Medication Management of Co-Occurring Opioid Use Disorder in Mental Health Settings

A Guide for Practitioners

Preface

Psychiatrists, nurse practitioners, and other clinicians who work in mental health settings are in an optimal position to treat co-occurring opioid use and mental health disorders (COD-opioid). The U.S. Food and Drug Administration has approved buprenorphine, naltrexone, and methadone as treatments for opioid use disorder (OUD). Of these, buprenorphine/naloxone (e.g., Suboxone®, Bunavail®, Zubsolv®), buprenorphine (e.g., Subutex®, Sublocade®), and naltrexone extended-release injectable suspension (e.g., Vivitrol®) are available outside federally certified opioid treatment programs and are appropriate for use in mental health settings to enhance the effectiveness of mental health treatment. This “how-to” guide can help practitioners identify clients with COD-opioid in mental health settings and treat these clients with an appropriate medication. It also offers a provider strategy for managing buprenorphine/naloxone or naltrexone extended-release injectable suspension in mental health settings. This guide is for those working in mental health settings and integrated co-occurring disorder programs and other clinicians who prescribe medication for OUD for people with mental health conditions. This guide is not intended to provide comprehensive guidance to federally certified opioid treatment programs.

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## Contents

Preface ................................................................................................................................. iii
Abbreviations ......................................................................................................................... vi
Acknowledgments ..................................................................................................................... vii
Quick-Start Guides: Initiating Medications for Opioid Use Disorder (MOUD) in Mental Health Settings ................................................................................................................................. 1
  QUICK-START GUIDE 1: Medication Management of COD-Opioid 2
  QUICK-START GUIDE 2: Prescribing Considerations: MOUD 3
  QUICK-START GUIDE 3: Prescribing Considerations: Co-Occurring Substance Use Disorders Other Than COD-Opioid 4
  QUICK-START GUIDE 4: Prescribing Considerations: Psychiatric Comorbidities 5
Prescribing MOUD in Mental Health Settings ........................................................................... 6
  MOUD in the Mental Health Setting 6
  The Role of Mental Health Clinicians in MOUD Treatment 6
  Medications and Psychosocial Support for COD-Opioid 6
  How This Guide Can Help 7
  Management of MOUD via Telehealth 7
Evaluating Clients for COD-Opioid .......................................................................................... 8
  Talking to Clients About Their Opioid Use 8
  Identifying Clients with OUD 8
  Diagnosing OUD 9
  Documenting COD-Opioid 11
Prescribing MOUD to Clients with COD-Opioid .................................................................... 13
  Discussing COD-Opioid with Clients 13
  Prescribing Naloxone 14
  Selecting the Right Medication 15
  Continuing MOUD 17
  Medication Management Counseling 17
  Urine Toxicology and Lab Testing 19
  Legal Liability and MOUD 20
  Additional Resources 20
### Addressing Other Substance Use and Psychiatric Comorbidities That Are Common in Clients with COD-Opioid

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addressing Other Substance Use</td>
<td>21</td>
</tr>
<tr>
<td>Addressing Common Psychiatric Comorbidities</td>
<td>22</td>
</tr>
<tr>
<td>Additional Psychosocial Services</td>
<td>24</td>
</tr>
<tr>
<td>Treatment Planning</td>
<td>24</td>
</tr>
</tbody>
</table>

### Appendixes

- **Appendix A.** DSM-5 OUD Diagnosis Worksheet ...........................................25
- **Appendix B.** Overdose Education and Naloxone Distribution ..................27
- **Appendix C.** Treating Tobacco Use Disorder in Mental Health Settings ........28
- **Appendix D.** Medications for Stimulant Use Disorders in Mental Health Settings 29
- **Appendix E.** Identifying Opioid Withdrawal Syndrome .............................32
- **Appendix F.** Buprenorphine/Naloxone Treatment for Clients with COD-Opioid 33
- **Appendix G.** Client Handout ...........................................................................42
- **Appendix H.** Additional Resources for the Treatment of COD-Opioid in Mental Health Settings .................................................................46

### References ...........................................................................................................59
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAM</td>
<td>American Society of Addiction Medicine</td>
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<tr>
<td>AUD</td>
<td>alcohol use disorder</td>
</tr>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>COD-opioid</td>
<td>co-occurring opioid use and mental health disorders</td>
</tr>
<tr>
<td>COWS</td>
<td>Clinical Opiate Withdrawal Scale</td>
</tr>
<tr>
<td>DSM-5</td>
<td><em>Diagnostic and Statistical Manual of Mental Disorders</em>, 5th edition</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
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<tr>
<td>IM</td>
<td>intramuscular</td>
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<tr>
<td>LAI</td>
<td>long-acting injectable</td>
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<tr>
<td>LFT</td>
<td>liver function test</td>
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<tr>
<td>MAT</td>
<td>medication-assisted treatment</td>
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<tr>
<td>MOUD</td>
<td>medication for opioid use disorder</td>
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<tr>
<td>NIDA</td>
<td>National Institute on Drug Abuse</td>
</tr>
<tr>
<td>NM-ASSIST</td>
<td>National Institute on Drug Abuse Modified Alcohol, Smoking and Substance Involvement Screening Test</td>
</tr>
<tr>
<td>OTP</td>
<td>opioid treatment program</td>
</tr>
<tr>
<td>OUD</td>
<td>opioid use disorder</td>
</tr>
<tr>
<td>PCSS</td>
<td>Providers Clinical Support System</td>
</tr>
<tr>
<td>PDMP</td>
<td>prescription drug monitoring program</td>
</tr>
<tr>
<td>PRN</td>
<td>when necessary</td>
</tr>
<tr>
<td>PTSD</td>
<td>posttraumatic stress disorder</td>
</tr>
<tr>
<td>QHS</td>
<td>every night at bedtime</td>
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<tr>
<td>SAMHSA</td>
<td>Substance Abuse and Mental Health Services Administration</td>
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<tr>
<td>SNRI</td>
<td>serotonin–norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>SUD</td>
<td>substance use disorder</td>
</tr>
<tr>
<td>TAPS</td>
<td>Tobacco, Alcohol, Prescription Medication, and Other Substance Use</td>
</tr>
<tr>
<td>TID</td>
<td>three times daily</td>
</tr>
<tr>
<td>TIP</td>
<td>Treatment Improvement Protocol</td>
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Acknowledgments

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Quick-Start Guides: Initiating Medication for Opioid Use Disorder (MOUD) in Mental Health Settings

The following “quick-start” guides are intended to guide clinicians working in mental health settings to identify and treat clients with co-occurring opioid use and mental health disorders (COD-opioid) with MOUD in these settings. The medication strategy outlined in the quick-start guides is appropriate for the majority of clients with COD-opioid, and the general strategy is to offer MOUD as soon as COD-opioid has been identified, prior to additional lengthy assessments. A trial of MOUD generally should be offered to all clients with COD-opioid, including those who decline to participate in psychosocial treatment and/or who decline referrals to other treatment programs.

The four quick-start guides are as follows:

- **Quick-Start Guide 1**: Medication Management of COD-Opioid
- **Quick-Start Guide 2**: Prescribing Considerations: MOUD
- **Quick-Start Guide 3**: Prescribing Considerations: Co-Occurring Substance Use Disorders Other Than COD-Opioid
- **Quick-Start Guide 4**: Prescribing Considerations: Psychiatric Comorbidities
# QUICK-START GUIDE 1: Medication Management of COD-Opioid

<table>
<thead>
<tr>
<th>ACTION</th>
<th>DETAILS</th>
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<tbody>
<tr>
<td><strong>Screen</strong> for and assess readiness to address opioid use disorder (OUD)</td>
<td>- National Institute on Drug Abuse Modified Alcohol, Smoking and Substance Involvement Screening Test (NM-ASSIST) (for adults) (<a href="https://www.nida.nih.gov">NIDA</a>, undated-b)&lt;br&gt;- Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool (for adults) (<a href="https://www.nida.nih.gov">NIDA</a>, undated-d)&lt;br&gt;- Adolescent screening tools:&lt;br&gt;  - Screening to Brief Intervention (NIDA, undated-c)&lt;br&gt;  - Brief Screener for Tobacco, Alcohol, and Other Drugs (<a href="https://www.nida.nih.gov">NIDA</a>, undated-a)&lt;br&gt;- A list of evidence-based screening and assessment tools is available in NIDA, 2021.</td>
</tr>
<tr>
<td><strong>Check</strong> the prescription drug monitoring program (PDMP) report</td>
<td>Each state PDMP is listed at Prescription Drug Monitoring Program Training and Technical Assistance Center, undated. Review PDMP information to assess the pattern of controlled substances that the client has been prescribed and implications for the client's OUD.</td>
</tr>
<tr>
<td><strong>Diagnose</strong> using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (see Appendix A)</td>
<td>Document the diagnosis of OUD as a secondary diagnosis in the client’s chart and treatment plan.</td>
</tr>
<tr>
<td><strong>Offer treatment</strong> with an MOUD and a prescription for naloxone</td>
<td>Ask whether the client is interested in a medication to help them reduce problem opioid use. Co-prescription of naloxone annually is required by many state regulations and is best practice. See Prescribe to Prevent, undated-a.</td>
</tr>
<tr>
<td><strong>Prescribe</strong> and provide instruction about how the client should take medications</td>
<td><strong>Buprenorphine/naloxone:</strong> 8-mg/2-mg tabs/films, take as directed. #28 with refills if the client has barriers to follow-up in the clinic&lt;br&gt;or&lt;br&gt;Administer buprenorphine extended-release injection or naltrexone extended-release injectable suspension and&lt;br&gt;- <strong>Naloxone:</strong> 4-mg/0.1-mL nasal spray kit, #2, 2 refills or&lt;br&gt;- <strong>Naloxone:</strong> 1-mg/mL or 0.4-mg/1-mL naloxone vials #2, two refills with either 3-mL syringe or Luer-Jet® Luer-Lock needleless syringe and either mucosal atomizer devices or 23–25-gauge 1–1.5-inch intramuscular (IM) needles. See Quick-Start Guide 2: Prescribing Considerations for more information.</td>
</tr>
<tr>
<td><strong>Offer lab testing/toxicology</strong></td>
<td>Toxicology testing is not universally required for MOUD to be initiated and managed. Clients with OUD served in settings without the availability of on-site toxicology testing can be referred to a local laboratory or affiliated clinic to obtain any recommended toxicology testing. For clients for whom adherence to MOUD is uncertain, and in situations in which there is not unambiguous improvement following the initiation of MOUD, recommend offering point-of-care immunoassay testing for opioids, oxycodone, methadone, buprenorphine, benzodiazepines, barbiturates, amphetamine, methamphetamine, and cocaine. Fentanyl testing is usually ordered as a separate test. Send the sample for testing for other substances, such as phencyclidine and/or tetrahydrocannabinol, only if there is a clinical reason to assess for these other substances. &lt;br&gt;&lt;br&gt;<strong>Urime:</strong> human chorionic gonadotropin (hCG) in appropriate clients of childbearing age. <strong>Note:</strong> Do not withhold buprenorphine/naloxone from clients with OUD if lab testing has not been performed. For clinically disputed or equivocal results, if the result will change your clinical approach, send the sample for quantitative laboratory confirmatory testing of the questioned substance(s). <strong>Serum tests are not required to treat OUD.</strong> However, when clients have a co-occurring mood, anxiety, or psychotic disorder, consider complete blood count, complete metabolic panel, HIV, hepatitis, rapid plasma regain, thyroid-stimulating hormone vitamins B12 and D, hemoglobin A1C, and lipid panel, as appropriate to the client’s medical history.</td>
</tr>
<tr>
<td><strong>Refer</strong> to additional appropriate services if the client is interested</td>
<td>If the client is interested in additional addiction treatment services beyond what is available in your mental health setting, conduct a level-of-care assessment and support an appropriate referral. Refer clients who require inpatient alcohol or sedative withdrawal management to withdrawal management (“detoxification”) settings.</td>
</tr>
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QUICK-START GUIDE 2: Prescribing Considerations: MOUD

<table>
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<tr>
<th>ACTION</th>
<th>DETAILS</th>
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| Discuss starting MOUD | ● The initial treatment priority is offering MOUD as quickly as feasible, prior to lengthy assessments or treatment-planning sessions.  
● If a client is in opioid withdrawal and/or has used opioids within the prior seven days, sublingual buprenorphine/naloxone is the first-line option.  
● For clients with a week or more of abstinence from most opioids, either a buprenorphine medication or naltrexone extended-release injectable suspension can be feasibility offered. |

Prescribe MOUD

- **Buprenorphine/naloxone**: 8-mg/2-mg tabs/flms, take as directed, #28 with refills if the client has barriers to follow-up in the clinic  
or  
Administer buprenorphine extended-release injection or naltrexone extended-release injectable suspension and  
  - **Naloxone**: 4-mg/0.1-mL nasal spray kit, #2, 2 refills or  
  - **Naloxone**: 1-mg/mL or 0.4-mg/1-mL naloxone vials #2, two refills with either 3-mL syringe or Luer-Jet® Luer-Lock needleless syringe and either mucosal atomizer devices or 23–25-gauge 1–1.5-inch intramuscular (IM) needles.  

