).
- b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

**Note:** This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

*Specify if:*

**In early remission:** After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids," may be met).

**In sustained remission:** After full criteria for opioid use disorder were previously met, none of the criteria for opioid use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, "Craving, or a strong desire or urge to use opioids," may be met).

*Specify if:*

**On maintenance therapy:** This additional specifier is used if the individual is taking a prescribed agonist medication such as methadone or buprenorphine and none of the criteria for opioid use disorder have been met for that class of medication (except tolerance to, or withdrawal from, the agonist). This category also applies to those individuals being maintained on a partial agonist, an agonist/antagonist, or a full antagonist such as oral naltrexone or depot naltrexone.

**In a controlled environment:** This additional specifier is used if the individual is in an environment where access to opioids is restricted.

**Coding based on current severity:** Note for ICD-10-CM codes: If an opioid intoxication, opioid withdrawal, or another opioid-induced mental disorder is also present, do not use the codes below for opioid use disorder. Instead, the comorbid opioid use disorder is indicated in the 4th character of the opioid-induced disorder code (see the coding note for opioid intoxication, opioid withdrawal, or a specific opioid-induced mental disorder). For example, if there is comorbid opioid-induced depressive disorder and opioid use disorder, only the opioid-induced depressive disorder code is given, with the 4th character indicating whether the comorbid opioid use disorder is mild, moderate, or severe: F11.14 for mild opioid use disorder with opioid-induced depressive disorder or F11.24 for moderate or severe opioid use disorder with opioid-induced depressive disorder.

*Specify current severity:*

**305.50 (F11.10) Mild:** Presence of 2–3 symptoms.

**304.00 (F11.20) Moderate:** Presence of 4–5 symptoms.

**304.00 (F11.20) Severe:** Presence of 6 or more symptoms.

DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; ICD-10-CM = *International Classification of Diseases*, 10th Revision, Clinical Modification.

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Long-term pharmacotherapy for opioid use disorder doubles the rate of abstinence relative to behavior therapy alone.<sup>32</sup> Stand-alone behavior therapy is reserved for patients who decline medications. Adding behavior therapy

to buprenorphine may not improve patient outcomes, with some studies showing benefit and others showing no improvement in treatment retention or illicit opioid use.<sup>33,34</sup> Given this evidence, participation in behavior therapy

**TABLE 2**

### Comparison of Methadone, Buprenorphine, and Naltrexone for Opioid Use Disorder

Factors	Methadone	Buprenorphine	Naltrexone (Vivitrol)
Adverse effects	Sedation may occur Constipation Hypogonadism Prolonged QT interval Drug-drug interactions Overdose is possible at high dose or in combination with other drugs	Sedation rare Headache Nausea Constipation Insomnia/hypomania in predisposed patients	Injection site reactions Headache Depression Insomnia Increased alanine transaminase Increased creatine phosphokinase Difficult pain management Decreased tolerance and may therefore increase risk of overdose if return to use
Effectiveness	Most studied compared with buprenorphine and naltrexone Treatment retention superior to low-dose buprenorphine; equivalent to high-dose buprenorphine <sup>15</sup> Associated with decreases in mortality (all-cause mortality is three times higher when methadone is stopped <sup>16</sup> ), opioid use, HIV transmission, and risky behaviors <sup>16,17</sup>	At doses > 16 mg, treatment retention equivalent to methadone <sup>16</sup> and higher than naltrexone <sup>18,19</sup> All-cause mortality reduced by 50% <sup>16</sup> Much more effective than placebo at treatment retention (risk ratio = 1.82) and decreased illicit opioid-positive urine samples <sup>15</sup>	Least well studied compared with methadone and buprenorphine Oral form is ineffective Monthly intramuscular form has better treatment retention than nonpharmacologic therapies but the lowest treatment retention of the three medication options Patients who successfully complete induction phase may have treatment retention similar to those on buprenorphine <sup>18,19</sup> Has not been shown to decrease all-cause or drug-specific mortality <sup>20</sup>
Location of maintenance treatment	Federally certified opioid treatment program	Primary care clinic, psychiatric clinic, prenatal clinic, substance use disorder treatment program, opioid treatment program, or any outpatient setting	Primary care clinic, psychiatric clinic, substance use disorder treatment program, opioid treatment program, or any outpatient setting
Patient considerations	No withdrawal required for treatment initiation Initially must be seen daily	Mild withdrawal required for treatment initiation, usually 8 to 48 hours of abstinence May need to be seen one to two times per week initially, can typically be spaced to monthly visits	Must completely withdraw from opioids before treatment initiation, usually 7 to 14 days of abstinence May be seen monthly for injections
Regulatory considerations <sup>21</sup>	Must be administered in opioid treatment program or be dispensed to inpatient hospitalized for another diagnosis	Prescriber must have a Drug Enforcement Administration waiver or be providing addiction treatment incidental to hospitalization for another diagnosis	No restrictions on prescribing Must be stored in clinic refrigerator and administered by trained staff

