Tools of the Trade

Resources for the Use of Methadone and Naltrexone

Compiled by clinical consultants and project staff of Missouri's State Opioid Response Grant

September, 2019

The information presented in this handbook was retrieved and consolidated from the following resources:

- Alkermes, Inc. Human Prescription Drug Label

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd11c435-b0f0-4bb9-ae78-60f101f3703f

- American Society of Addiction Medicine National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use TREATMENT IMPROVEMENT PROTOCOL --Tip 43

http://adaiclearinghouse.org/downloads/TIP-43-Medication-Assisted-Treatment-for-Opioid-Addiction-in-Opioid-Treatment-Programs-51.pdf

- American Society of Addiction Medicine National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use TREATMENT IMPROVEMENT PROTOCOL --Tip 63

https://store.samhsa.gov/product/TIP-63-Medications-for-Opioid-Use-Disorder-Full-Document-Including-Executive-Summary-and-Parts-1-5-/SMA19-5063FULLDOC

- The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use *(PCSS MAT Training: Providers' Clinical Support System for Medicated Assisted Treatment*

https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24

- The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use *(PCSS MAT Training: Providers' Clinical Support System for Medicated Assisted Treatment* Module

http://pcssnow.org/wp-content/uploads/2016/03/PCSS_MAT-Kampman-Guideline-final1.pdf

- Policy and Procedure Manual of the Office Based Addiction Treatment Program for the use of Buprenorphine and Naltrexone Formulations in the Treatment of Substance Use Disorders

file:///C:/Users/ruizap/Downloads/23_Clinical_Guidelines_National.pdf

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IDENTIFYING PATIENTS WHO MAY BE APPROPRIATE FOR METHADONE TREATMENT

Methadone is recommended for patients who may benefit from daily dosing and supervision in an Opioid Treatment Program (OTP), or for patients for whom buprenorphine for the treatment of Opioid Use Disorder (OUD) has been used unsuccessfully in an OTP or Office-Based Opioid Treatment (OBOT) setting.

Methadone is a treatment option recommended for patients who are physiologically dependent on opioids, able to give informed consent, and who have no specific contraindications for agonist treatment when it is prescribed in the context of an appropriate plan that includes psychosocial intervention.

Methadone is contraindicated for the following conditions:

- Patients with known hypersensitivity to methadone hydrochloride.
- Patients experiencing respiratory depression (in the absence of resuscitative equipment or in unmonitored settings).
- Patients with acute bronchial asthma or hypercapnia (also known as hypercarbia).
- Patients with known or suspected paralytic ileus.

Methadone should be used with caution for the following conditions:

- Patients with decompensated liver disease (eg, jaundice, ascites) due to increased risk of hepatic encephalopathy.
- Patients with respiratory insufficiency.
- Patients with concomitant substance use disorders, particularly patients with sedative, hypnotic, or anxiolytic use disorders. Interactions between methadone and hypnotics, sedatives, or anxiolytics may be life-threatening.
- Patients with regular or risky alcohol use.
- Patients with concomitant psychiatric diagnoses that impair their ability to maintain daily attendance at an OTP.
- Patients with low levels of physical dependence to opioids should be started with low doses of methadone.

CONSIDERATIONS PRIOR TO INDUCTION ON METHADONE

When considering a patient's eligibility for methadone treatment, consider the following:

- Obtain a thorough drug and medication history, including results of drug and other laboratory tests. When adding any drugs to a therapeutic regimen, start with low doses, increase slowly, and monitor patient reactions closely.
- Educate patient about the risks of drug interactions, potentially lethal drugs or medications during agonist-based pharmacotherapy, possible cardiovascular risks, and possible effects of deviating from dosage schedules and amounts.
- Substitute alternative medications that do not interact with opioid treatment medications or have the least potential for interaction.
- Consider whether administering other medications with or without food or altering dosing schedules might reduce the risk of drug interactions.
- Simplify the medication regimen to make it easier for the patient to adhere to it.
- Adjust opioid medication dosage based on patient response to avoid drug interaction, but be vigilant for signs of withdrawal or sedation.
- Increase drug testing and monitoring of drug serum levels. Advise patient of the physical signs of adverse interactions, and explain what to do if these occur.
- Be aware of concomitant diseases (e.g., liver disease) that might influence the potential for adverse drug interactions.

TYPES OF SETTINGS FOR THE PRESCRIPTION OF METHADONE

The choice of available treatment options for addiction involving opioid use should be a shared decision between clinician and patient. Clinicians should consider the patient's preferences, past treatment history, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone in the treatment of addiction involving opioid use.