**Sublingual buprenorphine/naloxone instructions:**  
For buprenorphine/naloxone, instruct the client to stop use of opioids and wait until they are in mild to moderate opioid withdrawal, and then to self-administer one-half to one tab of buprenorphine/naloxone under their tongue and hold it there until it is fully dissolved; see Randhawa, Brar, and Nolan, 2020.  
The recommended initial dose of buprenorphine/naloxone is 4 mg/1 mg to 8 mg/2 mg.  
Clients can titrate up by 4 mg/1 mg to 8 mg/2 mg in one-hour increments to 16 mg/4 mg during the first day and can self-titrate from 16 mg/4 mg to 24 mg/6 mg on or after the second day, if needed.  
In general, prescriptions of buprenorphine/naloxone of two weeks or more for those with a starting dose of more than 4 mg/1 mg are more likely to increase treatment success.  
Some clients who use fentanyl heavily will better tolerate smaller initial doses of buprenorphine/naloxone, such as 1 mg/0.25 mg or 2 mg/0.5 mg twice daily that are titrated up to the typical 16-mg/4-mg daily dosing (Randhawa, Brar, and Nolan, 2020; see the same for a further discussion of this dosing strategy).  
Write refills if there is any concern about the client not having consistent telephone or transportation access that would interrupt their ability to easily follow up with the clinic for follow-up appointments.  

**Naloxone education:**  
Instruct the client on how to use naloxone in case of opioid overdose (see Appendix B).  

**For clients who decline to accept buprenorphine and naltrexone:**  
Discuss with the client, and, if they agree, refer them to an opioid treatment program that is convenient to the client to start methadone maintenance treatment.  

**For clients who decline to accept MOUD:**  
Encourage the client to return to the clinic for a subsequent visit, and continue to offer MOUD when the client is ready to consider medication treatment options.  

Follow up with the client within the first week of treatment (by phone is fine).
## QUICK-START GUIDE 3: Prescribing Considerations: Co-Occurring Substance Use Disorders Other Than COD-Opioid

<table>
<thead>
<tr>
<th>ACTION</th>
<th>DETAILS</th>
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<tbody>
<tr>
<td><strong>Screen for and assess readiness to address co-occurring alcohol use and mental health disorder (COD-alcohol), tobacco use disorder, and/or stimulant use disorder.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>If alcohol use disorder (AUD)</strong></td>
<td></td>
</tr>
<tr>
<td>Consider naltrexone extended-release injectable suspension</td>
<td>Naltrexone extended-release injectable suspension 380 mg IM monthly if the client has stopped all opioid use for at least a week, including not taking buprenorphine or methadone.</td>
</tr>
<tr>
<td><strong>Consider</strong> acamprosate, topiramate, or gabapentin for individuals on buprenorphine or methadone to avoid opioid antagonism</td>
<td>Start acamprosate 333 mg three times daily (TID) for three days, then increase to 666 mg by mouth TID and/or Start topiramate 25–50 mg every night at bedtime (QHS) and titrate 150–300 mg QHS as tolerated. If starting topiramate, do not neglect to offer contraception to appropriate clients of childbearing age.</td>
</tr>
<tr>
<td><strong>Consider psychosocial support for AUD</strong></td>
<td>Link the client to appropriate AUD counseling and to community supports, such as Alcoholics Anonymous, undated; Medication-Assisted Recovery Anonymous, undated; and/or SMART Recovery, undated.</td>
</tr>
<tr>
<td><strong>If tobacco use disorder</strong></td>
<td>Treatment with nicotine replacement therapy, varenicline, and/or bupropion are recommended medication approaches for smoking cessation. See Appendix C for tobacco use disorder treatment guidance.</td>
</tr>
<tr>
<td><strong>Consider psychosocial support for tobacco use disorder</strong></td>
<td>Link the client to appropriate smoking cessation counseling and to community supports. See Smokefree.gov, undated, for a list of options.</td>
</tr>
<tr>
<td><strong>If stimulant use disorder</strong></td>
<td>See Appendix D for a discussion of treatment options for stimulant use disorder.</td>
</tr>
<tr>
<td>Consider prescribing off-label medications for stimulant use disorder</td>
<td>Contingency management involves giving clients tangible rewards to reinforce positive behaviors, such as abstinence or treatment adherence. See section H10 of Appendix H for resources discussing contingency management.</td>
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## QUICK-START GUIDE 4: Prescribing Considerations: Psychiatric Comorbidities

<table>
<thead>
<tr>
<th>ACTION</th>
<th>DETAILS</th>
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<tbody>
<tr>
<td><strong>If a mood, anxiety, or psychotic disorder</strong></td>
<td></td>
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</tbody>
</table>
- Buprenorphine and naltrexone are appropriate for clients receiving psychiatric medications, so start medication treatments that are otherwise considered appropriate in clients who take MOUD.  
- Avoid starting benzodiazepines in clients with OUD, but do not withhold buprenorphine or naltrexone from clients prescribed benzodiazepines.  
- The benefit of benzodiazepine treatments for severe psychiatric conditions, such as catatonia, may outweigh the risks associated with the use of benzodiazepines in clients with OUD. |
| **For posttraumatic stress disorder (PTSD)** | 
- Offer prazosin; start 1 mg QHS and titrate every three to four days in 1-mg QHS increments until symptoms improve.  
- Additionally, offer selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressants, which are also first-line medication treatments for PTSD in clients without unstabilized bipolar disorder.  
- Individual and group counseling options are available. |
| Counsel the client to not stop taking medications without medical advice | 
- For prazosin, increase dose until nightmares and hypervigilance resolve or until there is persistent dizziness or other adverse effects that do not resolve within a week.  
- For SSRIs/SNRIs, start low and titrate as tolerated. It may take six to eight weeks for maximum benefit, so counsel clients not to stop these medications prematurely. |
| Consider other psychosocial treatment and support | 
- Individual and group counseling options are appropriate for a variety of mental health conditions.  
- MOUD support retention of clients with COD-opioid in psychosocial treatment. |
| If such symptoms as insomnia, nightmares, anxiety, or other concerns are present, such as hepatic or renal disease | 
- Insomnia: trazodone, diphenhydramine, or doxepin. Avoid benzodiazepines or sedatives/hypnotics.  
- Anxiety: SSRI, SNRI, or tricyclic antidepressant, plus consider when necessary (PRN) hydroxyzine, propranolol, or clonidine. Avoid benzodiazepines.  
- Nightmares: doxazosin if prazosin is not tolerated.  
- Okay to prescribe buprenorphine/naloxone if client is already on a benzodiazepine or other sedative, drinks alcohol, or has hepatitis C. Warn clients that benzodiazepines and heavy alcohol use can be dangerous when mixed with opioids.  
- Do not prescribe prazosin, doxazosin, or clonidine in combination with each other (because of risk of hypotension). |
Prescribing MOUD in Mental Health Settings

MOUD in the Mental Health Setting
Long-term use of prescription opioids is common in individuals with mental illness and is a risk factor for heroin use and the development of OUD (Barry et al., 2016; Compton et al., 2016; Jones, 2013; Kern, Akerman, and Nordstrom, 2014; Proctor et al., 2013; Shiner et al., 2017). People with mood and anxiety disorders are twice as likely to use opioid medications as people without mental health problems and are more than three times as likely to use them nonmedically (Davis et al., 2017; Feingold et al., 2018). Opioid use can cause or exacerbate psychiatric symptoms for people with co-occurring mental health disorders (Kampman, Comer, and Cunningham, 2015).

Clients with co-occurring disorders are far more likely to receive mental health care than substance use treatment (50 percent versus 20 percent, respectively) (Harris and Edlund, 2005). This suggests that providing treatment for people with COD-opioid in mental health settings is an important way to increase access to care. Substantial evidence documents the impact of untreated OUD on clients’ mental health, functioning, and quality of life (Volkow et al., 2019).

The Role of Mental Health Clinicians in MOUD Treatment
Clinicians working in mental health settings play an important role in identifying and treating clients with COD-opioid. Successfully addressing COD-opioid involves sequencing treatment to allow MOUD to be offered as quickly as possible, prior to lengthy assessments or treatment-planning sessions. MOUD can rapidly stabilize clients’ OUD, which increases their ability to successfully participate in other components of mental health treatment.

Medications and Psychosocial Support for COD-Opioid
Buprenorphine/naloxone (Suboxone®, Bunavail®, Zubsolv®), buprenorphine (Subutex®, Sublocade®), and naltrexone extended-release injectable suspension (Vivitrol®) are medications approved by the U.S. Food and Drug Administration (FDA) for OUD and are feasible for use by mental health prescribing clinicians to treat appropriate clients with COD-opioid. Clients who receive medication and prescriber-delivered counseling and advice (medication management visits) outside specialty substance use treatment can achieve similar outcomes to those of clients receiving specialty treatment (American Society of Addiction Medicine [ASAM], 2020a).

Optimal treatment for clients with COD-opioid must also address mental health needs. OUD is associated with an increased risk of suicidal ideation and depressive episodes.
Vulnerability because of psychosocial dysfunction in clients with OUD contributes to the elevated risk for suicidal ideation. Individuals with OUD often experience stigma, which fosters a deflated self-attitude that holds clients back from mental health recovery (Moran, Knudsen, and Snyder, 2019).

**How This Guide Can Help**

This guide provides guidelines for identifying COD-opioid clients and offering MOUD. It also provides an overview of the medication support process. The guide can be used in conjunction with the COD toolkit for implementing treatment for people with COD-opioid in outpatient mental health settings (Watkins et al., 2021). Buprenorphine medications prescribed for the indication of OUD are approved for individuals aged 16 years and older, and the dosing protocols are not different for adults and for clients under the age of 18. Naltrexone extended-release injectable suspension is FDA-approved for individuals aged 18 years and older. The use of these medications in adolescents is reviewed in the ASAM National Practice Guideline for the Treatment of Opioid Use Disorder (ASAM, 2020a).

Although this guide focuses on the outpatient setting, buprenorphine, buprenorphine/naloxone, or naltrexone are feasible to offer to clients in all mental health settings, including short- and long-term inpatient psychiatric hospitals, residential settings, day treatment settings, and outpatient settings.

**Management of MOUD via Telehealth**

MOUD can be prescribed remotely using telehealth modalities. The approach described in this manual can be feasibly delivered via telehealth modalities. The following national guidance reviews the major adaptation considerations:

- **Use of Telemedicine While Providing Medication Assisted Treatment (MAT)** (U.S. Drug Enforcement Administration, 2018)
- **Telemedicine and Prescribing Buprenorphine for the Treatment of Opioid Use Disorder** (U.S. Department of Health and Human Services, 2018)
- **Frequently Asked Questions (and Answers!): Treating Opioid Use Disorder via Telehealth — Tips for Primary Care Providers** (Providers Clinical Support System [PCSS], 2020)
Evaluating Clients for COD-Opioid

This section provides an overview of the steps for evaluating a client for COD-opioid in mental health settings. The section provides prompts to help identify potential COD-opioid, DSM-5 criteria for diagnosing an OUD, and guidelines for determining whether treatment with MOUD is appropriate.

Talking to Clients About Their Opioid Use

Clients can become disengaged when their opioid use is introduced for discussion. They might deny that they have a problem with opioids or minimize the extent of their opioid use when they are not ready to discuss it. Clients with chronic pain may fear that their pain medication will be taken away. Even clients who are motivated to change their drug use behavior often are ambivalent about participating in a specialized OUD treatment because of experiences with stigma or fear that they might fail to meet their own or others’ expectations.

As a result, it is critical that clinicians be vigilant when clients may perceive the clinician’s comments to be judgmental. It also is important for clinicians to use a motivational and nonconfrontational approach when discussing opioid use with clients. Providers should build rapport with clients and use such normalizing statements as “many clients use opioids when they are struggling with [mental health symptoms].”

Identifying Clients with OUD

The first step in determining whether a client is appropriate for treatment with MOUD is to assess them for an OUD diagnosis.

There are various screening tools that can be used to select which clients to further assess for a diagnosis of OUD. The NIDA Drug Use Screening Tool: Quick Screen (NM-ASSIST) is one option for adults, and a briefer tool for adults is the TAPS (NIDA, undated-b; NIDA, undated-d). A list of screening tools for adolescents and other populations is available at NIDA, 2021.

For new clients and for returning clients with recently disclosed use of intoxicants, checking your state PDMP can yield important collateral information. Many states have laws requiring prescribers to check the state PDMP associated with prescribing controlled substances, including buprenorphine. Each state PDMP is listed at PDMPassist.org (Prescription Drug Monitoring Program Training and Technical Assistance Center, undated). Review information from the PDMP to assess the pattern of controlled substances that the client has been prescribed and implications for the client’s diagnosis.
Clients with a history of accidental drug overdoses, especially if these resulted in emergency room visits, should be assessed for an OUD diagnosis.

**Diagnosing OUD**
An OUD is a problematic pattern of opioid use leading to clinically significant impairment or distress. A diagnosis of a current OUD is made when clients meet **two or more** of the following DSM-5 criteria for OUD in the past 12 months:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or there are unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities that are necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids, is experienced.
5. Opioid use is recurrent, resulting in a failure to fulfill role obligations at work, school, or home.
6. Opioid use is continued, 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. Opioid use is recurrent in situations in which it is physically hazardous.
9. Opioid use is continued, 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.
11. Withdrawal, as manifested by either of the following (see Appendix E for instructions on identification of opioid withdrawal):
    a. the characteristic opioid withdrawal syndrome
    b. opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.
Important Caveats

- Clients with two or more “yes” responses in the past 12 months meet the criteria for a current OUD and might be appropriate candidates for treatment with buprenorphine/naloxone or naltrexone extended-release injectable suspension.

