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.[329]
  - 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.**

Exhibit 3D.5. Key Points of Patient Education for Buprenorphine

Before starting OUD treatment with buprenorphine, patients should:

- Tell providers the prescribed and over-the-counter medications they take, to allow drug interaction assessment.
- Understand the goal of the first week of treatment: To improve withdrawal symptoms without oversedation.
- Tell providers if they feel sedated or euphoric within 1 to 4 hours after their dose.
- Be given the appropriate buprenorphine medication guide.
- Know possible side effects, including:
  - Headache.
  - Nausea.
  - Sweating.
  - Sexual dysfunction.
  - Dizziness.
  - Vomiting.
  - Constipation.
- Agree to store medication securely and out of the reach of others.
- Alert providers if they discontinue medications, start new ones, or change their medication dose.
- Understand that discontinuing buprenorphine increases risk of overdose death upon return to illicit opioid use.
- Know that use of alcohol or benzodiazepines with buprenorphine increases the risk of overdose and death.
- Understand the importance of informing providers if they become pregnant.
- Tell providers if they are having a procedure that may require pain medication.
- Be aware of resources through which to obtain further education for
  - Themselves: *Decisions in Recovery: Treatment for Opioid Use Disorder* (https://store.samhsa.gov/product/SMA16-4993).
  - Their families and friends: *Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends* (www.ct.gov/dmhas/lib/dmhas/publications/MAT-InfoFamilyFriends.pdf).

Initiating Buprenorphine Treatment

It can be helpful to use a buprenorphine treatment agreement for patients treated in office-based settings (see Chapter 3D Appendix for a sample treatment agreement).

Induction can occur in the office or at home. Most clinical trials were conducted with office-based induction, and extant guidance recommends this approach.[316] However, office-based induction can be a barrier to treatment initiation. Home induction is increasingly common.[317]

Office-Based Induction

Providers can perform office-based induction by ordering and storing induction doses in the office or by prescribing medication and instructing patients to bring it to the office on the day of induction. **Office-based induction allows providers to:**

- Ensure **that patients know how to take medication** without swallowing or spitting it out if they have too much saliva or experience unpleasant tastes. Tell them to wait to eat or drink until the medication is totally dissolved.
- **Enhance the therapeutic relationship.**
- **Verify the presence of opioid withdrawal and absence of precipitated opioid withdrawal.**
- **Ensure the lack of sedation 1 to 2 hours after the first dose in patients taking sedatives.**
- **Use time between doses for patient self-assessment.** See the Chapter 3D Appendix for sample goal-setting forms that help patients identify treatment goals and triggers for use.

Buprenorphine/Naloxone Home Dosage Schedule: Films or Tablets

Name: _____ **Date:** _____

Procedure for taking buprenorphine:

- Let the medication dissolve under your tongue for at least 10 minutes. Do not suck on it.*
- Do not eat, drink, or smoke cigarettes for 30 minutes after you take your medication.
- Wait 2 hours between each dose.

The maximum dose is 16 mg/4 mg. If you reach this dose, you cannot increase further without calling the office first. The office phone number is _____ [insert phone number].

Day 1 Induction Day (In Office): You have taken a total dose of _____ mg.

Day 2 in the Morning: Take the total dose you took on **Day 1** = _____ mg.

- If you experience withdrawal 2 hours later, you may take one 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.
- If you continue to experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet or ¼ of an 8 mg/2 mg film or tablet.
- Record your withdrawal symptoms: _____.

Your total dose on **Day 2 cannot** exceed _____ mg. Record your total dose on **Day 2**: _____ mg.

Day 3 in the Morning: Take the total dose you took on **Day 2** = _____ mg.

- If you experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.
- If you continue to experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.

Your total dose on **Day 3 cannot** exceed _____ mg. Record your total dose on **Day 3**: _____ mg.

Day 4 in the Morning: Take the total dose you took on **Day 3** = _____ mg.

- If you experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.
- If you continue to experience withdrawal 2 hours later, you may take one more 2 mg/0.5 mg film or tablet.
- Record your withdrawal symptoms: _____.

Your total dose on **Day 4 cannot** exceed _____ mg. Record your total dose on **Day 4**: _____ mg.

Day 5 to next visit: In the morning, take the total dose you took on **Day 4** = _____ mg.