The venue in which treatment is provided is as important as the specific medication selected. OTPs offer daily supervised dosing of methadone, and increasingly of buprenorphine. In accordance with the Federal law (21 CFR §1306.07), office-based opioid treatment (OBOT), which provides medication on a prescribed weekly or monthly basis, is limited to buprenorphine.

Federal and state-approved OTPs dispense methadone and supervise medication administration. Treatment should include relapse monitoring with frequent testing for alcohol and other relevant

psychoactive substances. Testing for methadone and buprenorphine is recommended to ensure adherence and detect possible diversion.

METHADONE INDUCTION

The first methadone dose for patients tolerant to opioids is generally between 10 mg and 30 mg (30 mg is the maximum first dose per federal OTP regulations). After the first dose, patients should remain for observation for 2 to 4 hours if possible to see whether the dose is sedating or relieves withdrawal signs.

If withdrawal symptoms lessen, the patient should return the next day to be reassessed and to continue the dose induction process. If sedation or intoxication occurs after the first dose, the patient should stay under observation at the clinic until symptoms resolve. In this case, the patient should be reassessed the following day, and the subsequent day's dose should be substantially reduced. Extremely rarely, the patient will need to be treated for overdose with naloxone. If necessary, begin rescue breathing and call 9-1-1.

If the patient shows neither sedation nor reduction of objective signs of opioid withdrawal during the 2- to 4-hour waiting period, administer another 5 mg dose. A final 5 mg dose after another waiting period of 2 to 4 hours can be administered if necessary.

The maximum total methadone dose on the first day of treatment should not exceed 40 mg. However, caution dictates against exceeding a total first day's dose of 30 mg except in rare cases. In such cases, the patient should be carefully monitored on subsequent days to rule out over-sedation.

Patients transferring from another OTP whose methadone dose and last date of medication administration can be confirmed by the medical staff and documented in the medical record can be continued on the same methadone dose administered in the original OTP, even if the dose exceeds the maximum permitted 40 mg. For some patients, the lower range of initial doses is best. Dose with 10 mg to 20 mg in patients who:

- Are age 60 and older.
- May have lower levels of opioid tolerance based on their recent history.
- Use sedating medications, such as benzodiazepines, antipsychotics, or antidepressants.
- Engage in problematic or risky drinking or have alcohol use disorder.
- Take medications that can increase methadone serum levels or are stopping medications that decrease methadone serum levels.

- Have medical disorders that may cause hypoxia, hypercapnia, or cardiac arrhythmias. These include:
    - Asthma, chronic obstructive pulmonary disease, and kyphoscoliosis.
    - Obesity.
    - Sleep apnea.
    - QTc prolongation.
    - Cor pulmonale.
    - Electrolyte abnormalities, such as hypokalemia or hypomagnesemia
    - A family history of cardiac arrhythmias, fainting or dizziness, or sudden death

DOSING AND MAINTENANCE

Methadone has a long half-life and care must be taken to avoid too rapid dose increases during the first 1–3 weeks of treatment, so as to avoid increasing the dose before the full effect of the last dose has been realized. Dosing should be based on patients achieving goals of treatment, can vary widely between patients, and doses do not correlate well with blood levels.

Trough and peak plasma levels of methadone (or methadone blood levels) may be used in addition to clinical evaluation to assess the safety and adequacy of a patient's dose, particularly in patients who seem to be rapid metabolizers and may need a split dose. A relatively low dose of methadone (i.e., <30mg a day) can lessen acute withdrawal, but it is often not effective in suppressing cravings and blocking the effects of other opioids.

Though a few patients respond to a maintenance dose of 30–60 mg per day, most patients fare better if their initial 30–40 mg per day dose is gradually raised to a maintenance level of 60–120 mg per day, which typically creates sufficient tolerance to minimize a euphoric response if patients self-administer additional opioids. Multiple randomized trials have found that patients have better outcomes, including retention in treatment, with higher doses (80–100 mg per day) than lower doses.[1],[2]Though not well studied, doses above 120 mg per day are being used with

1 Strain EC, Bigelow GE, Liebson IA, et al. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. J Am Med Assoc 1999; 281:1000–1005.

some patients as blockade of opioid effects is becoming increasingly more difficult due to the increased purity of heroin and strength of prescription opioids.