- Tolerance to and withdrawal from opioids that clients are taking as prescribed under appropriate medical supervision do not imply that the client has an OUD unless other OUD diagnostic criteria (beyond tolerance and withdrawal) are also met.

- Clients with a past OUD and current risk of relapse also could be considered for treatment with buprenorphine/naloxone or naltrexone extended-release injectable suspension.

- Clients with fewer than two “yes” responses might still be appropriate for medication treatment at the discretion of the treating clinician and/or psychiatrist, nurse practitioner, or other prescriber.

Dialogue to Facilitate Discussion

To help identify the presence of a current OUD, ask the client,

- Do you feel like you need to use more opioids than you previously did to get the same effect?
- Do you feel ill when you don’t use opioids (i.e., do you have withdrawal symptoms)?
- Do you feel like you end up using more opioids than you intended?
- Do you find yourself craving (having a strong desire to use) opioids?
- Have you been unable to stop or reduce your opioid use when you have tried in the past?
- Are you spending more and more time getting opioids, using opioids, or recovering from opioid use?
- Does your opioid use get in the way of you doing other things that don’t involve opioids, such as work or family activities?
- Do you find that you have given up doing things, such as work or family activities, because of your opioid use?
- Do you find yourself continuing to use opioids, despite problems caused or worsened by opioid use?
- Have any bad things happened as a result of your opioid use? Do you continue to use opioids even though it causes these bad things to happen?
For clients with problematic opioid use who do not meet the DSM-5 criteria for OUD, the clinician should advise them to stop using opioids, explain how their opioid consumption could be affecting their health, and schedule a follow-up visit to reassess their opioid use. During a follow-up assessment or during visits with a mental health clinician, counselor, peer, and/or community worker, if clients are identified as having an OUD, they might be appropriate for treatment with medication at that time.

**Documenting COD-Opioid**

When assessing the client, complete the *DSM-5 OUD diagnosis worksheet* (see Appendix A) and document OUD as a diagnosis. In most mental health systems of care, OUD should be documented as a secondary diagnosis and listed on the treatment plan. (Note: The client’s counselor or clinician might have done this step; check the diagnosis list first.)

**Important Specifications**

*Specify whether the client is...*

... *in early remission.* After full criteria for OUD were met, none of the criteria for an OUD have been met for at least three months but for less than 12 months (with the exception that criterion 4, craving, may be met).

... *in sustained remission.* After full criteria for OUD were met, none of the criteria for OUD have been met at any time during a period of 12 months or longer (with the exception that criterion 4, craving, may be met).

*Specify whether the client is on maintenance therapy.* This additional specifier is used if the individual is taking methadone, buprenorphine, or naltrexone and none of the criteria for OUD have been met for methadone or buprenorphine (except tolerance to, or withdrawal from, either of these two medications).

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

*Code based on current severity.* For International Classification of Diseases, 10th Revision, Clinical Modification (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 OUD. Instead, the comorbid OUD is indicated in the fourth character of the opioid-induced disorder code. For example, if there is comorbid opioid-induced depressive disorder and OUD, only the opioid-induced depressive disorder code is given, with the fourth character indicating whether the comorbid OUD is mild, moderate, or severe: F11.14
for mild OUD with opioid-induced depressive disorder or F11.24 for moderate or severe OUD with opioid-induced depressive disorder.

Specify current severity using the following codes:

- 305.50 (F11.10) mild: presence of two or three symptoms
- 304.00 (F11.20) moderate: presence of four or five symptoms
- 304.00 (F11.20) severe: presence of six or more symptoms.
Prescribing MOUD to Clients with COD-Opioid

In this section, we review the process for treating COD-opioid clients with MOUD in the mental health setting. MOUD should be offered without delay, and naloxone should always be offered and discussed when an OUD diagnosis is made.

Physicians, nurse practitioners, and physician assistants will need a Drug Addiction Treatment Act 2000 waiver to prescribe buprenorphine/naloxone for the indication of OUD to outpatients.

The patient’s ability to participate in mental health treatment often requires the OUD to be stabilized with medications. In this section, we describe how to discuss this treatment with clients and include information on following up through support visits. This section also includes a prescriber summary and COD-opioid prescribing strategy.

Discussing COD-Opioid with Clients

After identifying a client with COD-opioid, the clinician should discuss treatment options with the client using a nonjudgmental, nonconfrontational, motivational approach.

Be mindful that accusing the client or directing them to stop using opioids too forcefully risks the client defending their drug use behavior.

Share with the client:

- “I am concerned that your opioid use is affecting your well-being.”
- “My assessment is that your opioid use is causing you or others harm.”
- “I recommend that you consider a medication that can help reduce the effects of opioid withdrawal and that can help you cut down or stop your opioid use.”
- “These medications work well for most clients, and I am happy to help.”
- “Ultimately, change is up to you.”
- “Is this something you are willing to try?”

If the client is NOT willing to discuss treatment for their OUD, say
“As I said, you are the only one who can accept the treatment offered to you. I am ready to help you if you decide to learn more about medications and counseling that can help you with opioid problems.”

“May I see you in the future to discuss this again?”

If the client IS willing to discuss treatment for their OUD, say

“As I mentioned, there is a medication [I/the psychiatrists here] can prescribe that might help keep you out of opioid withdrawal and that can help you reduce or stop using opioids. I’d like to tell you more about this.”

“I also can give you information on counseling available at the clinic and elsewhere, as well as information on self-help groups that other clients of mine have found helpful. Are you interested in these resources?”

The clinician should then discuss the specifics of MOUD and/or refer the client to see the psychiatrist or other prescribing clinician, who can discuss the medications. The clinician also could recommend specific self-help groups, such as Medication-Assisted Recovery Anonymous, Narcotics Anonymous, Alcoholics Anonymous, SMART Recovery, and other community-based self-help opportunities.

Clients who are not interested in changing their opioid use should continue to attend future visits to discuss their opioid use; change should be revisited during these visits.

**Prescribing Naloxone**

For all clients with COD-opioid, even for clients who are not interested in taking MOUD, inquire about the presence of naloxone in their home or shelter and whether family members, friends, or shelter staff are trained to use it in case a new supply is needed. Make this inquiry at the first visit and regularly at each office visit. All clients with COD-opioid should be prescribed naloxone following the use of their initial naloxone supply at least once per year.

Naloxone is administered by bystanders via nasal spray or through a needle into the shoulder or leg muscle to individuals who are in an opioid overdose (which is when someone is unconscious or in a semiconscious state and breathing poorly after using opioids; people are not reliably able to self-administer naloxone when they are in an overdose). Clients at particularly elevated risk of overdose include those who have prior opioid overdoses; those who use synthetic opioids, such as fentanyl and carfentanil; and those who use opioids with sedatives, such as benzodiazepines, barbiturates, hypnotics, alcohol, and/or gabapentin. Clients who use opioids should be advised to never use while alone and to use the resources available at
neverusealone.com to minimize their risk of fatal overdose (Never Use Alone, undated-a).

Mental health clinics in states with laws supporting naloxone distribution can also distribute naloxone under a standing order without requiring a specific prescription from a clinician at that clinic. This mechanism for naloxone distribution is a useful secondary option when clients have more-frequent interactions with clinicians, counselors, and peers without prescribing authority.

» See Appendix B for more on prescribing and distributing naloxone to clients with COD-opioid and to the friends and family of individuals with COD-opioid.

Selecting the Right Medication

Buprenorphine/Naloxone

Buprenorphine/naloxone treats both opioid withdrawal syndrome and OUD. It is the most commonly used MOUD in the United States and is reviewed extensively in this guide.

Some clients do not accept—or respond to—buprenorphine/naloxone in mental health settings. For clients with COD-opioid who are currently opioid abstinent (for seven to 14 days, depending on the opioid), initiating naltrexone extended-release injectable suspension is a feasible option.

Clients who tolerate buprenorphine/naloxone but who do not consistently adhere to sublingual medication treatment may benefit from parenteral (subcutaneous injection) administration of buprenorphine extended-release injection. For further information, see

» highlights about prescribing buprenorphine extended-release injection (FDA, 2017b)


In case of pregnancy, historic guidance was provided to transition clients from buprenorphine/naloxone to the equivalent dose in the monoproduct form of buprenorphine (Subutex®), which is an alternative to buprenorphine/naloxone in which the buprenorphine in the tablet is not formulated with naloxone. However, there is more-recent evidence that the buprenorphine/naloxone combination product is safe and effective throughout the peripartum period, and it is not necessary to automatically switch from buprenorphine/naloxone to the buprenorphine monoproduct when a
patient with OUD is pregnant (Debelak et al., 2013; Jumah et al., 2016; Nguyen et al., 2018; Wiegand et al., 2015).

For clients with pregnancies in the second or third trimester, consider consulting with an obstetrics specialist to discuss initiating buprenorphine medications during pregnancy. If a pregnant client requests to be newly initiated on buprenorphine treatment, consultation with an addiction specialist and/or obstetrician-gynecologist who is experienced in treating OUD is recommended, because hospitalization may be appropriate for some pregnant clients during treatment initiation.

For comprehensive instructions for prescribing buprenorphine/naloxone, see Appendix F. For a home induction brochure for patients, see Appendix G.

**Extended-Release Naltrexone**

Clients with COD-opioid who have stopped using opioids may be candidates for naltrexone extended-release injectable suspension as an alternative to buprenorphine if they have been off opioids entirely for seven to 14 days, depending on the opioid. Note that the oral form of naltrexone has not been shown to be effective in treatment of OUD; however, there is evidence supporting the use of naltrexone extended-release injectable suspension for OUD. For instructions on using extended-release naltrexone, consult the following resources:

- PCSS MAT virtual brochure (PCSS, undated-b)
- PCSS MAT video (PCSS, 2017).

**Methadone**

Some clients do not accept or respond to buprenorphine in usual outpatient settings and would benefit from referral to an opioid treatment program (OTP) for OTP-managed buprenorphine/naloxone or treatment with methadone. Clinicians working in mental health clinics should determine which OTPs are available in the area that is convenient to the clients that they serve.

A comprehensive review of MOUD, including methadone, can be found in the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Improvement Protocol (TIP) 63 (SAMHSA, 2020b).
**Continuing MOUD**

Maintenance therapy with MOUD has better outcomes than medically supervised withdrawal with buprenorphine or methadone (Kleber, 2007). Clients who are ambivalent about the duration of MOUD treatment should be reassured that they can be safely and comfortably tapered off these medications if it becomes clinically appropriate and that many patients benefit from lifelong treatment with these medications.

After initial stabilization with buprenorphine/naloxone, medical visits can be adjusted to every two weeks, monthly, and up to every three months, based on provider and client agreement. The target dose range that has been found to be most likely to prevent relapse is 16 mg/4 mg–24 mg/6 mg sublingual daily.

Especially early in treatment, it may be difficult for clients to keep appointments. The key to successful treatment is keeping the client engaged. Therefore, giving the client the opportunity to reschedule the visit, or, if your clinic permits, to be seen as a walk-in client, is likely to best support remission from OUD.

**Clients are at increased risk of relapse when taking buprenorphine intermittently.** Worrisome signs may manifest as frequent no-shows or low levels or negative levels of buprenorphine metabolites in urine toxicology tests. In these cases, or if the client expresses interest in a long-acting formulation of buprenorphine, consider buprenorphine extended-release injection, which is a different medication formulation and alternative route of administration compared with sublingual buprenorphine/naloxone. However, do not withhold buprenorphine/naloxone from clients with OUD solely because of their opioid or other drug use.

**Medication Management Counseling**

Clients who are being treated with MOUD should receive brief medication management counseling from their prescribing clinician during each clinic visit.

**Important things to remember when discussing ongoing MOUD with clients:**

- Changing opioid use is a process. Clients who have not quit using opioids but have made progress (e.g., cut down, attended counseling sessions or self-help meetings) should be validated and encouraged to sustain these changes and continue their efforts to reduce their opioid use.

- Adherence to the medication is critical for success.
● Attendance at counseling or self-help programs should be encouraged but not required for clients who are responding to MOUD and clinician-delivered medication management counseling alone.

● Use a motivational approach and avoid confrontation; confrontation is likely to evoke discord and elicit resistance statements from the client.

**Agenda for medication management visits:**

● **Assess opioid use since the last visit**
  - Evoke permission, e.g., “I'd like to discuss your opioid use since our last visit, is that OK?”
  - Validate clients who make healthful steps to reduce opioid use or reduce the harm associated with their use of opioids.
  - For clients who did use opioids, be supportive.
    - Ask,
      - “Were you able to cut down some?”
      - “What were the circumstances that led you to use opioids?”
      - “Even though you did use opioids, it is good that you are here, and I will continue to help you change your opioid use.”
    - Help clients troubleshoot a plan to address their triggers for opioid use (e.g., deal with stress; avoid people, places, and things associated with drugs).

● **Assess medication adherence and any medication side effects**
  - Ask, “Clients often tell me that they sometimes miss taking their medication. Does this happen to you?”
  - Address any barriers to medication adherence or side effects.

● **Assess participation in counseling or a self-help program**
  - Clients who are doing well with medication and medication management counseling do not need to be mandated to attend specialized drug counseling or self-help groups.
  - Clients who are struggling to change their opioid use should be encouraged to increase participation in specialized drug counseling, peer services, or self-help groups. Encourage clients who are in Narcotics Anonymous to have a sponsor.
In subsequent visits, plan to continue the MOUD for as long as the client is benefiting from this medication. Clients who have not experienced a serious side effect and are making progress in reducing or stopping opioid use should receive ongoing medication treatment.