General Rules

- The maximum dose is 16 mg/4 mg. If you reach this dose, you cannot increase further without calling the office first. The office phone number is _____ [insert phone number].
- Please call if you have any questions. There are no "stupid" questions.
- Call us if you feel sleepy after your dose.
- Please bring this record to your next visit.
- It's okay to take Tylenol (acetaminophen) or Motrin (ibuprofen) for aches/pains.

BRING THIS WITH YOU TO YOUR NEXT APPOINTMENT, scheduled for _____ [insert date and time].

Notes:

*If prescribing the buccal film, ensure the patient understands that the buccal film is placed on the inner cheek (buccal mucosa) rather than sublingually (under the tongue).

M. Lofwall, February 27, 2017 (personal communication). Adapted with permission.

Sample Goal-Setting Form

Name: Date:

Category	**Current Situation Score** (10 = major problems and 0 = no problems).	**What Would Need To Change To Decrease This Score?**	**Priority Score** (10 = highest priority ["I really want to work on this."] and 1 = lowest priority ["I really do not want to work on this.").
Opioid Use			
Other Illicit Drug Use: _____			
Alcohol Use			
Tobacco Use			
Physical Health			
Mental Health			
Legal/Court Issues			
Finances			
Job/Employment			
Hobbies			
Family Relations			
Partner Relations			
Supportive Drug-Free Network			
Education			
Keeping Medication Safe (e.g., not giving it away, selling it, having it stolen)			
Other:			
Other:			

M. Lofwall, February 27, 2017 (personal communication). Adapted with permission.

Buprenorphine Treatment Agreement

This form is for educational/informational purposes only. It doesn't establish a legal or medical standard of care. Healthcare professionals should use their judgment in interpreting this form and applying it in the circumstances of their individual patients and practice arrangements. The information provided in this form is provided "as is" with no guarantee as to its accuracy or completeness.

Treatment Agreement

I agree to accept the following treatment contract for buprenorphine office-based opioid addiction treatment:

1. The risks and benefits of buprenorphine treatment have been explained to me.
2. The risks and benefits of other treatment for opioid use disorder (including methadone, naltrexone, and nonmedication treatments) have been explained to me.
3. I will keep my medication in a safe, secure place away from children (for example, in a lockbox). My plan is to store it [describe where and how].

Buprenorphine Treatment Agreement

4. I will take the medication exactly as my healthcare provider prescribes. If I want to change my medication dose, I will speak with my healthcare provider first. Taking more medication than my healthcare provider prescribes or taking it more than once daily as my healthcare provider prescribes is medication misuse and may result in supervised dosing at the clinic. Taking the medication by snorting or by injection is also medication misuse and may result in supervised dosing at the clinic, referral to a higher level of care, or change in medication based on my healthcare provider's evaluation.
5. I will be on time to my appointments and respectful to the office staff and other patients.
6. I will keep my healthcare provider informed of all my medications (including herbs and vitamins) and medical problems.
7. I agree not to obtain or take prescription opioid medications prescribed by any other healthcare provider without consulting my buprenorphine prescriber.
8. If I am going to have a medical procedure that will cause pain, I will let my healthcare provider know in advance so that my pain will be adequately treated.
9. If I miss an appointment or lose my medication, I understand that I will not get more medication until my next office visit. I may also have to start having supervised buprenorphine dosing.
10. If I come to the office intoxicated, I understand that my healthcare provider will not see me, and I will not receive more medication until the next office visit. I may also have to start having supervised buprenorphine dosing.
11. I understand that it's illegal to give away or sell my medication; this is diversion. If I do this, my treatment will no longer include unsupervised buprenorphine dosing and may require referral to a higher level of care, supervised dosing at the clinic, and/or a change in medication based on my healthcare provider's evaluation.
12. Violence, threatening language or behavior, or participation in any illegal activity at the office will result in treatment termination from the clinic.
13. I understand that random urine drug testing is a treatment requirement. If I do not provide a urine sample, it will count as a positive drug test.
14. I understand that I will be called at random times to bring my medication container into the office for a pill or film count. Missing medication doses could result in supervised dosing or referral to a higher level of care at this clinic or potentially at another treatment provider based on my individual needs.
15. I understand that initially I will have weekly office visits until I am stable. I will get a prescription for 7 days of medication at each visit.
16. I can be seen every 2 weeks in the office starting the second month of treatment if I have two negative urine drug tests in a row. I will then get a prescription for 14 days of medication at each visit.
17. I will go back to weekly visits if I have a positive drug test. I can go back to visits every 2 weeks when I have two negative drug tests in a row again.
18. I may be seen less than every 2 weeks based on goals made by my healthcare provider and me.
19. I understand that people have died by mixing buprenorphine with alcohol and other drugs like benzodiazepines (drugs like Valium, Klonopin, and Xanax).
20. I understand that treatment of opioid use disorder involves more than just taking medication. I agree to comply with my healthcare provider's recommendations for additional counseling and/or for help with other problems.
21. I understand that there is no fixed time for being on buprenorphine and that the goal of treatment is for me to stop using all illicit drugs and become successful in all aspects of my life.
22. I understand that I may experience opioid withdrawal symptoms when I stop taking buprenorphine.
23. I have been educated about the other two FDA-approved medications used for opioid dependence treatment, methadone and naltrexone.
24. I have been educated about the increased chance of pregnancy when stopping illicit opioid use and starting buprenorphine treatment and been informed about methods for preventing pregnancy