The optimal duration of treatment with methadone has not been established; however, it is known that relapse rates are high for most patients who drop out; thus long-term treatment is often needed. Treatment duration depends on the response of the individual patient and is best determined by collaborative decisions between the clinician and the patient. Treatment should be reinstituted immediately for most patients who were previously taking methadone and have relapsed or are at risk for relapse.[3]

POTENTIAL ADVERSE EFFECTS AND CHANGES IN DOSAGE

Possible side effects of methadone include the following[4]:

- Constipation
- Nausea
- Sweating
- Sexual dysfunction or decreased libido
- Drowsiness
- Amenorrhea
- Weight gain

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2 Strain EC, Stitzer ML, Liebson IA, et al. Dose-response effects of methadone in the treatment of opioid dependence. Ann Intern Med 1993; 119:23–27.

3 Comer, S., et al, PHD, Wyatt, S., Guideline Committee Members DO, A. A., PHD, et al, Woodworth, A., MS. (2015, June 1) Treatment Research Institute Technical Team Members. ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (J. Femino MD, FASAM & P. S. Mills MBA, ASAM, Executive Vice President, Eds.; M. M. Miller MD, FASAM, FAPA, Trans.). Retrieved from https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24 pg 29-30

4 Medications for Opioid Use Disorder For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. (2018). *TREATMENT IMPROVEMENT PROTOCOL --Tip 63*,3-23doi:https://store.samhsa.gov/system/files/tip63_fulldoc_052919_508.pdf

HHS Publication No. (SMA) 19-5063FULLDOC First released 2018. Revised 2019. U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment

- Edema

Higher methadone doses may be associated with increased risk of adverse effects, including prolongation of the QT interval and other arrhythmias, which in some cases have been fatal (the QT interval is the interval between the beginning of the Q deflection to the end of the T wave. Certain medications increase the QT interval which in turn can increase their chance of a patient to develop lethal arrhythmias). The US FDA issued a safety alert for methadone regarding these cardiac events. Clinicians, in consultation with patients, may need to consider the relative risk of adverse events due to QT prolongation with methadone as compared to the risk of morbidity and mortality of an untreated OUD. Changing to buprenorphine or naltrexone maintenance should be considered when risks of QT prolongation are high as they do not seem to significantly prolong the QT.

Certain medical factors may cause a patient's dosage requirements to change, including (but not limited to) starting, stopping, or changing the dosage of other prescription medications; onset and progression of pregnancy; onset of menopause; progression of liver disease; significant increase or decrease in weight; or aging (elderly patients are sometimes more sensitive to drugs such as opioids). Patient complaints of opioid craving, withdrawal symptoms, medication side effects, or intoxication always should be investigated and never should be dismissed. Mildly to moderately overmedicated patients might show "nodding" and closing of the eyes or might fall asleep at inappropriate times.

Patients might scratch their faces continuously, especially their noses. In some cases, sedation might occur but be unapparent, and some overmedicated patients might feel mildly stimulated. Nausea also can occur, particularly in newer patients. Patients should be told when overmedication is suspected, and their dosage should be reduced. Patients also might report feeling high or loaded and ask for a reduced dosage. Such a reduction can be helpful for patients committed to abstinence rather than ongoing medication maintenance because they may find physical reminders of intoxication discouraging, frightening, or relapse triggering.

Patients who report that they have vomited their medication pose special problems. The American Society of Addiction Medicine consensus panel recommends that only doses lost to witnessed emesis be replaced. Emesis 30 minutes after dosing can be handled by reassuring patients that the full dose has been absorbed. Emesis at 15 to 30 minutes after dosing can be handled by replacing half the dose, and the whole dose should be replaced if emesis occurs within 15 minutes of dosing.

If vomiting persists, it is important to remember that only a portion of the gut is emptied with forceful emesis; therefore, the risk of accumulated toxicity increases with repeated dose

replacements. **Causes of emesis including pregnancy should be explored.** Ingestion of smaller amounts of medication over a few minutes can be helpful and prudent, as can the occasional use of antiemetic medicines. [5]

DRUG INTERACTIONS

Significant medication interactions' to consider before starting methadone are as follows:

- Methadone may prolong the QT interval and should be used in caution with other agents that may also prolong the QT interval. These include class I or class III antiarrhythmic drugs, calcium channel blockers, some antipsychotics, and some antidepressants.
- Methadone is metabolized through the cytochrome P450 enzyme pathway. Many agents interact with this pathway including alcohol, anticonvulsants, antiretrovirals, and macrolide antibiotics.[6]

POTENTIAL TRIGGERED WITHDRAWAL

Environmental cues, including people, places, things, and feelings associated with drug taking, can be associated strongly with opioid craving and withdrawal. Such reactions may be identical to opioid withdrawal symptoms and can stimulate drug craving and relapse long after opioid use has stopped and physical dependence has been controlled. Environmental changes and other stressors can cause patients to perceive that a dose on which they were stabilized is no longer adequate and to experience increased drug craving. Events that increase the availability of substances of abuse, such as another person who uses drugs moving into a patient's home or new sources of illicit drugs, can intensify craving.