**Urine Toxicology and Lab Testing**

Toxicology testing is not universally required for MOUD to be initiated and managed. Toxicology testing should be offered to clients without a clear positive response to MOUD, when there is doubt about whether the client is adhering to MOUD, and when a clinician is considering initiating naltrexone extended-release injectable suspension to clients where the history of recent opioid use needs to be confirmed. In settings without an existing Clinical Laboratory Improvement Amendments Certificate of Waiver to conduct onsite testing, clients can be referred to community laboratories for testing or to other clinical sites that offer toxicology testing.

Mental health clinicians recommending the client’s participation in routine urine toxicology testing should emphasize that this testing is part of their treatment and stress that the testing is not meant to be punitive. It is important to obtain a full medication history, including timing of last drug use, over-the-counter medication, and herbal therapies, because of the potential that they might affect the toxicology results. The specific lab test recommendations are outlined earlier, in Quick-Start Guide 1.

For clients who are on buprenorphine prescriptions of one month or longer, it is recommended to check buprenorphine metabolites at least yearly to ensure appropriate use of medication. Clients who are prescribed buprenorphine who have confirmatory toxicology results that are consistent with buprenorphine nonadherence should be reevaluated for the appropriateness of ongoing buprenorphine treatment.

Prescribing clinicians should use clinical judgment regarding the decision to proceed with treatment; lab results alone (or a lack thereof) should not prohibit treatment. Because point-of-care tests and send-out screens may not be accurate, it is important to not change treatment in response to disputed or unexplained toxicology immunoassay results without obtaining a confirmation toxicology test for verification. It is helpful to discuss test results directly with the client to make a shared decision regarding next steps in treatment.

Additional laboratory recommendations are reviewed in Quick-Start Guide 1. Urine toxicology results and the PDMP should be reviewed routinely at each follow-up visit.
Legal Liability and MOUD
There is a misperception that treating clients with MOUD is associated with more legal liability than prescribing other medications. For clients with COD-opioid, treatment with MOUD is associated with significantly reduced rates of overdose, improved treatment retention, and reduced opioid use. Mental health settings are already seeing clients with COD-opioid, and clinics that do not offer MOUD to clients with COD-opioid actually risk greater liability from an adverse outcome associated with a failure to diagnose OUD or because of the failure to treat OUD with an MOUD than from the risk of providing COD-opioid clients with MOUD. The benefits of MOUD to treat clients with COD-opioid are frequently substantial, and the risks associated with MOUD are usually comparatively less significant. Additionally, federal laws prohibit discrimination against individuals with disabilities, and this can include clients with COD-opioid (Attorneys at the Legal Action Center, 2009). The best protection against legal liability is conducting complete assessments, communicating fully with clients, offering evidence-based treatments (specifically including MOUD to clients with COD-opioid), and high-quality documentation.

Additional Resources
SAMHSA’s TIP 63 publication, TIP 63: Medications for Opioid Use Disorder, was revised in May 2020 (SAMHSA, 2020b). Although some of the instructions in this guide may differ slightly from the recommendations in the SAMHSA manual, the SAMHSA manual contains an abundance of detail on MOUD. The recommended treatment options presented in this manual are current as of the date of publication, although prescribing clinicians should keep in mind that clinical guidelines may change over time.
Addressing Other Substance Use and Psychiatric Comorbidities That Are Common in Clients with COD-Opioid

Addressing Other Substance Use

There is a strong association between COD-opioid and other substance use disorders (SUDs). Many screening tools exist to assess for other SUDs, including the NM-ASSIST and the TAPS tool. Treatment for co-occurring SUDs is indicated when the patient is ready to participate in this screening.

Alcohol Use Disorder

AUD is common among people with mental illness and can co-occur with COD-opioid. Pharmacotherapy for COD-alcohol is effective and appropriate for delivery in mental health settings alongside mental health treatment.

» See the COD Toolkit for more on integrating COD-alcohol pharmacotherapy and psychosocial treatment in mental health settings (Watkins et al., 2021).
» See Medications for Alcohol Use Disorder in Mental Health Settings for detailed prescribing information (Hurley et al., 2019).

Tobacco Use Disorder

Tobacco use disorder is extraordinarily common among patients with COD-opioid, and successfully treating tobacco use disorder improves OUD and mental health treatment outcomes. Tobacco use is a major cause of early mortality for these clients. The recommended medication approach for smoking cessation is treatment with nicotine replacement therapy, varenicline, and/or bupropion. Tobacco cessation treatment is associated with no change or improvement in outcomes for other substance use.

» See Appendix C for tobacco use disorder treatment guidance.

Stimulant Use Disorder

Stimulant use disorder is also common among clients seeking mental health services. Clinics can consider distributing fentanyl test strips that clients can use to see whether their stimulants are adulterated with fentanyl, which they can use to inform their choices, because fentanyl use raises their risk of opioid overdose (Weicker et al., 2020). Addressing stimulant use disorder helps clients recover from their mental health condition and COD-opioid.

» See Appendix D for stimulant use disorder treatment guidance.
Other Substance Use
There are no FDA-approved medications for sedative, cannabis, hallucinogen, stimulant, or inhalant disorders or for SUDs other than alcohol, opioid, and tobacco use disorders. Psychosocial treatment remains the primary treatment for these other SUDs. Co-occurring SUDs should be addressed to the extent possible by the mental health clinicians, counselors, peers, and other relevant staff who are already working with the client. Some clients benefit from specialty SUD counseling that is available outside the mental health clinic to achieve remission and recovery for these conditions.

Addressing Common Psychiatric Comorbidities
Many patients with COD-opioid have insomnia, anxiety, nightmares, and medical comorbidities, such as hepatitis or other types of liver diseases. Insomnia, in particular, is a common condition in patients with COD-opioid and, when untreated, can make response to treatment for mental health conditions more challenging. Table 1 shows common psychiatric symptoms and conditions among patients with COD-opioid and recommended pharmacotherapy.

Table 1. Common Symptoms and Conditions Among Patients with COD-Opioid and Recommended Pharmacotherapy

<table>
<thead>
<tr>
<th>SYMPTOM or CONDITION</th>
<th>PHARMACOTHERAPY</th>
</tr>
</thead>
</table>
| **Insomnia**<br>(Rios et al., 2019) | For patients with OUD and insomnia, consider underlying diagnoses that may affect sleep, such as sleep apnea and PTSD. In addition to reviewing sleep patterns, consider such medications as trazodone or diphenhydramine, which are effective—although not FDA-approved—treatments for insomnia.  
  ● Trazodone 50 mg QHS (can titrate up dose if necessary and tolerated)  
  ● Diphenhydramine 50 mg QHS (can titrate up dose if necessary and tolerated)  
  ● Doxepin 10 mg QHS (can titrate up dose if necessary and tolerated). |
| **Anxiety**<br>(Garakani et al., 2020) | An SSRI or SNRI is recommended as first-line treatment for anxiety. In addition to an SSRI or SNRI, consider  
  ● Buspirone, start 7.5 mg twice daily (BID), and titrate to a usual dose of 15 mg BID. The FDA-recommended maximum is 30 mg BID. The following medications are not FDA-approved for anxiety but are effective for many clients and can be prescribed to be taken as needed in combination with daily SSRI or SNRI treatment:  
  ● Hydroxyzine 25–50 mg TID PRN anxiety (avoid if the patient is taking another antihistamine)  
  ● Propranolol 10 mg TID PRN anxiety (avoid if the patient is on another beta blocker or has hypotension)  
  ● Clonidine, 0.1 mg BID to four times daily (QID) PRN anxiety (avoid if the patient is on an alternative medication that lowers the heart rate or blood pressure)  
  ● Prazosin; start at 1 mg QHS and titrate dose up as patient tolerates because doses of 5 mg QHS or more are often needed for hypervigilance and nightmares. See section H11 of Appendix H for detailed dosing instructions (Singh et al., 2016). |
<table>
<thead>
<tr>
<th>SYMPTOM or CONDITION</th>
<th>PHARMACOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the patient’s blood pressure does not tolerate or respond to prazosin, consider doxazosin 1 mg and titrate up in 1-mg increments every week to effect as tolerated.</td>
<td></td>
</tr>
</tbody>
</table>
| Nightmares (Singh et al., 2016) | ● Prazosin; start at 1 mg QHS and titrate dose up as patient tolerates because doses of 5 mg QHS or more are often needed for hypervigilance and nightmares. See Appendix F for detailed dosing instructions.  
● If the patient’s blood pressure does not tolerate or respond to prazosin, consider doxazosin 1 mg and titrate up in 1-mg increments every week to effect as tolerated. |
| Hepatic or renal disease (Elkader and Sproule, 2005) | Treatment with buprenorphine is generally safe.  
● It is okay to prescribe to patients with cirrhosis and chronic hepatitis C; however, liver function should be monitored. Clients with synthetic hepatic dysfunction disease may experience decreased clearance and therefore require decreased dosage. Do not withhold buprenorphine from patients with cirrhosis and chronic hepatitis C while liver function tests (LFTs) are pending or not yet obtained. |
| Tobacco use disorder (Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff, 2008) | ● The recommended medication approach for smoking cessation is treatment with nicotine replacement therapy, varenicline, and/or bupropion. See Appendix C for tobacco use disorder treatment guidance. |
| Other considerations | ● Avoid benzodiazepines and hypnotics (zolpidem, eszopiclone, and zaleplon) in patients with COD-opioid and with other co-occurring SUDs (FDA, 2016).  
● Do not withhold buprenorphine/naloxone from patients taking benzodiazepines, taking other sedatives, or consuming alcohol (FDA, 2017a).  
● Avoid antipsychotic medications unless the patient has a condition for which the FDA has approved use of these medications (Thompson et al., 2016). |
Additional Psychosocial Services
Successful treatment for clients with COD-opioid requires addressing both their mental health and their OUD. A history of trauma is common among clients with OUD and should be addressed during treatment.

All clients should be offered a full menu of psychosocial services in an individualized manner. These services should be continuously offered but not required as a condition of pharmacotherapy. Clients can benefit from medications for OUD even if they choose not to participate in psychosocial treatment (Amato et al., 2011).

Psychosocial treatments include individual and group counseling and involve approaches that include cognitive behavioral therapy, motivational enhancement therapy or motivational interviewing, community reinforcement, contingency management, peer services, self-help, family therapy, and computer-based or phone-based interventions. Consider offering a group meeting that focuses on trauma and that uses the Trauma Recovery and Empowerment Model and Seeking Safety evidence-based model (SAMHSA, 2014; Seeking Safety, undated).

A discussion of the role and variety of different models of psychosocial support integrated with MOUD can be found in Moran, Knudsen, and Snyder, 2019.

Additionally, if, after several months of treatment, clients are not making progress toward their opioid use goals, they should be encouraged to enter a treatment setting where a higher intensity of treatment can be provided (e.g., specialty outpatient or inpatient drug treatment program). However, MOUD should not be withheld from a client benefiting from a medication in this class if the client does not pursue psychosocial treatment or a higher intensity of care.

Treatment Planning
Shared decisionmaking with the patient regarding treatment is essential to supporting patient adherence and should involve a review of medication options for OUD. Prescribing clinicians establish the medication component of the patient’s treatment plan and, therefore, should review the indications, risks, benefits, and alternatives to pharmacotherapy with the patient. (See Quick-Start Guide 2, Prescribing Considerations: MOUD, at the start of this guide, and Step 2, Task 9 of the COD-opioid toolkit [Watkins et al., 2021].)
APPENDIX A

DSM-5 OUD Diagnosis Worksheet

<table>
<thead>
<tr>
<th>Client’s name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worksheet for DSM-5 criteria for diagnosis of OUD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnostic criteria</strong></td>
<td>Meets criteria?</td>
</tr>
<tr>
<td>(Current diagnosis requires meeting two or more criteria in the PAST 12 MONTHS)</td>
<td>Yes □ No □ Notes/supporting information</td>
</tr>
<tr>
<td>(1) Opioids often are taken in larger amounts or over a longer period than was intended.</td>
<td></td>
</tr>
<tr>
<td><strong>Possible prompts:</strong></td>
<td></td>
</tr>
<tr>
<td>● Are you using more opioids than you planned?</td>
<td></td>
</tr>
<tr>
<td>(2) There is a persistent desire or are unsuccessful efforts to cut down or control opioid use.</td>
<td></td>
</tr>
<tr>
<td><strong>Possible prompts:</strong></td>
<td></td>
</tr>
<tr>
<td>● Can you stop using opioids when you want to?</td>
<td></td>
</tr>
<tr>
<td>(3) A great deal of time is spent in activities that are necessary to obtain opioids, use opioids, or recover from their effects.</td>
<td></td>
</tr>
<tr>
<td><strong>Possible prompts:</strong></td>
<td></td>
</tr>
<tr>
<td>● Do you spend a great deal of your time using opioids, getting opioids, or recovering from the effects of using them?</td>
<td></td>
</tr>
<tr>
<td>(4) Craving, or a strong desire or urge to use opioids, is present.</td>
<td></td>
</tr>
<tr>
<td>(5) Recurrent opioid use resulting in a failure to fulfill role obligations at work, school, or home.</td>
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<tr>
<td>(6) Continued opioid use, despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.</td>
<td></td>
</tr>
</tbody>
</table>
(7) Important social, occupational, or recreational activities are given up or reduced because of opioid use.