Other specific items unique to my treatment include:

Patient Name (print): _____ Patient Signature: _____ Date: _____

This form is adapted from ASAM's Sample Treatment Agreement, which they will update periodically; their most current version of the agreement is available online (www.asam.org/docs/default-source/advocacy/sample-treatment-agreement30fa159472bc604ca5b7ff000030b21a.pdf?sfvrsn=0).

Adapted with permission.[345]

Patient Urine Drug Screen and Medication Count Monitoring Form

Patient Name: _____

Dates To Be Called: _____

Called for:

□ Urine Drug Screen

□ Medication Count at □Office or □Pharmacy FOR:

□ Buprenorphine/Naloxone

□ Other (list drug: _____, _____, _____)

Documentation of Phone Call to Patient

Patient was called at _____ (insert phone #) on _____ (date) at ___:___ (time) and informed of monitoring required (described above) within the next _____ hours.

Check One:

□ I spoke with patient

□ Message left on answering machine/voicemail

□ Message left with _____

□ Other _____

Signature of Staff Member Making Phone Call: _____

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Pharmacy Tablet/Film Count Form

(Note: Before sending this form, discuss with the pharmacist to explain goals and procedures and to ensure agreement and understanding.)

Date: _____

To: Pharmacists @ _____ Pharmacy

From: Healthcare Provider: _____
Clinic Address: _____
Phone Number: _____

My patient, _____, is starting office-based buprenorphine treatment for opioid dependence.

As part of monitoring this treatment, we ask the patient to do buprenorphine tablet/film counts at random times (we call the patient when it's time for a pill/film count).

The above-named patient lives much closer to your pharmacy than to our treatment clinic. It would be a big help to me and this patient if you would be able to perform periodic tablet/film counts on his/her buprenorphine and then fax this form to us.

On the days we call the patient for a random tablet/film count, the patient would come to your pharmacy with his or her pill bottle. When we call the patient to go for a random tablet/film count, we will fax this form to you. We would appreciate if you could record the tablet/film count results on this form and fax it back to us the same day. This would be a real help to me in monitoring my patient's treatment and also a great service to the patient.

Thank you very much for your help with this! Sincerely,

_____

Buprenorphine/Naloxone Formulation: _____
Dose per Tablet/Film: _____
Total # of tablets/films remaining in bottle: _____
Fill date on bottle: _____
Total # of tablets/films dispensed on fill date: _____
Tablet/film count correct? □ Yes □ No

Please fax this back to: _____

Thank You!

M. Lofwall, February 27, 2017 (personal communication). Adapted with permission.

or stopping medications that are CYP450 3A4 enzyme inhibitors or inducers for overdosing/underdosing of buprenorphine or coadministered medication. Exhibit 3D.3 lists these medications, including some anticonvulsants, antibiotics, and HIV medications (Exhibit 3D.4 lists more HIV medications). More information on drug–drug interactions is available online (www.drugs.com/drug-interactions/buprenorphine-index.html?filter=3&generic_only=).