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[5] Batki, S. L., M.D., Kauffman, J. F., R.N., M.P.H., LADC, CAS, Marion, I., MA, Parrino, M. W., M.P.A., & Woody, G. E., M.D. (2005). Medication-Assisted Treatment For Opioid Addiction in Opioid Treatment Programs. *A Treatment Improvement Protocol--Tip 43*,76-77. doi:https://www.naabt.org/documents/TIP43.pdf

[6] Comer, S., et al, PHD, Wyatt, S., Guideline Committee Members DO, A. A., PHD, et al, Woodworth, A., MS. (2015, June 1) Treatment Research Institute Technical Team Members. ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (J. Femino MD, FASAM & P. S. Mills MBA, ASAM, Executive Vice President, Eds.; M. M. Miller MD, FASAM, FAPA, Trans.). Retrieved from https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24 pg 24

When their discomfort resumes after a period of abstinence, patients might feel that they are weak willed. They need reassurance that this reaction is a condition of their brain chemistry, not a weakness of will. In animal models, withdrawal symptoms have been conditioned to appear with environmental cues after months of abstinence from opioids. (Self and Nester, 1998.) Increased medication dosages are appropriate in such cases, although efforts also should focus on resolving the troublesome situations such as developing ways to avoid people, places, and things that trigger opioid craving or relapse. Conversely, diminished triggers and reduced drug availability can diminish drug craving and might indicate the possibility of decreasing medication dosage if a patient prefers.

TAKE HOME DOSES AND CONTINGENCY CONTRACTING

The American Society of Addiction Medicine consensus panel believes that **any manipulation of dosage as either a positive or a negative consequence of behavior is inappropriate and has no place in OUD treatment**. The only type of contingency contracting related to medication that should be supported in medical OUD treatment is that associated with take-home medication. Take-home medication is controlled by Federal regulations, and access is based on several factors, including drug abstinence, OTP attendance, length of time in treatment, and overall functioning. An increase in medication dosage should not be a reward for positive behavior change, although not everyone in the field shares this viewpoint. (However, providing extra take-home doses as an incentive to decrease substance misuse and increase treatment program participation has been found effective and is a medically ethical practice.) Although the consensus panel acknowledges important behavioral aspects of addiction and the value of contingency management as an aid to behavioral change, using medication dosage as a reward or punishment is considered inappropriate.[7]

SWITCHING FROM METHADONE TO BUPRENORPHINE OR NALTREXONE AND TAPERING

Switching from methadone to another medication for the treatment of OUD may be appropriate if the patient experiences intolerable side effects or is not successful in attaining or maintaining treatment goals through the use of methadone.

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[7] Batki, S. L., M.D., Kauffman, J. F., R.N., M.P.H., LADC, CAS, Marion, I., MA, Parrino, M. W., M.P.A., & Woody, G. E., M.D. (2005). Medication-Assisted Treatment For Opioid Addiction in Opioid Treatment Programs. *A Treatment Improvement Protocol--Tip 43*,76-77. doi:https://www.naabt.org/documents/TIP43.pdf

Patients switching from methadone to buprenorphine in the treatment of OUD should be on low doses of methadone before switching medications. Patients on low doses of methadone (30–40 mg per day or less) generally tolerate transition to buprenorphine with minimal discomfort, whereas patients on higher doses of methadone may experience significant discomfort in switching medications.

Patients switching from methadone to oral naltrexone or extended-release injectable naltrexone must be completely withdrawn from methadone and other opioids before they can receive naltrexone. The only exception would apply when an experienced clinician receives consent from the patient to embark on a plan of naltrexone facilitated opioid withdrawal management.

Patients who discontinue agonist therapy with methadone or buprenorphine and then resume opioid use should be made aware of the risks associated with opioid overdose, and especially the increased risk of death.[8]

Work with methadone clinic staff to coordinate the methadone taper and with the transition to buprenorphine/naloxone:

1. Establish with both patient and methadone clinic that, if the transition to buprenorphine/naloxone is unsuccessful (e.g., patient begins to experience withdrawal that interferes with functioning or leads to return to use, or patient does not tolerate the medication), the patient may return to methadone treatment without a gap in treatment.