**Possible prompt:**
- *Does your opioid use get in the way of doing other things that do not involve opioids? For example, do you miss work because of opioid use or spend less time with family or friends who do not use opioids?*

(8) Recurrent opioid use in situations in which it is physically hazardous is present.

(9) Opioid use is continued, despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.

**Possible prompts:**
- *Have any bad things happened as a result of your opioid use, either to you or to other people?*
- *Do you continue to use opioids even though your opioid use is causing harm?*

(10) Tolerance, as defined by either of the following:
   a. a need for markedly increased amounts of opioids to achieve intoxication or the desired effect
   b. a markedly diminished effect with continued use of the same amount of opioids.

(11) Withdrawal, as manifested by either of the following:
   a. the characteristic withdrawal syndrome for opioids (see Appendix E)
   b. opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

**Possible prompt:**
- *Do you have symptoms, such as anxiety, shaking, sweating, or nausea, when you do not use opioids?*
APPENDIX B

Overdose Education and Naloxone Distribution

The following overdose education and naloxone programs are effective in reducing opioid overdose deaths in people with COD-opioid:

- prescribing information and patient education resources from prescribetoprevent.org (Prescribe to Prevent, undated-b)
- a comparison of naloxone products that are available for prescription (Prescribe to Prevent, 2017)
- an issue brief on naloxone distribution strategies (Weiner, Murphy, and Behrends, 2019)
- a guide that contrasts pharmacy naloxone dispensing with naloxone distribution (Naloxone Saves, undated)
- Never Use Alone resources (Never Use Alone, undated-b).
APPENDIX C

Treating Tobacco Use Disorder in Mental Health Settings

The prevalence of smoking is higher among those with COD-opioid than among the general population. People with tobacco use disorder and COD-opioid are at increased risk of ongoing use of opioids, poor quality of life, and premature mortality. In a national U.S. sample of people in recovery with OUD and other SUDs, those who initiated or maintained tobacco use were more likely than nonsmokers to relapse to SUD (Vlad, Arnsten, and Nahvi, 2020).

Clients with COD-opioid and tobacco use disorder often require smoking-cessation medications in higher doses, for longer durations than people who do not have COD-opioid, and in combination with behavioral smoking-cessation treatments to reduce and eliminate their tobacco use. For more information, see the following smoking-cessation treatment resources:

- The National Partnership on Behavioral Health and Tobacco Use webpage (University of California San Francisco, undated)

- *Kansas Tobacco Guideline for Behavioral Health Care: An Implementation Toolkit* (Tobacco Control Legal Consortium, 2018)

- *Implementing Tobacco Cessation Treatment for Individuals with Serious Mental Illness: A Quick Guide for Program Directors and Clinicians* (SAMHSA, 2019)

- the American Psychiatric Association’s Smoking Cessation Resources (American Psychiatric Association, undated)


- table of smoking cessation medications (University of California San Francisco, 2021)

- smokefree.gov webpage (Smokefree.gov, undated).
Clients with COD-opioid are more likely than members of the general population to use stimulants, such as methamphetamine or cocaine (Chan et al., 2020).

SAMHSA has published a resource guide, called *Treatment of Stimulant Use Disorders*, that describes the following four psychosocial approaches to addressing stimulant use disorder:

- motivational interviewing
- contingency management
- community reinforcement approach
- cognitive behavioral therapy (SAMHSA, 2020a, p. 10).

All of these approaches to addressing stimulant use disorders can be incorporated as components of a comprehensive mental health treatment plan, although patients with more-severe stimulant use disorder may require higher-intensity specialty SUD treatment to achieve stimulant use disorder remission.

As of the date of the publication of this guide, there are no FDA-approved medications to treat stimulant use disorders. However, there is a subset of psychiatric medications that have some off-label efficacy to help some patients with stimulant use disorders decrease their stimulant use. Psychiatrists, advanced practice nurses, physician assistants, clinical pharmacists, and other prescribing clinicians who are familiar with the use of these medications for other psychiatric indications should consider the appropriate use of these medications when their potential benefits, which may include reduced stimulant use in some patients, outweigh their risks.

Next, we provide lists of off-label medications for methamphetamine use disorder and cocaine use disorder, respectively.
Off-Label Medications for Methamphetamine Use Disorder

- **methylphenidate sustained release** (moderate to high dose in frequent users or those with attention-deficit/hyperactivity disorder [ADHD])
  - Start methylphenidate sustained release 18 mg daily for seven days, then 36 mg daily for seven days, then 56 mg daily thereafter (Ling et al., 2014; Miles et al., 2013).

- **mirtazapine** (two small studies)
  - Start mirtazapine at 15 mg QHS and increase to 30 mg QHS after seven days (Coffin et al., 2020; Colfax et al., 2011).

- **bupropion** (low-level users who will adhere)
  - Start bupropion hydrochloride extended-release 150 mg daily for seven days, then 300 mg daily thereafter (Heinzerling et al., 2014).

- **topiramate** (low-level users)
  - Start 25 mg QHS and titrate up in 25–50-mg increments as tolerated over a month until the patient is taking either 100 mg BID or 200 mg QHS, or until the patient’s maximum tolerated dose is reached (Siefried et al., 2020).
  - Do not neglect to provide contraceptive treatments to appropriate patients of childbearing age who are prescribed topiramate.

- **naltrexone** (for those who have already stopped using methamphetamine for two or more weeks) (Siefried et al., 2020)
  - Administer naltrexone extended-release injectable suspension 380 mg via IM injection monthly. Oral naltrexone is ineffective at addressing COD-opioid in outpatients who are not participating in observed oral dosing treatments.

- **naltrexone extended-release injectable suspension in combination with bupropion** hydrochloride extended-release (Trivedi et al., 2021)
  - Administer naltrexone extended-release injectable suspension 380 mg via IM injection every three weeks in combination with bupropion XL titrated at 150 mg on day 1, 300 mg on day 2, and 450 mg daily beginning on day 3.
  - Doses can be reduced to alleviate adverse effects, although in the trial, the prescribing clinicians were encouraged to attempt to raise the dose back up to the 450 mg daily dose.
- **dextroamphetamine sustained release** (one small study) (Longo et al., 2010)
  - Start initial dose of dextroamphetamine sustained release at 20 mg daily, then increase by 10 mg daily until stabilized or until a maximum of 110 mg daily (off-label dosage) has been reached.

**Off-Label Medications for Cocaine Use Disorder**

- **methamphetamine sustained release** (Mooney et al., 2009)
  - Start 5 mg daily on day 1, then 10 mg daily on day 2, then 15 mg daily on day 3, then 20 mg daily on day 4, then 30 mg daily thereafter.

- **mixed amphetamine salts–extended release** (high dose) (Levin et al., 2015)
  - mixed amphetamine salts 80 mg daily (off-label dosage)

- **dextroamphetamine sustained release** (Grabowski et al., 2001; Nuijten et al., 2016)
  - dextroamphetamine sustained-release 60 mg daily

- **modafinil** (if the client does not have AUD) (Chan et al., 2020; Kampman et al., 2015)
  - modafinil 100 mg daily

- **topiramate** (low-level users)
  - Start 25 mg QHS and titrate up in 25–50-mg increments as tolerated over a month until the patient’s maximum tolerated dose is reached (Siefried et al., 2020).
  - Do not neglect to provide contraceptive treatments to appropriate patients of childbearing age who are prescribed topiramate (Siefried et al., 2020).

- **combination of mixed amphetamine salts–extended release and topiramate**
  - Start mixed amphetamine salts extended release at 10 mg daily and titrate over two weeks up to a maximum of 60 mg daily or until the patient’s maximum tolerated dose is reached.
  - Concurrently start topiramate 25 mg QHS and titrate up in 25–50-mg increments as tolerated over a month until the patient is taking either 100 mg BID or 200 mg QHS, or until the patient’s maximum tolerated dose is reached (Levin et al., 2020; Mariani et al., 2012).

- **sertraline** (abstinent from cocaine and experiencing depression)
  - Start at 50 mg daily and titrate over three weeks to 200 mg daily (Bashiri et al., 2017; Mancino et al., 2014; Oliveto et al., 2012).
To identify opioid withdrawal syndrome in a client,

- ask the client about their history with opioid withdrawal
- assess for the symptoms of opioid withdrawal syndrome. These symptoms usually show up 12 to 24 hours after the last use of short-acting opioids (such as heroin, morphine, oxycodone, hydrocodone) and include
  - yawning
  - sweating or chills
  - enlarged pupils
  - restlessness and inability to sit still
  - joint and bone aches
  - anxiety, irritability, fast heartbeat
  - shaking or twitches
  - bumpy skin (gooseflesh or piloerection)
  - watery eyes or runny nose
  - lost appetite, stomach cramps
  - nausea, vomiting, or diarrhea

Three or more of these symptoms implies that clinically significant withdrawal syndrome is present. If in doubt about opioid withdrawal, use the Clinical Opiate Withdrawal Scale (COWS) to determine the level of withdrawal, but a formal COWS score does not need to be documented to diagnose opioid withdrawal syndrome (Wesson and Ling, 2003).
APPENDIX F

Buprenorphine/Naloxone Treatment for Clients with COD-Opioid

Overview
In this appendix, we offer specific guidance on treating clients with COD-opioid with buprenorphine/naloxone.

This section contains information about buprenorphine and procedures for

- determining whether individuals are appropriate for treatment with sublingual buprenorphine and buprenorphine/naloxone
- initiating treatment
- assessing side effects and managing follow-up visits
- determining stages of treatment with buprenorphine.

About Buprenorphine
Buprenorphine is an opioid partial agonist/antagonist that is FDA-approved for the treatment of OUD by physicians in an office-based setting. It is a Schedule III controlled substance and requires that physicians obtain a U.S. Drug Enforcement Agency waiver (i.e., an “X” waiver) to prescribe it for office-based treatment of OUD.

Like methadone treatment, buprenorphine treatment involves treating OUD with an opioid medication. But although methadone is a full opioid agonist, buprenorphine is a partial opioid agonist/antagonist with minimal additional opioid effects at doses above the maximum recommended daily dose (32 mg—known as a “ceiling effect”). As a result, buprenorphine is safer than methadone. The risk of overdose from buprenorphine is relatively low, even if the patient takes sedatives and/or alcohol.

Naloxone, an opioid antagonist, is added to buprenorphine (buprenorphine/naloxone) to make intravenous buprenorphine use more aversive and less rewarding. When taken sublingually as prescribed, the naloxone in buprenorphine/naloxone is poorly orally absorbed and does not affect the client’s medication response. However, injection or insufflation of buprenorphine/naloxone will precipitate opioid withdrawal in a physiologically opioid-dependent person.
Buprenorphine/naloxone (which is generic and available under the brand names Suboxone®, Bunavail®, and Zubsolv®) can be taken sublingually, orally, or buccally.

There is a sublingual buprenorphine-only formulation without naloxone (which is generic and previously known by the trade name Subutex®), which should generally not be used except in cases of credible and verified intolerance to the oral naloxone component of buprenorphine/naloxone because this formulation has a higher risk of nonprescribed use via intravenous and insufflation routes and diversion than the buprenorphine/naloxone formulations.

For patients who tolerate and respond to sublingual formulations of buprenorphine/naloxone, there is a buprenorphine extended-release injection formulation available: Sublocade®.

**Which Clients Are Appropriate for Treatment with Buprenorphine/Naloxone?**

Clients are appropriate for treatment if they
- are interested in a medication for OUD
- are motivated to reduce or stop opioid use
- have received information and/or referrals to counseling and self-help programs (e.g., Narcotics Anonymous, SMART Recovery)
- are able to adhere to medication instructions and attend outpatient clinic visits.

Clients who have responded poorly to buprenorphine/naloxone in the past are eligible to receive a subsequent trial of buprenorphine/naloxone. However, some clients with more significant instability may be more appropriate for treatment in a specialty (i.e., inpatient or methadone) program.

**What Are the Most Common Side Effects of Buprenorphine/Naloxone?**

- Constipation is the most common side effect. Clients should be instructed to use a bowel regimen, including stool softeners, fiber, plenty of liquids, regular physical activity, and laxatives, as necessary to prevent severe constipation.
- Sedation, headache, or nausea may result when doses of buprenorphine/naloxone are too high.
- Clients treated with long-term buprenorphine/naloxone will experience mild to moderate opioid withdrawal when buprenorphine/naloxone is discontinued; this may be minimized by a slow taper.

Transitioning from methadone at daily doses higher than 40 mg to buprenorphine/naloxone is complicated and should generally be undertaken by
clinicians who are experienced in the use of buprenorphine. Clinicians who are new to buprenorphine/naloxone treatment should consult a colleague who is more experienced in the use of buprenorphine/naloxone for guidance in these instances. PCSS features an online message board where clinical experts answer questions related to buprenorphine/naloxone treatment: See PCSS, undated-a.

**What Are the Stages of Treatment with Buprenorphine/Naloxone?**

Treatment with buprenorphine/naloxone can be divided into the following stages:

- assessment
- initiation (transition from other opioid[s] to buprenorphine/naloxone)
- stabilization
- maintenance.

The optimal length of treatment with buprenorphine/naloxone has not been established, but research studies strongly support better outcomes with long-term maintenance treatment. Many successful clients are treated with buprenorphine/naloxone indefinitely to prevent relapse to opioid use.