Monitor responses to buprenorphine in patients taking nonnucleoside reverse transcriptase inhibitors. Changes in buprenorphine concentrations can be clinically significant.[284]

Combination antiretroviral therapy (atazanavir/ritonavir) increases buprenorphine and norbuprenorphine serum concentrations.[285] Case reports have demonstrated signs of buprenorphine excess (sedation). Decreasing buprenorphine can improve this symptom.[286] Other research has demonstrated no need to adjust the buprenorphine dose among patients taking atazanavir.[287]

Exhibit 3D.3. Partial List of Medications Metabolized by Cytochrome P450 3A4

Inhibitors (Potentially Increase Blood Levels of Buprenorphine)	Substrates		Inducers (Potentially Decrease Blood Levels of Buprenorphine)
Amiodarone	Alprazolam	Loratadine	Carbamazepine
Atazanavir	Amlodipine	Losartan	Dexamethasone
Atazanavir/Ritonavir	Astemizole	Lovastatin	Efavirenz
Clarithromycin	Atorvastatin	Miconazole	Ethosuximide
Delavirdine	Carbamazepine	Midazolam	Nevirapine
Erythromycin	Cisapride	Navelbine	Phenobarbital
Fluconazole	Clindamycin	Nefazodone	Phenytoin
Fluoxetine	Clonazepam	Nelfinavir	Primidone
Fluvoxamine	Cyclobenzaprine	Nicardipine	Rifampin
Grapefruit Juice	Cyclosporine	Nifedipine	
Indinavir	Dapsone	Nimodipine	
Itraconazole	Delavirdine	Ondansetron	
Ketoconazole	Dexamethasone	Oral Contraceptives	
Metronidazole	Diazepam	Paclitaxel	
Miconazole	Diltiazem	Prednisone	
Nefazodone	Disopyramide	Progestins	
Nelfinavir	Doxorubicin	Quinidine	
Nicardipine	Erythromycin	Rifampin	
Norfloxacin	Estrogens	Ritonavir	
Omeprazol	Etoposide	R-Warfarin	
Paroxetine	Felodipine	Saquinavir	
Ritonavir	Fentanyl	Sertraline	
Saquinavir	Fexofenadine	Simvastatin	
Sertraline	Glyburide	Tacrolimus	
Verapamil	Ifosfamide	Tamoxifen	
Zafirlukast	Indinavir	Verapamil	
Zileuton	Ketoconazole	Vinblastine	
	Lansoprazole	Zileuton	
	Lidocaine		

Note: Consult a point-of-service medical reference application for the most up-to-date drug–drug interactions before making medication management decisions.

Adapted from material in the public domain.[288]

DSM-5 Opioid Use Disorder Checklist.[7]

Patient's Name:

Date of Birth:

Worksheet for DSM-5 Criteria for Diagnosis of Opioid Use Disorder

Diagnostic Criteria (Opioid Use Disorder requires at least 2 criteria be met within a 12-month period	**Meets criteria?** Yes OR No	**Notes/Supporting information**
1. Opioids are often taken in larger amounts or over a longer period of time than intended		
2. There is a persistent desire or unsuccessful effort to cut down or control opioid use		
3. A lot of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects		
4. Craving or a strong desire to use opioids		
5. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home		
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids		
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use		
8. Recurrent opioid use in situations in which it is physically hazardous		
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids		
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) markedly diminished effect with continued use of the same amount of an opioid		
11. *Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same—or a closely related—substance is taken to relieve or avoid withdrawal symptoms		

*This criterion is not met for individuals taking opioids solely under appropriate medical supervision.

Severity

Mild: two or three symptoms; moderate: four or five symptoms; severe: six or more symptoms

Signed_____Date_____

Learning How OUD Medications Work

The following sections describe how each of the OUD medications functions (Exhibit 4.5; see also Part 3 of this TIP for greater detail). Discuss questions or concerns about a patient's medication, side effects, or dosage with the patient's prescriber after getting the patient's consent.