2. Educate patients regarding appropriate methadone dose levels for transferring to buprenorphine/naloxone. To decrease the level of physical opioid dependence and minimize the chance for precipitated withdrawal, most patients will need to have their dose tapered to 30mg before beginning buprenorphine/naloxone treatment. Inform patient that the tapering and transitioning period may include discomfort and increased risk for relapse.

Choose approach:

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[8] Comer, S., et al, PHD, Wyatt, S., Guideline Committee Members DO, A. A., PHD, et al, Woodworth, A., MS. (2015, June 1) Treatment Research Institute Technical Team Members. ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (J. Femino MD, FASAM & P. S. Mills MBA, ASAM, Executive Vice President, Eds.; M. M. Miller MD, FASAM, FAPA, Trans.). Retrieved from https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24 pg 23-24

Provide target methadone dose: 20–30 mg daily for one to two weeks prior to transition is optimal, but not always necessary.

Alternate approach: taper methadone dose to the point of patient experiencing moderate opioid withdrawal, with objective withdrawal symptom documentation via COWS, then initiate buprenorphine/naloxone.

Inpatient detoxification is another option to assist a patient in the transition from methadone to buprenorphine/naloxone. Advise patient to arrange for time off from work and family support with childcare and other responsibilities during the transition, as discomfort may last 1–2 weeks. Timing for last methadone dose/first buprenorphine/naloxone dose is difficult to predict:

Generally, at least 36–96 hours after the last methadone dose, but utilizing clinical assessment and judgment is essential.

Long half-life of methadone (storage in body tissues, especially liver) causes unpredictable clearance.

Initiation of buprenorphine/naloxone should be guided by withdrawal symptoms objectively documented with a COWS score of 13–15, rather than by time since last methadone dose. Clonidine, anxiolytics (including benzodiazepines), and NSAIDs may be used to manage distressing withdrawal symptoms and be continued during induction if prescribed by provider. More intensive stabilization support may be needed (e.g., telephone contact up to 3 times daily, until maintenance dosing is attained). Frequent visits, adequate supports, and a supportive environment to assist in the transition are important.

Providers should be experienced in induction prior to transitioning a patient from methadone maintenance to buprenorphine/naloxone.

Having the patient go to an inpatient detoxification clinic to make this transition can be a safer, more effective way to get the patient from methadone maintenance to buprenorphine/naloxone.

Induction recommendations:

Once a COWS score of 13–15 is documented, start buprenorphine/naloxone at 2mg/0.5mg sublingually, as prescribed.

Continue to dose patient as prescribed until physical withdrawal symptoms have been reduced to manageable levels or are absent. Patients transitioning from methadone may require higher dosing initially and then a taper down over time.

Continue induction according to patient’s prescription order, assessing symptoms of withdrawal and cravings.

Manage symptoms with adjunctive comfort medications, as appropriate, with provider input. Comfort medications include agents to minimize nausea, vomiting, and diarrhea. Also, encourage copious oral hydration prior to induction.

Support and access to providers are critical components to assist patients make this transition and not jeopardize their recovery. [9]

IDENTIFYING PATIENTS WHO MAY BE APPROPRIATE FOR NALTREXONE TREATMENT

Oral Naltrexone

Because oral naltrexone has high rates of non-adherence and the potential for overdose upon relapse, this treatment is best for candidates who can be closely supervised and who are highly motivated. There is a risk of opioid overdose if the patient ceases naltrexone and then uses opioids. Groups that may benefit from oral naltrexone include steadily-employed patients, those who have been using drugs for only a short time (e.g., younger patients), those with high levels of motivation and social support, and those under threat of legal sanctions.

Extended-Release Injectable Naltrexone (XR-NTX)

Regarding opioid use, extended-release injectable naltrexone is FDA approved for relapse prevention, not OUD. This is because it cannot be taken when opioids are still in one's system/a patient is physically dependent. XR-NTX may be especially useful for patients who have contraindications to buprenorphine and methadone; patients confined to drug-free environments such as prison or inpatient rehabilitation; patients living in areas where agonist treatment is not available; or individuals who are highly motivated and desire to taper off their current agonist therapy. Because it is an FDA-approved for the treatment of alcohol use disorder, it may be well suited for patients with co-occurring opioid and alcohol use disorders.