In the next section, we describe each stage of treatment.

**Assessment**

**Prior to starting buprenorphine/naloxone,**

- complete a history and physical exam (or review if previously completed)
- confirm that the client has OUD (see the OUD diagnosis worksheet in Appendix A)
- check a PDMP report (controlled-substance prescriptions)
- carefully review all opioids that the client is using, with attention to longer-acting opioids (methadone, Oxycontin, MS-Contin) versus shorter-acting opioids (heroin, Vicodin, etc.).

**Starting Buprenorphine/Naloxone (Initiation)**

Because buprenorphine/naloxone is a high-affinity partial opioid agonist, it will precipitate opioid withdrawal in clients who are actively experiencing opioid intoxication. Therefore, clients must stop opioid use and be experiencing at least mild opioid withdrawal symptoms prior to starting buprenorphine/naloxone.

The amount of time that clients typically wait after their last opioid use until mild withdrawal sets in (which is when they would benefit from taking buprenorphine/naloxone) varies, depending on whether they are using short-acting
opioids (shorter wait) or long-acting opioids (longer wait). Clients are usually in opioid withdrawal by 12 hours following their last use of short-acting opioids (for example, heroin, Vicodin, Norco, immediate-release oxycodone); 24 hours following their last use of intermediate-acting opioids (for example, OxyContin, MS Contin); and 72 (or more) hours for long-acting opioids (for example, methadone) after their last use of methadone.

Regardless, the client should take their initial dose of buprenorphine/naloxone based on their withdrawal symptoms, not based on time alone.

Because buprenorphine is a relatively weak partial agonist, clients on high doses of opioids (for example, more than 40 mg of methadone per day) might not be successful starting buprenorphine/naloxone (or buprenorphine monotherapy). Patients who intend to transition their MOUD from methadone to buprenorphine/naloxone (or buprenorphine) should have their medical provider gradually taper down their methadone dose to 40 mg per day or lower prior to initiating buprenorphine/naloxone (or buprenorphine).

The following is an overview of the day-by-day initiation process:

- **The client must WAIT** until they are experiencing at least mild physical opioid withdrawal symptoms prior to taking the first dose of sublingual buprenorphine/naloxone.
- Sufficient opioid withdrawal corresponds to three or more opioid withdrawal symptoms, as described in Appendix E.
- Once the client has three or more opioid withdrawal symptoms present, they should self-administer one-half to one buprenorphine/naloxone 8-mg/2-mg tab or film under their tongue and let it dissolve. Clients with a lower opioid tolerance or who are more tentative about the timing of their first dose should start with a 4-mg/1-mg film (or half of the 8-mg/2-mg film or tablet if the 4-mg/1-mg film is not available).
- **WAIT** one hour after the first buprenorphine/naloxone film.
  - If the client’s withdrawal symptoms are the same or worse, then they should take a second buprenorphine/naloxone 4-mg/1-mg to 8-mg/2-mg dose under the tongue and allow it to dissolve (up to a total of 16 mg/4 mg).
  - If the client’s withdrawal is better, then wait. The client can take the second buprenorphine/naloxone 4-mg/1-mg to 8-mg/2-mg dose later if the withdrawal symptoms start to get worse again.
- The target dose for day 1 is 16 mg/4 mg (two 8-mg/2-mg tabs or films).
• Rarely, clients may require more than 16 mg on day 1 for severe withdrawal symptoms, but never administer more than 32 mg in a 24-hour period.
• If the client has minimal or no withdrawal symptoms in the morning of day 2, then the client should take the same dose (same number of buprenorphine/naloxone 8-mg/2-mg tabs or films) in the morning as the client took in total on day 1.
• If the client feels withdrawal in the morning of day 2, then they should take the same dose as day 1 PLUS an additional 4-mg/1-mg to 8-mg/2-mg tab or film.
• If withdrawal begins to get worse later in the day, the client should take an additional 4-mg/1-mg to 8-mg/2-mg tab or film.
• Rarely, clients may require more than 24 mg/6 mg on day 2 for severe withdrawal symptoms, but never administer more than 32 mg/8 mg in a 24-hour period.

By day 3, the client should be stabilized on a dose of buprenorphine/naloxone, most likely between 8 mg/2 mg and 16 mg/4 mg per day. Rarely, clients may require doses higher than 16 mg per day to fully relieve opioid withdrawal symptoms or reduce opioid cravings, but clients should never take more than 32 mg/8 mg per day because higher doses are less safe and no more effective.

Review a written home-initiation instruction sheet with the client and answer any questions.
• Advise the client to obtain the buprenorphine/naloxone, to pick a day to start the initiation, to follow the home-initiation instruction sheet (Appendix G), and to call the clinic or come in if there are any problems.
• Prescribe a sufficient supply, typically #28, of buprenorphine/naloxone 8-mg/2-mg tabs or films for the client to take 16 mg/4 mg (two tabs or films) per day until their return appointment, which should be within the next seven to 14 days. Smaller amounts with more-immediate follow-up may be necessary for some clients.
• Prescribe refills if the patient has barriers to follow-up visits in the clinic, such as unstable access to the telephone, unstable access to transportation, or a history of no-show visits.
• Consider calling the client to check in on their progress within the first three days of their starting buprenorphine/naloxone.

Starting buprenorphine/naloxone in clients that use fentanyl
Fentanyl is a short-acting opioid with an elimination half-life of approximately four hours, but continuous and extended fentanyl use can result in the distribution of
fentanyl in the body that results in longer elimination times following cessation of fentanyl use.

The preceding dosing instructions can sometimes lead to precipitated withdrawal when starting buprenorphine/naloxone in clients with continuous and extended fentanyl use.

For these clients, there is an alternative dosing strategy that begins before the client stops using fentanyl: Start smaller initial doses of buprenorphine/naloxone, such as 0.5 mg/0.125 mg (one-quarter of a 2-mg tab or film) twice daily, then 1 mg/0.25 mg (one-half of a 2-mg tab or film) twice daily, then 2 mg/0.5 mg twice daily, which is subsequently titrated up to a more typical buprenorphine/naloxone dose. See Randhawa, Brar, and Nolan, 2020, for further discussion of this alternative dosing strategy.

**Stabilization**

During buprenorphine/naloxone stabilization (approximately the first week following completion of initiation), clients will stabilize on a daily dose of buprenorphine/naloxone (an average of 16 mg/4 mg per day with a usual range between 4 mg/1 mg and 24 mg/6 mg daily), depending on their level of opioid withdrawal and cravings.

Clients who continue to experience opioid withdrawal and cravings require higher doses. Sedation, headaches, and nausea symptoms that are not accompanied by other opioid withdrawal symptoms indicate that the dose may be too high and may abate following dose reduction.

Clients may administer the total daily dose once daily or split the dose during the day according to their preferences.

Once stabilized, the client should begin to feel well. This is an optimal time to begin to assist the client in arranging a program of counseling or behavioral support to address their OUD. Clients who are unable to achieve stabilization on buprenorphine/naloxone should be referred to a specialty addiction program.
Maintenance
During maintenance, the following tasks should be performed during follow-up visits:

- ask about community or family support that clients have received (if no support, discuss options)
- ask about adherence to buprenorphine/naloxone
- ask about any opioid use in addition to buprenorphine/naloxone and discuss triggers for ongoing use
- ask about changes in mental health symptoms since initiating buprenorphine/naloxone
- ask about the use of tobacco, sedatives, alcohol, stimulants, and other drugs
- conduct urine drug screen to test for the presence of buprenorphine and the absence of other intoxicants
- determine whether changes in dose are needed
- assess whether the client is attending psychosocial or counseling sessions.

Encourage attendance and provide referrals or assistance in accessing counseling if needed, but do not withhold buprenorphine/naloxone from clients just because they are not participating in counseling.

Following stabilization (when the client is on a stable dose and opioid withdrawal and cravings are manageable), clients enter the buprenorphine/naloxone maintenance phase. Research strongly supports better outcomes with longer treatment. A rule of thumb is that clients should be stable with opioid abstinence, have sufficient relapse-prevention skills typically acquired through counseling, and have established social support for continued abstinence prior to considering discontinuing buprenorphine. For most clients, this will mean treatment with buprenorphine/naloxone for several months, during which time they will work to establish these supports. Once they are stable, clients may be seen once per month or less frequently for assessment, a urine drug screen, and additional medication, if needed.

Transitioning to Buprenorphine Extended-Release Injection
Clients benefit when they take buprenorphine consistently. For patients who benefit from sublingual buprenorphine/naloxone but who have barriers to adherence, when there are concerns with diversion or misuse, and/or when the client expresses interest in
a long-acting formulation of buprenorphine, consider buprenorphine extended-release injection, which is a long-acting medication formulation with subcutaneous injection route of administration compared with sublingual buprenorphine/naloxone. For further information, see

» highlights about prescribing buprenorphine extended-release injection (FDA, 2017b)

Troubleshooting and Frequently Asked Questions

How should clients be tapered off of buprenorphine/naloxone?

Clients who choose to discontinue buprenorphine/naloxone should taper slowly to minimize withdrawal symptoms. Taper buprenorphine/naloxone slowly, to 2 mg/0.5 mg buprenorphine/naloxone per day or lower, prior to discontinuing. Various tapering schedules have been proposed, but the most important aspect of the taper is that it is slow to minimize the development of opioid withdrawal symptoms or cravings, which could precipitate relapse. Reducing the buprenorphine/naloxone dose by 2 mg/0.5 mg every week or two is usually comfortable for the client. Faster tapers are safe but risk precipitating relapse if the client is too uncomfortable.

What if a client relapses to opioid use during treatment?

Clients who relapse to opioid use during office-based treatment with buprenorphine/naloxone may respond to an increase in buprenorphine/naloxone dose and/or an increase in the frequency or intensity of counseling or behavioral support. Also assess the client for side effects, abuse, and diversion. Clients who do not tolerate buprenorphine/naloxone or who may be misusing or diverting buprenorphine/naloxone should be referred to a specialty addiction treatment program. Clients who are making overall progress in treatment may experience intermittent lapses and should not be discontinued from treatment if they can reestablish opioid abstinence following a lapse.

What if clients are using sedatives or alcohol during treatment?

Advise clients that mixing sedatives or alcohol with opioids increases the risk of overdose, but do not withhold buprenorphine/naloxone from clients with COD-opioid who are using alcohol and/or sedatives: The harm caused by untreated COD-opioid outweighs the risk of combining buprenorphine/naloxone with sedatives and/or alcohol.

What if a client needs analgesics while on buprenorphine/naloxone?

Buprenorphine-treated clients who require analgesics for acute pain should be treated with nonopioid analgesics, if possible. Clients who require the temporary use
of opioid analgesics (e.g., for minor surgery or dental procedures) may continue buprenorphine/naloxone while receiving a short course of opioid analgesics. Buprenorphine/naloxone may block the analgesic effect of the opioid to some degree, but continuing the buprenorphine/naloxone to avoid the development of opioid withdrawal is usually preferable in these cases. Clients requiring major analgesia (e.g., for major surgery or major trauma) should be referred to an addiction or pain-management specialist.

**What if a client becomes pregnant?**

**Buprenorphine/naloxone should not be abruptly discontinued if a client becomes pregnant.** Opioid withdrawal may be dangerous to the fetus, and treatment with buprenorphine during pregnancy is likely to be less dangerous than opioid relapse. Therefore, continue buprenorphine in a client who becomes pregnant and arrange for consultation with an obstetrics specialist who is familiar with buprenorphine and OUD treatment. Buprenorphine/naloxone is safe to continue throughout the peripartum period.

**What if a client has elevated LFTs?**

Clients with LFT elevations should be treated with buprenorphine/naloxone at the usual doses, but clients with decompensated liver disease with synthetic dysfunction (such as clinically apparent ascites and/or laboratory evidence of hypoproteinemia, hypoalbuminemia, thrombocytopenia, and/or coagulopathies) should be started on a lower dose of buprenorphine/naloxone (such as 2 mg/0.5 mg to 4 mg/1 mg). Clients who develop worsening hepatitis in response to buprenorphine/naloxone should have a hepatitis evaluation. Rarely, these clients may require switching to methadone treatment at a federally licensed OTP if they have an idiosyncratic hepatic inflammatory response to buprenorphine.

**What if a client requests a refill before the next visit or misses a visit?**

Clients who request an early refill of buprenorphine/naloxone should be assessed for possible diversion (a urine drug screen that is negative for buprenorphine and its metabolites suggests diversion). If there is no sign of diversion, the client’s dose should be assessed. Clients experiencing opioid withdrawal symptoms or opioid cravings while on buprenorphine/naloxone may need a dose increase but should be advised to not increase the dose without first discussing it with their doctor. Clients who run out of buprenorphine/naloxone because of missed visits should be counseled on the importance of adherence to visits. Clients who regularly miss visits may not be appropriate for buprenorphine/naloxone treatment in a mental health care setting.
**Suboxone® (buprenorphine/naloxone) to help with opioid addiction**

Begin taking the tablets or films (buprenorphine/naloxone) once you are feeling seriously dope-sick or experiencing opioid withdrawal.

If you are no longer in withdrawal but want to use this medication to reduce opioid cravings, start by taking one-half to one full tablet or film strip. Let your clinician know how much you have been taking each day and when you need a refill.