Information from references 15-21.

**TABLE 3****Treatment of Opioid Use Disorder in Specific Populations**

Population	Methadone	Buprenorphine	Naltrexone (Vivitrol)
Adolescents <sup>22</sup>	<b>Parental consent requirements vary by state</b> In most cases, minors are restricted from methadone treatment	Approved by the FDA for treatment of adolescents 16 years and older Most common treatment among adolescents	Not approved by the FDA for use in adolescents but is used in clinical practice
Inpatients	<b>Drug Enforcement Administration regulations permit continuing or newly starting inpatients on medication-assisted treatment<sup>21</sup>; additional regulations may vary by state. See <a href="https://www.bridgetotreatment.org/resources">https://www.bridgetotreatment.org/resources</a> for more information.</b>		
Starting medications	Starting dosage for inpatients: 20 to 30 mg for first dose, may give additional 10 mg if not sedated after 4 hours Maximum dosages: day 1, 40 mg; day 2, 50 mg; day 3, 60 mg; thereafter, increase by 10 mg every 5 days as needed for cravings or withdrawal <sup>11</sup>	Starting dosage: 4 to 8 mg for first dose, when clinical opiate withdrawal scale score is $\geq 8$ in most cases. <sup>11</sup> Give additional doses per usual buprenorphine initiation protocols Typical dosage: day 1, 4 to 12 mg; day 2, 4 to 16 mg, depending on clinical opiate withdrawal scale scores and cravings Titrate to elimination of withdrawal and cravings	Dosage: 380 mg intramuscularly every 4 weeks Consider naloxone challenge before first dose
Discharge <sup>21</sup>	Patient may return for administered doses for up to 72 hours or must go to an opioid treatment program Prescribing methadone for the treatment of opioid use disorder is illegal	Buprenorphine-waivered physician, nurse practitioner, or physician assistant must write discharge prescription or patient may return for administered doses for up to 72 hours	Any clinician may prescribe and intramuscularly administer before discharge
<b>Pain</b>			
Acute pain or surgery <sup>23</sup>	Full dose should be continued (consider three times daily) Use additional opioid and nonopioid analgesics as needed	Full dose should be continued (consider three times daily) in most cases Rarely may decrease to 8 to 12 mg to optimize analgesia Use additional opioid and nonopioid analgesics as needed	Hold naltrexone Opioids will be much less effective; use nonopioid analgesics such as ketamine and regional blocks If opioids are prescribed, administer high doses of opioids in a closely monitored setting because the risk of oversedation increases as naltrexone dissociates from opioid receptors
Chronic pain <sup>23</sup>	Analgesia lasts 4 to 8 hours, so daily dosing in opioid treatment programs is insufficient for pain management Rarely provide additional opioids or split-dose methadone Maximize nonopioid pain management	Sublingual formulation is not approved by the FDA for pain but is effective <sup>24</sup> Transdermal and IV forms are approved for pain but not for opioid use disorder Analgesia lasts 8 hours for sublingual form; can be divided into three times daily dosing for patients with chronic pain and opioid use disorder Excellent first-choice opioid for moderate- to high-risk patients	Challenging because it blocks action of opioid analgesics Maximize nonopioid pain management

FDA = U.S. Food and Drug Administration; IV = intravenous.