Exhibit 4.5. FDA-Approved Medications Used To Treat OUD: Key Points

Medication	How It's Taken	Why It Works	Side Effects	Notes
Buprenorphine	Tablet dissolved under the tongue or film dissolved under the tongue or against the inside of the cheek. Taken once daily, every other day, or three times a week. It also comes as an implant that lasts 6 months or as an injection that lasts 1 month.	Partially activates the opioid receptor. Reduces craving and blocks the euphoric effect of opioids.	Can cause constipation, headache, nausea, insomnia, excessive sweating, or opioid withdrawal. Overdose is possible but less likely than with methadone. Overdose death risk is increased if buprenorphine is taken with alcohol or intravenously in combination with benzodiazepines or other CNS depressants. Neonatal opioid withdrawal syndrome.	Less sedating than methadone. Prescribers must have a special SAMHSA waiver but don't need to be part of a federally certified OTP. Can be prescribed through pharmacies or provided via OTPs.
Methadone	Liquid or tablet once daily. Dose may be divided for twice-daily dosing if medically necessary.	Fully activates the opioid receptor. Reduces craving and blocks the euphoric effect of opioids.	Can cause constipation, sleepiness, sweating, swelling of hands and feet, sexual dysfunction, heart arrhythmias, low blood pressure, fainting, and substance misuse. Can cause overdose death if increased too rapidly, taken in a much higher than usual dose, or taken concurrently with some substances and medications, particularly CNS depressants such as alcohol or benzodiazepines. Neonatal opioid withdrawal syndrome.	Initially requires visits 6 to 7 times per week to an OTP. Patients can decrease attendance gradually based on time in treatment and clinical stability.
Naltrexone	Daily tablet (can also be taken three times a week) or monthly injection in buttock.	Occupies the opioid receptors. Reduces craving and blocks the euphoric effect of opioids.	Can cause nausea, headache, dizziness, fatigue, liver toxicity, depression and suicidality, muscle cramps, fainting, loss of or decreased appetite or other appetite disorders; in the extended-release injectable formulation, can cause pain, swelling, and other complications at the injection site. Patient must complete withdrawal and stay opioid abstinent for at least 7 days before starting naltrexone and longer (e.g., 10 or more days) for long-acting opioids, such as methadone.	Tablets are rarely effective. Monthly injections are more effective than tablets.

Educate patients and their families about what to expect from naltrexone treatment (Exhibit 3C.3). A naltrexone medication guide should be dispensed to patients with each injection. Caution them about increased risk of overdose if they stop treatment and return to illicit opioid use or attempt to override the receptor blockade of XR-NTX. Document education in the medical record. Chapter 3C Appendix has a patient education counseling tool for XR-NTX.

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.

Educate patients and their families about what to expect from naltrexone treatment (Exhibit 3C.3). A naltrexone medication guide should be dispensed to patients with each injection. Caution them about increased risk of overdose if they stop treatment and return to illicit opioid use or attempt to override the receptor blockade of XR-NTX. Document education in the medical record. Chapter 3C Appendix has a patient education counseling tool for XR-NTX.

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.

Initiating XR-NTX treatment

Storage and preparation

A pharmacy will send XR-NTX and its diluent in a refrigerated package with two sets of administration needles (1.5 and 2 inches), a 1-inch preparation needle, and a needle protection device.

The XR-NTX microspheres are temperature sensitive. When the carton arrives from the pharmacy, store it in a refrigerator at 36 to 46 degrees Fahrenheit (2 to 8 degrees Celsius). The refrigerator should have a working thermometer; check the temperature regularly.

withdrawal than could occur with a full 50 mg dose. This lower dose may also reduce nausea associated with the first naltrexone dose. The dose can be increased to 50 mg daily on the second day.

To increase adherence, arrange for directly observed administration of oral naltrexone. This is more feasible if patients who tolerate a daily dose of 50 mg are switched to a 3-days-per-week regimen for a total weekly dose of 350 mg (e.g., administer 100 mg on Monday and Wednesday and 150 mg on Friday). A member of the patient's social network (e.g., spouse) may also directly observe therapy.

Duration of treatment

The optimal length of treatment with oral naltrexone is not known. In general, the longer patients take an effective medication, the better their outcomes.

Use of illicit opioids during treatment with oral naltrexone is a cause of concern and may be a precursor to treatment discontinuation.[206] Some patients will initially test the opioid blockade with illicit opioids and then discontinue opioid use. However, others will continue using illicit opioids.[207]

If patients continue to test the blockade, immediately discuss alternative treatment plans that include:

- Increased counseling.
- Switching to XR-NTX.
- Closer monitoring.
- Directly observed oral naltrexone therapy.
- Residential treatment.
- Assessment for the appropriateness of buprenorphine or methadone.

Naltrexone Dosing Summary

XR-NTX

- Before administering XR-NTX, keep it at room temperature for about 45 minutes.
- Use the correct needle length to ensure 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 4 weeks or once per month.

Oral Naltrexone

- Use in limited circumstances after discussing risks and benefits, as well as alternative treatment options, with the patient.
- Do the naloxone challenge.
- The first oral naltrexone dose should be 25 mg.
- The dose can be increased on the second day to 50 mg daily if necessary.
- If desired, switch patients who tolerate a daily dose of 50 mg to a 3-days /week regimen for a total weekly dose of 350 mg.

Chapter 3C Appendix

Sample XR-NTX Treatment Agreement

This form is for educational/informational purposes only. It doesn't establish a legal or medical standard of care. Healthcare professionals should use their judgment in interpreting this form and applying it to the circumstances of their individual patients and practice arrangements. The information provided in this form is provided "as is" with no guarantee as to its accuracy or completeness.