---

**HOW TO TAKE BUPRENORPHINE/NALOXONE**

**TO START**

If you have used another opiate recently, **wait** until you feel **at least three** of the following*:

- excessive yawning
- enlarged pupils
- joint and bone aches
- shaking or twitches
- watery eyes
- runny nose
- nausea
- vomiting
- diarrhea
- sweating or chills
- restlessness or inability to sit still
- agitation and irritability
- racing heartbeat
- bumpy skin (gooseflesh)
- loss of appetite or stomach cramps

**Before you start**, you should be about halfway to the worst dope sickness you have had.

For many people, this means:

- **12 hours** after taking heroin, morphine, Vicodin, Norco, or oxycodone
- **16 to 24 hours** after taking a long-acting opioid, such as Oxycontin or MS Contin
- **24 to 72 hours** after taking methadone; it can be very unpredictable.

**Rely on what you feel.**

*These are known as withdrawal symptoms or symptoms of being dope-sick.*

---

**DAY 1**

- Keep the tablet or film under your tongue and let it dissolve. **Do not** swallow or chew.

- **After one hour**, how are you feeling?
  - **IF good**: There is nothing more to do.
  - **IF you are still having the withdrawal symptoms or are feeling worse**: Place another tablet or film under your tongue.

**Date:**

**Time:**

**My dose:**

**___ mg**

**___ tablets/films**

---
DAY 2

⇒ **IF you feel good the next day,** take the same number of total tablets or pieces of film that you took the day before.

⇒ **IF you feel withdrawal symptoms or have cravings,** you can place another tablet or film strip under your tongue.

**Day 3**

⇒ **IF you feel good,** you can take the same number of tablets or pieces of film that you took the day before or split it up however you want to throughout the day.

⇒ **IF you are taking LESS than four tablets AND you have cravings later in the day,** you can take the fourth tablet at whatever time of the day you want.

**How much should I take?**

**DO NOT** take more than four whole tablets or strips of film per day:

<table>
<thead>
<tr>
<th>8 mg</th>
<th>OR</th>
</tr>
</thead>
</table>

The 8 mg. sublingual film can be cut into smaller doses if you want to take less:

<table>
<thead>
<tr>
<th>8 mgs.</th>
<th>4 mgs.</th>
<th>2 mgs</th>
</tr>
</thead>
</table>

To receive more medication, please contact:

Name:

Organization:

Location:

Phone:

Notes:

This figure was adapted with attribution from the *How to Start Buprenorphine/Naloxone at Home (Suboxone Induction)* guide by Matt Perez. Revisions to this document were supported by the California (CA) Bridge Program and by the National Health Foundation through a Sierra Health Foundation MAT Access Points Project award. The handout was developed in partnership with Los Angeles County Department of Health Services, CA Bridge, and the Center for Care Innovation’s Addiction Treatment Starts Here program. The image of the mouth on the previous page is from FDA, 2012, p. 4; the image of the film sizes with the dime is from Perez, 2018, p. 1.
Suboxone® (buprenorfina-naloxona) ayuda en la adicción a los opioides.
Comience a tomar las tabletas u hojas una vez que se sienta enfermo debido a la abstinencia de opioides. Si no tiene síntomas de abstinencia, pero desea usar esta medicina para evitar las ganas de usar opioides, empiece por tomar la mitad a una tableta u hoja.

Informe al personal la cantidad de medicina que ha estado tomando cada día y avíse cuando necesite más medicamento.

¿CÓMO TOMAR BUPRENORFINA-NALOXONA?

INICIO
Si usted ha usado otro opioide recientemente, ESPERE hasta que sienta POR LO MENOS tres de los siguientes síntomas:
✓ bostezo excesivo
✓ pupilas dilatadas
✓ dolor de huesos y articulaciones
✓ temblores
✓ ojos llorosos
✓ nariz congestionada
✓ náusea
✓ vómito
✓ diarrea
✓ sudor o escalofríos
✓ incapacidad para quedarse quieto
✓ ansiedad, irritabilidad
✓ palpitaciones
✓ piel de gallina
✓ pérdida de apetito, dolores estomacales

Antes de comenzar con el tratamiento, usted debe estar en la media de los peores síntomas de abstinencia que haya experimentado.

Para la mayoría de las personas, estos síntomas se presentan en un período de:
• 12 horas después de haber usado heroína o tomado morfina, Vicodin, Norco u oxicodona
• 16 a 24 horas después de haber tomado oxicodona o MSContin de liberación prolongada
• 24 a 72 horas después de haber tomado metadona, ya que puede ser impredecible.

Confíe en cómo se siente.

* Estos síntomas se conocen como síntomas de abstinencia.

DÍA 1

• Coloque la tableta/hoja debajo de su lengua y deje que se disuelva. No la trague o mastique.

• Después de 1 hora, ¿Cómo se siente?
  ⇨ SI SE SIENTE BIEN, no tiene que hacer nada.

  ⇨ SI TODAVÍA TIENE SÍNTOMAS DE ABSTINENCIA o se siente peor, coloque otra tableta u hoja debajo de su lengua.

Fecha: __________  
Hora: __________  
Mi dosis:  
_____ tabletas/hojas  
_____ mg
DÍA 2

⇒ SI SE SIENTE BIEN, tome el mismo número de pastillas u hojas que tomó el día anterior.

⇒ SI PRESENTA SÍNTOMAS DE ABSTINENCIA o tiene deseos de consumir opioides, puede tomar otra tableta u hoja debajo de la lengua.

Fecha: _______
Hora: _______
Mi dosis: _____ tabletas/hojas _____ mg

DÍA 3

⇒ SI SE SIENTE BIEN, tome el mismo número de pastillas u hojas que tomó el día anterior, o divídalo como desee durante el día.

⇒ SI ESTÁ TOMANDO MENOS DE 4 TABLETAS y presenta ansiedad por consumir opioides durante el día, puede tomar una cuarta tableta u hoja a cualquier hora que desee.

Fecha: _______
Hora: _______
Mi dosis: _____ tabletas/hojas _____ mg

¿CUÁNTO DEBO TOMAR?

NO más de 4 tabletas / hojas enteras por día

La película sublingual de 8 mg. se puede cortar en dosis más pequeñas si desea tomar menos:

<table>
<thead>
<tr>
<th>8 mg.</th>
<th>4 mg.</th>
<th>2 mg.</th>
</tr>
</thead>
</table>

Para obtener más medicamento, favor de contactar:

Nombre: 
Organización: 
Ubicación: 
Número de teléfono: 
Notas: 

Adaptado de las instrucciones de Cómo Empezar Buprenorfina/Naloxona en Casa (Suboxone) por Matt Perez. Las revisiones de este documento fueron patrocinadas por la Fundación Nacional de Salud por medio del apoyo de la Fundación Sierra Health MAT Access Points Project y desarrollado en colaboración con el Departamento de Servicios de la Salud del Condado de Los Angeles, CA Bridge, y el Programa El Tratamiento de la Adicción Empieza Aquí del Centro de Innovación del Cuidado.

APPENDIX H
Additional Resources for the Treatment of COD-Opioid in Mental Health Settings

This appendix offers additional resources for medication management of clients with COD-opioid. Resources are provided in subsections H1 to H11.

**H1. TAPS Screening Questions (Source: SAMHSA, 2020b, p. 2-37)**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Did you use heroin?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If &quot;Yes,&quot; answer the following questions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Have you tried and failed to control, cut down, or stop using heroin?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Has anyone expressed concern about your use of heroin?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Did you use a prescription opiate pain reliever (for example, Percocet or Vicodin) not as prescribed or that was not prescribed for you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If &quot;Yes,&quot; answer the following questions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Have you tried and failed to control, cut down, or stop using an opiate pain reliever?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Has anyone expressed concern about your use of an opiate pain reliever?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
H2. Overview of MOUD (Source: SAMHSA, 2020b, p. 3-7)

EXHIBIT 3A.1. OUD Medications: An Overview (continued)

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>BUPRENORPHINE*</th>
<th>METHADONE</th>
<th>XR-NTX**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TRANSMUCOSAL</td>
<td>DEPOT</td>
<td></td>
</tr>
<tr>
<td>Administration</td>
<td>Daily (or off-label less than daily dosing regimens) administration of sublingual or buccal tablet or film. Subdermal implants every 6 months, for up to 1 year, for stable patients. Monthly subcutaneous injection of extended-release formulation in abdominal region for patients treated with transmucosal buprenorphine for at least 1 week.</td>
<td>Subdermal implants every 6 months, for up to 1 year, for stable patients. Monthly subcutaneous injection of extended-release formulation in abdominal region for patients treated with transmucosal buprenorphine for at least 1 week.</td>
<td>Daily oral administration as liquid concentrate, tablet, or oral solution from dispersible tablet or powder (unless patients can take some home). Every 4 weeks or once-per-month intramuscular injection.</td>
</tr>
<tr>
<td>Prescribing</td>
<td>Physicians, nurse practitioners (NPs), and physician assistants (PAs) need a waiver to prescribe. Until October 1, 2023, qualified clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives also can obtain a waiver to prescribe. Any pharmacy can fill a prescription for sublingual or buccal formulations. OTPs can administer/ dispense by OTP physician order without a waiver.</td>
<td>Prescribers must have a waiver (as for transmucosal buprenorphine) and complete the product’s REMS program. Providers of the implantable rods must complete additional training in their insertion and removal. Both the implantable rods and subdermal injections are available via restricted distribution programs and are not available in retail pharmacies. OTPs can be providers of depot formulations of buprenorphine, provided the above criteria are satisfied.</td>
<td>SAMHSA-certified OTPs can provide methadone for daily onsite administration or at-home self-administration for stable patients.</td>
</tr>
</tbody>
</table>

*Long-acting buprenorphine implants (every 6 months) for patients on a stable dose of buprenorphine are also available through implanters and prescribers with additional training and certification through the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program. Extended-release buprenorphine monthly subcutaneous injections are available only through prescribers and pharmacies registered with the Sublocade REMS Program.

**Naltrexone hydrochloride tablets (50 mg each) are also available for daily oral dosing but have not been shown to be more effective than treatment without medication or placebo because of poor patient adherence.
EXHIBIT 3B.1. Strategies for Managing Benzodiazepine Use by Patients in OUD Treatment

- Carefully assess the patient’s benzodiazepine use, including:
  - Intent of use.
  - Source (check the state’s prescription drug monitoring program [PDMP]).
  - Amount and route of use.
  - Binge use.
  - Prior overdoses.
  - Harms (e.g., car crashes, criminal acts, sleep trouble).
  - Co-use with other substances that further increase risk for respiratory depression and overdose.
  - Withdrawal history (e.g., seizures, delirium).

- Also assess for:
  - Psychiatric and medical comorbidity.
  - Motivation for change.
  - Psychosocial support system (obtain history from a significant other if the patient permits).

- Gauge level of care and setting needed (e.g., residential, outpatient). Inpatient treatment may be best for patients with poor motivation, limited psychosocial support, serious or complicated comorbidity, or injection or binge use.

- Coordinate with other prescribers. Some patients may have taken appropriately prescribed benzodiazepines for years with limited or no evidence of misuse. For such patients, tapering benzodiazepines may be contraindicated and unrealistic.

- Address comorbid mental disorders (e.g., anxiety, depression) with other medications or psychosocial treatments, when feasible.

- Provide medically supervised withdrawal from benzodiazepines or refer to specialty care for same.

- Create a treatment plan with built-in conditions (e.g., urine testing, more frequent visits, short medication supply).

- Frequently review patient progress and objective outcomes, such as:
  - Urine drug testing.
  - PDMP reports.
  - Psychosocial functioning.
  - Reports from significant others.

- Revise treatment plans as needed, and document the rationale for treatment decisions.