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**TABLE 3** (continued)

### Treatment of Opioid Use Disorder in Specific Populations

Population	Methadone	Buprenorphine	Naltrexone (Vivitrol)
Pregnancy <sup>25,26</sup>	<b>Methadone and buprenorphine (as mono-product without naloxone) are evidence based and effective; use shared decision-making. Naltrexone is not FDA approved for use in pregnancy.</b>		
Maternal factors	Higher treatment retention than buprenorphine <sup>27</sup> Reduces opioid use, IV use, overdose, and mortality	May have lower treatment retention than methadone <sup>27</sup> Reduces opioid use, IV use, overdose, and mortality	Scant evidence in pregnancy, generally avoided <sup>25</sup> May consider continuing in patients who become pregnant while stable on naltrexone
Neonatal factors	Reduces preterm birth and low birth weight compared with no treatment Higher risk of preterm birth, lower birth weight, and increased head circumference compared with buprenorphine <sup>28</sup>	Lower risk of preterm birth, higher birth weight, and increased head circumference than methadone or no treatment <sup>28</sup>	No trial data Small case series from women who became pregnant while receiving naltrexone show normal neonatal outcomes <sup>29</sup> Animal studies show possible increased fetal growth <sup>30</sup>
Neonatal abstinence syndrome <sup>27</sup>	More severe neonatal abstinence syndrome; longer hospitalization than buprenorphine	Less severe neonatal abstinence syndrome; shorter hospitalization than methadone	No data, but biologically unlikely to occur

FDA = U.S. Food and Drug Administration; IV = intravenous.

Information from references 11, and 21-30.

should not be a precondition of receiving pharmacotherapy.<sup>11</sup> Patients who engage in behavior therapy should seek therapists who support prescribing medication for opioid use disorder. Buprenorphine and naltrexone treatment can be integrated into family medicine clinics by using the Chronic Care Model.<sup>35</sup> Behavioral health integration and group visits can enhance this model but are not required for successful outcomes.<sup>36,37</sup> Studies have found no difference in outcomes for patients treated with buprenorphine in primary care vs. specialty addiction treatment.<sup>38</sup> Table 4 shows a holistic approach to providing primary care for opioid use disorder.<sup>39</sup>

### Methadone

#### MECHANISM

Methadone is a full agonist of the opioid receptor that prevents withdrawal, reduces cravings, and blunts the effects of other opioids.

#### EFFECTIVENESS

Methadone is the best studied medication for treating opioid use disorder and may be most effective for treatment retention.<sup>15</sup> Its use is associated with a decrease in all-cause

mortality of more than 50%,<sup>16</sup> decreases in HIV risk behaviors,<sup>40</sup> more than 50% decreased odds of hepatitis C virus incidence, and reduced use of nonprescribed opioids.<sup>17</sup>

### REGULATORY ISSUES

Methadone can be prescribed for pain in primary care settings and administered for opioid use disorder in hospital settings; however, it is legal to prescribe outpatient methadone for opioid use disorder only in a federally certified opioid treatment program. To refer patients, consult the Substance Abuse and Mental Health Services Administration's opioid treatment program directory (<https://dpt2.samhsa.gov/treatment/directory.aspx>). Patients referred to these programs will initially receive daily directly observed dosing with frequent urine drug testing and behavior therapy. With increasing stability, patients may visit the program less often.

### PATIENT SELECTION

Patients must have confirmed opioid use disorder and generally must be at least 18 years of age to enroll in an opioid treatment program. Patients with impaired liver function must also be monitored for oversedation, and

electrocardiography should be performed on patients at risk for prolonged QT interval or patients receiving more than 120 mg per day of methadone because of concern for increased risk of torsades de pointes.<sup>41-43</sup> Physicians should discuss with patients whether frequent visits to the program during the early months of maintenance therapy will help or hinder their stabilization.