Sample Treatment Agreement

I agree to accept the following treatment agreement for extended-release injectable naltrexone office-based opioid use disorder treatment:

1. The risks and benefits of extended-release injectable naltrexone treatment have been explained to me.
2. The risks and benefits of other treatment for opioid use disorder (including methadone, buprenorphine, and nonmedication treatments) have been explained to me.
3. I will be on time to my appointments and be respectful to the office staff and other patients.
4. I will keep my healthcare provider informed of all my medications (including herbs and vitamins) and medical problems.
5. I agree not to obtain or take prescription opioid medications prescribed by any other healthcare provider without consultation from my naltrexone prescriber.
6. If I am going to have a medical procedure that will cause pain, I will let my healthcare provider know in advance so that my pain will be adequately treated.
7. If I miss a scheduled appointment for my next extended-release naltrexone injection, I understand that I should reschedule the appointment as soon as possible because it is important to receive the medication on time to reduce the risk of opioid overdose should I return to use.
8. If I come to the office intoxicated, I understand that my healthcare provider will not see me.
9. Violence, threatening language or behavior, or participation in any illegal activity at the office will result in treatment termination from the clinic.
10. I understand that random urine drug testing is a treatment requirement. If I do not provide a urine sample, it will count as a positive drug test.
11. I understand that initially I will have weekly office visits until my condition is stable.
12. I can be seen every 2 weeks in the office starting the second month of treatment if I have two negative urine drug tests in a row.
13. I may be seen less than every 2 weeks based on goals made by me and my healthcare provider.
14. I understand that people have died trying to overcome the naltrexone opioid blockade by taking large amounts of opioids.
15. I understand that treatment of opioid use disorder involves more than just taking medication. I agree to follow my healthcare provider's recommendations for additional counseling and/or for help with other problems.
16. I understand that there is no fixed time for being on naltrexone, and that the goal of treatment is for me to stop using all illicit drugs and become successful in all aspects of my life.
17. I understand that my risk of overdose increases if I go back to using opioids after stopping naltrexone.
18. I have been educated about the other two FDA-approved medications used to treat opioid use disorder, methadone and buprenorphine, and I prefer to receive treatment with naltrexone.
19. I have been educated about the increased chance of pregnancy when stopping illicit opioid use and starting naltrexone treatment. I have been informed about methods for preventing pregnancy.
20. I have been informed that if I become pregnant during naltrexone treatment, I should inform my provider and have a discussion about the risks and benefits of continuing to take naltrexone.

Other specific items unique to my treatment include:

Patient Name (print): _____ Patient Signature _____ Date: _____

This form is adapted from ASAM's Sample Treatment Agreement, which they will update periodically; their most current version of the agreement is available online (www.asam.org/docs/default-source/advocacy/sample-treatment-agreement30fa159472bc604ca5b7ff000030b21a.pdf?sfvrsn=0).

Adapted with permission.[208]

Key Techniques for Reducing Injection Site Reactions.[210]

To reduce severe injection site reactions when administering XR-NTX via intramuscular injection, use the following techniques:

- **Use one of the administration needles provided with the XR-NTX kit to ensure that the injection reaches the gluteal muscle.** Use the 2-inch needle for patients who have more subcutaneous adipose tissue. Use the 1.5-inch needle for patients with less subcutaneous adipose tissue. Either needle is appropriate for use with patients who have average amounts of subcutaneous adipose tissue.
- **Use aseptic technique when administering intramuscularly.** Using a circular motion, clean the injection site with an alcohol swab. Let the area dry before administering the injection. Do not touch this area again before administration.
- **Use proper deep intramuscular injection technique into the gluteal muscle.** XR-NTX must not be injected intravenously, subcutaneously, or into adipose tissue. Accidental subcutaneous injection may increase the risk of severe injection site reactions.
  - **Administer the suspension by deep intramuscular injection into the upper outer quadrant of gluteal muscle,** alternating buttocks per monthly injection.
  - **Remember to aspirate for blood before injection.** If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the package and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.
  - **Inject the suspension in a smooth, continuous motion.**

A patient counseling tool is available to help you counsel your patients before administration about the serious risks associated with XR-NTX.

The above information is a selection of key safety information about the XR-NTX injection. For complete safety information, refer to the directions for use and the prescribing information provided in the m

Available online (www.vivitrolrems.com/content/pdf/patinfo-injection-poster.pdf).