Considerations before Prescribing Naltrexone

[9] LaBelle, C. T.; Bergeron, L. P.; Wason, K.W.; and Ventura, A. S. Policy and Procedure Manual of the Office Based Addiction Treatment Program for the use of Buprenorphine and Naltrexone Formulations in the Treatment of Substance Use Disorders. Unpublished treatment manual, Boston Medical Center, 2016.

The effectiveness of oral naltrexone is limited, given poor adherence and the requirement of 7 to 14 days of opioid abstinence before initiation. During this waiting period, patients may drop out of care. One study found significantly lower patient retention in treatment after incarceration for patients treated with oral naltrexone compared with methadone.[10]

Data is not available at present on the recommended length of treatment with oral naltrexone or XR-NTX. Duration of treatment depends on the response of the individual patient, the patient's individual circumstances, and clinical judgment.

Special consideration should be made in naltrexone dosing for incarcerated groups. Reentry into the community after imprisonment is a high-risk period for relapse to opioid misuse and overdose. Therefore, extended-release injectable naltrexone dosing before re-entry may serve to prevent relapse and overdose in the immediate period following release (though long-term follow up care is essential otherwise overdose risk returns to high levels).

TYPES OF SETTINGS FOR THE PRESCRIPTION OF NALTREXONE

Patients with OUD need to discontinue opioids and wait 7 to 14 days after the last opioid use (including any given for withdrawal treatment) before receiving oral naltrexone or XR-NTX. They can do so through medically supervised withdrawal in a controlled environment, such as an inpatient unit, residential addiction treatment program, correctional facility, or hospital, or on an outpatient basis. Financial issues and managed care constraints may influence patients' access to controlled treatment environments.

Various approaches to rapid naltrexone induction have been developed and more recently refined in research settings. Consider rapid induction in specialty addiction treatment programs, not general medical settings. It may be hard for providers in general medical settings to start XR-NTX successfully with patients who need medically supervised opioid withdrawal. Rapid induction approaches are likely beyond the scope of general outpatient care.

IMPORTANT NOTE ON NALTREXONE INDUCTION

Before administering naltrexone, it is important that the patient has been adequately detoxified from opioids. Naltrexone can precipitate severe withdrawal symptoms in patients who have

[10] Shearer, J., Wodak, A. D., & Dolan, K. A. (2007). Evaluation of a prison-based naltrexone program. International Journal of Prisoner Health, 3(3), 214–224.

opioids in their systems. As a general rule, patients should be free from short-acting opioids for about 6 days before starting naltrexone, and free from long-acting opioids such as methadone and buprenorphine for 7–10 days. A naloxone challenge can be used if it is uncertain whether the patient is no longer physically dependent on opioids. In the naloxone challenge, naloxone hydrochloride (a shorter-acting injectable opioid antagonist) is administered and the patient is monitored for signs and symptoms of withdrawal. A low-dose oral naltrexone challenge has been used as an alternative.

Patients should be seen frequently at the beginning of their treatment. Weekly or more frequent visits/communications are recommended until patients are determined to be stable. The stability of a patient is determined by an individual clinician based on a number of indicators which may include abstinence from illicit drugs, participation in psychosocial treatment and other recovery-based activities, and good occupational and social functioning. Stable patients can be seen less frequently, but should be seen at least monthly. [11]

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-day-per-week regimen for a total weekly dose of 350 mg.

Extended-Release Injectable Naltrexone (XR-NTX)

Administer XR-NTX every 4 weeks or once a month as a 380 mg IM gluteal injection. Alternate buttocks for each 4-week injection. Given the risk of severe injection site reactions, FDA requires a risk evaluation and mitigation strategy for XR-NTX including a patient counseling tool, a patient medication guide, and a visual aid to reinforce proper XR-NTX injection technique.

Examine patients within a week of administering their first XR-NTX dose. It can be clinically beneficial to maintain weekly contact in the first month to:

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[11] Medications for Opioid Use Disorder For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. (2018). *TREATMENT IMPROVEMENT PROTOCOL --Tip 63*,3-35-3-48.. doi:https://store.samhsa.gov/system/files/tip63_fulldoc_052919_508.pdf

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- Provide supportive counseling.
- Assess ongoing drug or alcohol use.
- Monitor side effects.
- Obtain drug testing.

Follow up on the status of referrals to counseling or other services.

Oral Naltrexone

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

Oral naltrexone may be taken daily in 50 mg doses or 3x weekly in two 100 mg doses, followed by one 150 mg dose.