### DOSING CONSIDERATIONS

Dosing protocols are set by federal regulations. Initially, patients receive a low dosage, typically 20 to 40 mg per day. The dosage should be slowly increased until the medication prevents cravings while still minimizing sedation. Methadone is more effective at higher daily dosages (80 to 120 mg) than at moderate dosages (40 to 50 mg).<sup>43</sup>

### Buprenorphine

A comprehensive discussion of buprenorphine can be found in a recent *American Family Physician* article.<sup>44</sup>

TABLE 4

#### Recommended Health Care Maintenance for People with Opioid Use Disorder

Screen for HIV, hepatitis B virus, hepatitis C virus, sexually transmitted infections, and tuberculosis (at least annually for most patients)

Vaccinate against hepatitis A, hepatitis B, tetanus, diphtheria-pertussis, influenza, and pneumococcus

Aggressively manage cardiac risk factors including hypertension, lipid control, and smoking, particularly for people who also use stimulants or tobacco

Treat other comorbid substance use disorders, including tobacco and alcohol use disorders

Treat comorbid psychiatric disorders

Educate patients about safer injection practices and provide clean injection equipment

Offer pre-exposure HIV prophylaxis for patients who inject drugs or have other risk factors

Prescribe naloxone and discuss precautions such as test shots and using with friends

Offer methadone, buprenorphine, or naltrexone (Vivitrol) to all patients

*Adapted from San Francisco Department of Public Health. Opioid Stewardship and Chronic Pain: A Guide for Primary Care Providers. San Francisco, Calif. March 2018.*

### MECHANISM

Buprenorphine is a partial agonist of the opioid receptor. At increasing doses, buprenorphine reaches a ceiling effect. This minimizes sedation, euphoria, and respiratory depression. It is therefore rare for patients to overdose on buprenorphine, with most overdoses occurring in children or in adults who combined buprenorphine with benzodiazepines or large amounts of alcohol.<sup>45,46</sup>

If a patient's opioid receptors are occupied by a full agonist such as heroin or prescription opioids, taking buprenorphine displaces the full agonist from the receptor and replaces it with a partial agonist, reducing receptor activation. This can cause precipitated withdrawal. Therefore, patients should be in mild to moderate withdrawal before receiving buprenorphine.

Buprenorphine can be coformulated with naloxone, an opioid antagonist that is not orally or sublingually bioavailable. Naloxone has no effect on patients who take the medication as prescribed. It is added as an abuse deterrent; if injected or inhaled, the naloxone will be absorbed and may cause withdrawal.

### EFFECTIVENESS

Buprenorphine and buprenorphine/naloxone are effective and can be prescribed in primary care clinics by appropriately trained clinicians. Buprenorphine, when provided in dosages of at least 16 mg per day, seems to be as effective as methadone at reducing illicit opioid use and for treatment retention.<sup>15</sup>

### REGULATORY ISSUES

To prescribe buprenorphine for opioid use disorder, a physician must be board certified in addiction medicine or addiction psychiatry or complete an eight-hour training session to receive a waiver from the Drug Enforcement Administration. Nurse practitioners and physician assistants need 16 additional hours of training. In hospital settings, physicians without Drug Enforcement Administration waivers are allowed to administer buprenorphine to treat withdrawal and opioid use disorder.

Without directly observed dosing, diversion of buprenorphine is a risk; however, minimal risk of overdose and limited euphoria occur. Most patients who use illicit buprenorphine do so to treat their withdrawal symptoms and to quit opioids rather than to achieve euphoria.<sup>47</sup>

### PATIENT SELECTION

Most patients with opioid use disorder are candidates for primary care prescription of buprenorphine. Previously, the U.S. Food and Drug Administration warned against prescribing buprenorphine to patients who used

benzodiazepines or alcohol because of the elevated risk of overdose. This warning was recently removed because failing to treat opioid use disorder in the setting of alcohol and benzodiazepine use is riskier than treatment.<sup>48</sup> Hepatotoxicity has been reported with buprenorphine use, and naloxone may have more potency in those with liver disease; therefore, patients with Child-Pugh scores of 7 or higher should be prescribed buprenorphine alone at a decreased dosage, and liver function tests should be monitored.<sup>11</sup> Patients receiving chronic opioids can be transitioned to buprenorphine for pain management with good effect<sup>49</sup> (*Table 3*<sup>11,21-30</sup>).