*Adapted with permission.*
H4. Medications for Managing Opioid Withdrawal Symptoms
(Source: SAMHSA, 2020b, p. 3-12)

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>MEDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Ondansetron, metoclopramide (avoid promethazine; it potentiates opioids)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Anxiety, irritability, sweating</td>
<td>Clonidine</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Diphenhydramine, trazodone</td>
</tr>
<tr>
<td>Pain</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
</tbody>
</table>
**EXHIBIT 3D.1. Buprenorphine Transmucosal Products for OUD Treatment**

<table>
<thead>
<tr>
<th>PRODUCT NAME/ACTIVE INGREDIENT</th>
<th>ROUTE OF ADMINISTRATION/FORM</th>
<th>AVAILABLE STRENGTHS</th>
<th>RECOMMENDED ONCE-DAILY MAINTENANCE DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bunavail</strong>[^2][^230]</td>
<td>Buccal film</td>
<td>2.1 mg/0.3 mg, 4.2 mg/0.7 mg, 6.3 mg/1 mg</td>
<td>Target: 8.4 mg/1.4 mg, Range: 2.1 mg/0.3 mg to 12.6 mg/2.1 mg</td>
</tr>
<tr>
<td>- Buprenorphine hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Naloxone hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Generic combination product[^229][^230]</strong></td>
<td>Sublingual tablet, film</td>
<td>2 mg/0.5 mg, 8 mg/2 mg</td>
<td>Target: 16 mg/4 mg, Range: 4 mg/1 mg to 24 mg/6 mg[^*^]</td>
</tr>
<tr>
<td>- Buprenorphine hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Naloxone hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Generic monoprodct[^230][^232]</strong></td>
<td>Sublingual tablet</td>
<td>2 mg, 8 mg</td>
<td>Target: 16 mg, Range: 4 mg to 24 mg[^*^]</td>
</tr>
<tr>
<td>- Buprenorphine hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Suboxone[^233][^234]</strong></td>
<td>Sublingual film</td>
<td>2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, 12 mg/3 mg</td>
<td>Target: 16 mg/4 mg, Range: 4 mg/1 mg to 24 mg/6 mg[^*^]</td>
</tr>
<tr>
<td>- Buprenorphine hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Naloxone hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zubsolv[^235][^236]</strong></td>
<td>Sublingual tablet</td>
<td>0.7 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</td>
<td>Target: 11.4 mg/2.9 mg, Range: 2.9 mg/0.71 mg to 17.2 mg/4.2 mg</td>
</tr>
<tr>
<td>- Buprenorphine hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Naloxone hydrochloride</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^*^]: Dosages above 24 mg buprenorphine or 24 mg/6 mg buprenorphine/naloxone per day have shown no clinical advantage.[^277][^238]

Adapted from material in the public domain.[^239]
H6. Buprenorphine Dose Adjustment (Source: SAMHSA, 2020b, p. 3-66)

EXHIBIT 3D.6. Adjusting the Buprenorphine Dose

When to increase the dose:
- Are patients taking medication correctly and as scheduled?
  - if they take at least 16 mg per day, mu-opioid receptors are approximately 80 to 95 percent occupied.236
  - if there are adherence problems, assess causes and intervene to promote adherence and proper administration (e.g., offer supervised dosing at the clinic, by a network support, at a pharmacy).
- If patients are taking doses correctly, a dose increase may be indicated, if certain conditions exist.
- Are patients taking other medications that may interfere with buprenorphine metabolism?
- If patients are taking doses properly, increase the dose if they still have opioid withdrawal (document with a clinical tool like COWS), opioid craving, or “good” effects (e.g., feeling “high”) from using illicit opioids.
  - Craving can be a conditioned response. It may not decrease with dose increases if patients spend time with people who use opioids in their presence.
  - Dose increases typically occur in 2 mg to 4 mg increments.
  - It will take about 5 to 7 days to reach steady-state plasma concentrations after a dose increase.
  - Offer psychosocial referrals to help decrease and manage cravings.
- Determine whether nonpharmacological problems are contributing to the need for increase.
  - For example, do patients show signs and symptoms of untreated major depressive or generalized anxiety disorders? Are they living in a chaotic household? Do they have childcare problems or financial difficulties? Are they experiencing trauma or trauma-related mental disorders?
  - Address or refer to counseling to address these problems.

When to decrease the dose:
- Decrease the dose when there is evidence of dose toxicity (i.e., sedation or, rarely, clearly linked clinically relevant increases in liver function tests).
- Hold the dose when there is acute alcohol or benzodiazepine intoxication.
Dosing Summary

Before administering naltrexone extended-release injectable suspension, keep it at room temperature for about 45 minutes.

- Use the correct needle length to ensure that the injection is in the gluteal muscle.
- Use the 2-inch needle for patients with more subcutaneous tissue and the 1.5-inch needle for patients with less adipose tissue.
- Use either length in patients with normal body habitus.
- Use proper aseptic technique.
- Use proper gluteal IM injection technique.
- Never inject intravenously or subcutaneously.
- Repeat the injection every four weeks or once per month.

**EXHIBIT 3C.3. Key Points of Patient Education for Naltrexone**

- Do not use any opioids in the 7 to 10 days (for short acting) or 10 to 14 days (for long acting) before starting XR-NTX, to avoid potentially serious opioid withdrawal symptoms. Opioids include:
  - Heroin.
  - Prescription opioid analgesics (including tramadol).
  - Cough, diarrhea, or other medications that contain codeine or other opioids.
  - Methadone.
  - Buprenorphine.
- Seek immediate medical help if symptoms of allergic reaction or anaphylaxis occur, such as:
  - Itching.
  - Swelling.
  - Hives.
  - Shortness of breath.
  - Throat tightness.
- Do not try to override the opioid blockade with large amounts of opioids, which could result in overdose.
- Understand the risk of overdose from using opioids near the time of the next injection, after missing a dose, or after stopping medications.
- Report injection site reactions including:
  - Pain.
  - Hardening.
  - Lumps.
- Blisters.
- Blackening.
- Scabs.
- An open wound.
- Some of these reactions could require surgery to repair (rarely).
- Report signs and symptoms of hepatitis (e.g., fatigue, abdominal pain, yellowing skin or eyes, dark urine).
- Report depression or suicidal thoughts. Seek immediate medical attention if these symptoms appear.
- Seek medical help if symptoms of pneumonia appear (e.g., shortness of breath, fever).
- Inform providers of naltrexone treatment, as treatment differs for various types of pneumonia.
- Inform all healthcare professionals of XR-NTX treatment.
- Report pregnancy.
- Inform providers of any upcoming medical procedures that may require pain medication.
- Understand that taking naltrexone may result in difficulty achieving adequate pain control if acute medical illness or trauma causes severe acute pain.
- Wear medical alert jewelry and carry a medical alert card indicating you are taking XR-NTX. A patient wallet card or medical alert bracelet can be ordered at 1-800-848-4876.

### EXHIBIT 2.12. Urine Drug Testing Window of Detection

<table>
<thead>
<tr>
<th>DRUG</th>
<th>POSITIVE TEST</th>
<th>WINDOW OF DETECTION*</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine; methamphetamine; 3,4-methylenedioxy-methamphetamine</td>
<td>Amphetamine</td>
<td>1-2 days</td>
<td>False positives with bupropion, chlorpromazine, desipramine, fluoxetine, labetalol, promethazine, ranitidine, pseudoephedrine, trazodone, and other common medications. Confirm unexpected positive results with the laboratory.</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Barbiturates</td>
<td>Up to 6 weeks</td>
<td>N/A</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Benzodiazepines</td>
<td>1-3 days, up to 6 weeks with heavy use of long-acting benzodiazepines</td>
<td>Immunoassays may not be sensitive to therapeutic doses, and most immunoassays have low sensitivity to clonazepam and lorazepam. Check with your laboratory regarding sensitivity and cutoffs. False positives with sertraline or oxaprozin.</td>
</tr>
</tbody>
</table>

*Detection time may vary depending on the cutoff.

Continued on next page

---

**EXHIBIT 2.12. Urine Drug Testing Window of Detection (continued)**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>POSITIVE TEST</th>
<th>WINDOW OF DETECTION*</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Buprenorphine</td>
<td>3-4 days</td>
<td>Will screen negative on opiate screen. Tramadol can cause false positives. Can be tested for specifically.</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Cocaine, benzoylecgonine</td>
<td>2-4 days; 10-22 days with heavy use</td>
<td>N/A</td>
</tr>
<tr>
<td>Codeine</td>
<td>Morphine, codeine, high-dose hydrocodone</td>
<td>1-2 days</td>
<td>Will screen positive on opiate immunoassay.</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Fentanyl</td>
<td>1-2 days</td>
<td>Will screen negative on opiate screen. Can be tested for specifically. May not detect all fentanyl-like substances.</td>
</tr>
<tr>
<td>Heroin</td>
<td>Morphine, codeine</td>
<td>1-2 days</td>
<td>Will screen positive on opiate immunoassay. 6-monoacetylmorphine, a unique metabolite of heroin, is present in urine for about 6 hours. Can be tested for specifically to distinguish morphine from heroin, but this is rarely clinically useful.</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Hydrocodone, hydromorphone</td>
<td>2 days</td>
<td>May screen negative on opiate immunoassay. Can be tested for specifically.</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>May not be detected</td>
<td>1-2 days</td>
<td>May screen negative on opiate immunoassay. Can be tested for specifically.</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Tetrahydrocannabinol</td>
<td>Infrequent use of 1-3 days; chronic use of up to 30 days</td>
<td>False positives possible with efavirenz, ibuprofen, and pantoprazole.</td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone</td>
<td>2-11 days</td>
<td>Will screen negative on opiate screen. Can be tested for specifically.</td>
</tr>
<tr>
<td>Morphine</td>
<td>Morphine, hydromorphone</td>
<td>1-2 days</td>
<td>Will screen positive on opiate immunoassay. Ingestion of poppy plant/seed may screen positive.</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Oxymorphone</td>
<td>1-1.5 days</td>
<td>Typically screens negative on opiate immunoassay. Can be tested for specifically.</td>
</tr>
</tbody>
</table>

*Detection time may vary depending on the cutoff.
H9. PTSD Screening and Diagnosis

Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)

The following screener can be used to screen for PTSD (Prins et al., 2015, p. 2). Those screening positive will require further assessment and, in case of diagnosis, access to treatment.

Sometimes things happen to people that are unusually or especially frightening, horrible, or traumatic. For example:

- a serious accident or fire
- a physical or sexual assault or abuse
- an earthquake or flood
- a war
- seeing someone be killed or seriously injured
- having a loved one die through homicide or suicide.

Have you ever experienced this kind of event? YES / NO
If NO, screen total = 0. Please stop here.
If YES, please answer the questions below.

In the past month, have you . . .

- had nightmares about the event(s) or thought about the event(s) when you did not want to? YES / NO
- tried hard not to think about the event(s) or went out of your way to avoid situations that reminded you of the event(s)? YES / NO
- been constantly on guard, watchful, or easily startled? YES / NO
- felt numb or detached from people, activities, or your surroundings? YES / NO
- felt guilty or unable to stop blaming yourself or others for the event(s) or any problems the event(s) may have caused? YES / NO

An answer of YES to three or more of these five questions is probable for the diagnosis of PTSD.
Diagnosing PTSD
The following resource provides comprehensive diagnosis instruction and information:


PTSD Medication

For the level of evidence for pharmacotherapy targeting PTSD symptoms, see

Aaron Saguil, “Psychological and Pharmacologic Treatments for Adults with PTSD,” American Family Physician, Vol. 99, No. 9, May 1, 2019, pp. 577–583.

For a discussion of additional medication treatments, see

**H10. Contingency Management**

Contingency management involves giving patients tangible rewards to reinforce positive behaviors, such as abstinence or treatment adherence. A drawing, usually for gift cards or other noncash prizes, following a negative urine toxicology result is a common strategy employed in community health settings. See, for example,

H11. Prazosin Instructions

The following is a set of instructions to share with patients being treated with prazosin.

Prazosin is a blood pressure medicine that blocks adrenaline in the brain and can make nightmares go away and help you sleep better. Prazosin has been widely studied in active duty members of the military and in veterans of all eras, and it may be helpful in treating posttraumatic stress symptoms.

Start at 1 mg and increase the dose slowly. Because it is a blood pressure medication, it may make your blood pressure drop and cause dizziness or lightheadedness. Do not increase the dose in increments larger than 1 mg (like in 2-mg increments at a time) unless your doctor tells you to. Prazosin is not a sedative or a sleeping pill.

Dosing instructions:

- **Start with one pill.** Take it one half hour or one hour before bed. Watch for dizziness or lightheadedness during the night and in the morning when you wake up. Be careful bending over (such as when doing yoga) and getting out of bed—that stand up slowly and only start walking if you do not feel lightheaded and your vision is normal. Otherwise, you could faint. For men: If you get up during the night to urinate, sit down on the toilet until you know how the medication affects you. Otherwise, urinating can drop your blood pressure and cause you to fall or pass out.

- Any dizziness or lightheadedness should be for a few minutes in the morning at most and go away completely after three or four days. Do not increase the dose of the medication until this side effect goes away. If, however, you are **not** having side effects but you are **still** having nightmares or sleep problems, increase the dose by one pill (1 mg). **Continue to increase the dose until the nightmares go away,** until you are sleeping better, or until you experience side effects that do not go away. **Never** increase the dose if you are having side effects—if side effects are not going away, decrease the dose and call your doctor or psychiatrist.

- There are pills with higher milligram doses (2 mg, 5 mg), so, as you get to higher doses, we can give you those so that you do not have to take as many pills.

- **You are starting at 1 mg, but the amount of medication you need will probably be much more than that.** Some patients need up to 30–40 mg of prazosin at night! If you are not having side effects, as long as the nightmares or sleep problems are continuing, keep increasing the dose. Prazosin can also help with daytime anxiety or adrenaline, so, if that is a problem for you, and you like the prazosin, in the future we can talk about having you take a lower daytime dose as well.
Sample schedule for the first month:

<table>
<thead>
<tr>
<th>SUN</th>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THUR</th>
<th>FRI</th>
<th>SAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg</td>
<td>1 mg</td>
<td>1 mg</td>
<td>→ 2 mg</td>
<td>2 mg</td>
<td>2 mg</td>
<td>→ 3 mg</td>
</tr>
<tr>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THUR</td>
<td>FRI</td>
<td>SAT</td>
</tr>
<tr>
<td>3 mg</td>
<td>3 mg</td>
<td>→ 4 mg</td>
<td>4 mg</td>
<td>4 mg</td>
<td>→ 5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THUR</td>
<td>FRI</td>
<td>SAT</td>
</tr>
<tr>
<td>5 mg</td>
<td>→ 6 mg</td>
<td>6 mg</td>
<td>6 mg</td>
<td>→ 7 mg</td>
<td>7 mg</td>
<td>7 mg</td>
</tr>
<tr>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THUR</td>
<td>FRI</td>
<td>SAT</td>
</tr>
<tr>
<td>→ 8 mg</td>
<td>8 mg</td>
<td>8 mg</td>
<td>→ 9 mg</td>
<td>9 mg</td>
<td>9 mg</td>
<td>→ 10 mg</td>
</tr>
</tbody>
</table>

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