Oral formula naltrexone may be considered for patients where adherence can be supervised or enforced.[12]

Extended-Release Injectable Naltrexone (XR-NTX)

XR-NTX must be suspended only in the diluent supplied in the carton and must be administered only with one of the administration needles supplied in the carton. The microspheres, diluent, preparation needle, and an administration needle with needle protection device are required for preparation and administration. Two thin-walled 1 1/2-inch needles with needle protection device and two 2-inch thin-walled needles with needle protection device have been provided to accommodate varying patient body habitus. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1 1/2-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus. A spare administration needle of each size is provided in case of clogging. Do not substitute any other components for the components of the carton.

Prior to preparation, allow the drug to reach room temperature (approximately 45 minutes).

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. A properly mixed suspension will be milky white, will not contain clumps, and will move freely down the wall of the vial.

The product should be prepared and administered by a healthcare provider.

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[12] *Kampman, Kyle. M.D. (2016).* The ASAM National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use *(PCSS MAT Training: Providers' Clinical Support System for Medicated Assisted Treatment*,32. http://pcssnow.org/wp-content/uploads/2016/03/PCSS_MAT-Kampman-Guideline-final1.pdf

The carton should not be exposed to temperatures exceeding 25°C (77°F). 7°F).The entire carton should be stored in the refrigerator (2 to 8°C, 36 to 46°F). Unrefrigerated, XR-NTX microspheres can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C (77°F). XR-NTX should not be frozen.

Prepare and administer the XR-NTX suspension using aseptic technique.

1. Remove the carton from refrigeration. Prior to preparation, allow drug to reach room temperature (approximately 45 minutes).
2. To ease mixing, firmly tap the XR-NTX microspheres vial on a hard surface, ensuring the powder moves freely.
3. Remove flip-off caps from both vials.
4. Wipe the vial tops with an alcohol swab.
5. Place the 1-inch preparation needle on the syringe and withdraw 3.4 mL of the diluent from the diluent vial. Some diluent will remain in the diluent vial.
6. Inject the 3.4 mL of diluent into the XR-NTX microsphere vial.
7. Mix the powder and diluent by vigorously shaking the vial for approximately 1 minute. Ensure that the dose is thoroughly suspended prior to proceeding to Step E.
   A properly mixed suspension will be milky white, will not contain clumps, and will move freely down the walls of the vial.
8. Immediately after suspension, withdraw 4.2 mL of the suspension into the syringe using the same preparation needle.
9. Select the appropriate needle for an intramuscular injection based on patient's body habitus:
   - 1 1/2-inch syringe
   - 2-inch syringe
10. Remove the preparation needle and replace with appropriately selected administration needle for immediate use.
11. Peel the blister pouch of the selected administration needle open halfway. Grip the base of the needle, not the safety sheath. Attach the luer connection to the syringe with an easy clockwise twisting motion.
12. Seat the needle firmly on the needle protection device with a push and clockwise twist.
13. Move the safety sheath away from the needle and toward the syringe barrel. Pull the sheath away from the needle -do not twist the sheath because it could result in loosening the needle.
14. Prior to injecting, tap the syringe to release any air bubbles, then push gently on the plunger until 4 mL of the suspension remains in the syringe. (The suspension is now ready for immediate administration.)
15. Using a circular motion, clean the injection site with the alcohol swab. Let the site dry before injecting. Do not touch the site again before giving injections.
16. Administer the suspension by deep intramuscular (IM) injection into a gluteal muscle, alternating buttocks per monthly injection. Remember to aspirate for blood before injection.

17. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.
18. Inject the suspension in a smooth and continuous motion. (XR-NTX must not be given intravenously or subcutaneously.)
19. After the injection is administered, cover the needle by pressing the needle protection device against a flat surface using a one-handed technique to activate the safety mechanism away from self and others.
20. Visually confirm needle is fully engaged into the needle protection device. Dispose of used and unused items in appropriate waste containers (See nih.gov.)

Blockade testing: It is expected that approximately 50% of patients will 'test' blockade often same day as discharge. Make sure sufficient levels of naltrexone are present on discharge (oral supplementation if NTX-XR is given on the day of discharge.) Most commonly patients will test 1-3 times with low doses of opioid during the first few days after discharge, after which they are reassured blockade works and do not return to use. Some patients will use large amounts, for 1-3 weeks, trying to get high. Very few patients will continue using, often IV, even though they are blocked, but are interested in staying on naltrexone.