### DOSING CONSIDERATIONS

Patients must be in mild to moderate withdrawal before initiating treatment. Medication initiation can safely occur at home.<sup>50</sup> Over ensuing days, the patient's dose should be titrated up to eliminate withdrawal symptoms and to reduce cravings. Typical doses range from 12 mg to 24 mg; higher doses are associated with improved treatment retention and reduced illicit opioid use.<sup>11</sup>

### Naltrexone

#### MECHANISM

Naltrexone is an antagonist of the opioid receptor. Upon binding, it provides opioid blockade, limiting the effect of other opioids and reducing cravings.<sup>51</sup>

#### EFFECTIVENESS

Oral naltrexone (Revia) is rarely effective for patients with opioid use disorder because of low treatment adherence.<sup>18</sup> Intramuscular naltrexone reduces cravings and opioid use, but its effectiveness is limited by high drop-out rates during treatment induction. Patients who successfully initiate intramuscular naltrexone therapy appear to have rates of opioid abstinence similar to patients receiving buprenorphine.<sup>19</sup> Unlike buprenorphine and methadone, naltrexone has not been shown to reduce the risk of mortality and overdose.<sup>20</sup> Patients receiving naltrexone lose their opioid tolerance; therefore, a greater risk of overdose could occur if patients return to using opioids.<sup>52</sup>

#### REGULATORY ISSUES

Naltrexone can be prescribed by any physician. The medication must be stored in a refrigerator and administered by trained staff.

#### PATIENT SELECTION

Patients must abstain from opioids for seven to 14 days before initiating naltrexone therapy to avoid precipitated withdrawal. The intramuscular formulation has been associated with rare injection site reactions and transaminitis.<sup>11</sup>

In addition, patients receiving naltrexone will not respond to standard doses of opioids (*Table 3*<sup>11,21-30</sup>). With severe pain, patients may require alternative medications, regional or general anesthesia, or high dosages of opioids. Naltrexone should be withheld before elective surgery, and patients should wear medical alert jewelry or carry a wallet card with information about the medication.

### DOSING CONSIDERATIONS

Intramuscular naltrexone is administered in a dosage of 380 mg every four weeks. To confirm that the patient has completed opioid withdrawal, a naloxone challenge (i.e., 0.8 mg subcutaneously) may be administered before the first dose of naltrexone.<sup>11</sup>

### Reducing Harm

All patients should be offered pharmacotherapy for opioid use disorder; however, some may not stop using, and others may return to use. It is important to discuss various harm reduction strategies with all patients who have a history of opioid use disorder. For more information, see *American Family Physician's* comprehensive article about caring for people who inject drugs.<sup>53</sup>

### NALOXONE

The key medication for harm reduction in opioid use disorder is naloxone. Naloxone should be prescribed to any patient who receives chronic prescribed opioids (particularly in dosages greater than or equal to 50 morphine mg equivalents daily<sup>54</sup>), has a history of opioid use disorder, or uses illicit drugs.<sup>55,56</sup> Nonmedical opioids, benzodiazepines, cocaine, and methamphetamine may be contaminated with fentanyl and other synthetic opioids, placing all people who use illicit drugs at risk of opioid overdose.<sup>57</sup> Naloxone should be prescribed to friends or family who might witness an overdose. Most states have laws that allow prescribing to third parties; these laws protect prescribers and bystanders who administer naloxone.<sup>58</sup> Intranasal formulations are easily administered by individuals with minimal training. Patients typically appreciate being offered naloxone and do not increase unsafe use patterns (e.g., taking extra doses, mixing with other drugs) after receiving the prescription.<sup>59</sup> Visit <https://www.prescribetoprevent.org> for more information.

**Data Sources:** A PubMed search was completed using the search terms opioid use disorder treatment; buprenorphine; methadone; naltrexone; buprenorphine in pregnancy; methadone in pregnancy; naltrexone in pregnancy; pain buprenorphine; pain naltrexone; pain methadone; buprenorphine in hospital; methadone in hospital; naltrexone in hospital; buprenorphine adolescent; methadone adolescent; and naltrexone adolescent.

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In addition, we used Essential Evidence Plus, the Cochrane database, the DEA website, the CDC website, and the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Improvement Protocol website. Search dates: April 15 to May 1, 2018.

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