Additional concerns

Rarely, NTX is quickly metabolized, blood levels are low and patients may become re-dependent while receiving NTX as recommended.

Some patients have increased craving and may use in weeks 3-4. This is a high risk time when the blockade is wearing off. In these patients, more frequent injection or oral supplementation is needed. Most commonly, the first sign of relapse is missing doses/injections. The blockade fully wears off 2-3 days after oral and 5-6 weeks after injectable doses.

Risk of overdose is significant if patient decides to stop taking naltrexone, stop attending treatment and resumes opiate use. Consider transition onto an agonist medication to decrease the risk of overdose if unable to comply with NTX.[13]

Additional supports and involving network members may be useful to improve adherence, as well as:

- Inpatient stabilization and another attempt at antagonist treatment

[13] Alkermes, Inc. Human Prescription Drug Label (2018, December 20). DailyMed - VIVITROL - naltrexone. Retrieved July 22, 2019, from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd11c435-b0f0-4bb9-ae78-60f101f3703f

- Residential treatment/supportive Recovery Home
- Transition onto agonist medication

POTENTIAL ADVERSE EFFECTS

Both Formulations

Naltrexone, both oral and extended-release injectable, is generally well tolerated. Apart from opioids, it does not typically interact with other medications. Most common side effects can include (in random order): insomnia, lack of energy/ sedation, anxiety, nausea, vomiting, abdominal pain/cramps, headache, cold symptoms, joint and muscle pain. For XR-NTX, to reduce injection site reactions in obese patients, a longer needle size may be used.

Discuss the risks and benefits of continuing naltrexone with patients who become pregnant while receiving naltrexone treatment and whose OUD is in remission. Unlike methadone and buprenorphine, naltrexone has not been extensively researched in pregnant populations and is not recommended for use.

Precipitated opioid withdrawal can occur in patients who used illicit opioids recently or switched from an opioid agonist medication. Symptoms may be severe enough for hospitalization. To avoid precipitated withdrawal from either formulation, patients should typically stop use of short-acting opioid agonists for 7 to 10 days and long acting agonists for 10 to 14 days.[14]

Extended-Release Injectable Naltrexone (XR-NTX)

Possible side effects of XR-NTX include:

- Insomnia.
- Injection site pain.
- Hepatic enzyme abnormalities.
- Nasopharyngitis.

With XR-NTX, severe injection site reactions may occur (e.g., cellulitis, hematoma, abscess, sterile abscess, necrosis). Some cases may require surgical intervention and may result in significant scarring.

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[14] Medications for Opioid Use Disorder For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. (2018). *TREATMENT IMPROVEMENT PROTOCOL --Tip 63*,3-36-39.. doi:https://store.samhsa.gov/system/files/tip63_fulldoc_052919_508.pdf

HHS Publication No. (SMA) 19-5063FULLDOC First released 2018. Revised 2019. U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment

Patients are vulnerable to opioid overdose death after completing the every-4-weeks or once-monthly dosing period, missing a dose, or stopping treatment. Additionally, trying to override the opioid blockade with high opioid doses may cause overdose.

As with any IM injection, use caution in patients with thrombocytopenia or a coagulation disorder.

Hepatitis has been associated with XR-NTX, often in the presence of other potential causes of hepatic toxicity (e.g., alcohol liver disease, viral hepatitis). Monitor liver function tests during treatment. Stop naltrexone in the presence of acute hepatitis and severe liver disease. Initiate or refer patients to treatment for hepatitis.

Use cautiously in patients with moderate to-severe renal impairment, because the medication is eliminated primarily through the kidneys.

Hypersensitivity reactions can occur, including rash, urticaria, angioedema, and anaphylaxis.

Monitor patients with OUD for depression and suicidal ideation. Naltrexone use has been occasionally associated with dysphoria, although it's unclear whether this is a side effect of the medication or a manifestation of underlying depression or depressed mood related to OUD. Monitor patients for depression, which is common with OUD.

HOW TO ADDRESS REQUEST TO DISCONTINUE NALTREXONE

Like buprenorphine and methadone, barring contraindications, patients should continue taking naltrexone as long as they benefit from it and want to continue. Published data on the long-term effectiveness of naltrexone compared to methadone or buprenorphine does not yet exist.

- When patients wish to discontinue naltrexone, engage in shared decision making and explore:
    - Their reasons for wanting to discontinue.
    - The risks and benefits of discontinuing.
    - Problem-solving strategies that can help them make an informed choice.
    - Their appropriateness of switching buprenorphine or methadone treatment.

Discourage discontinuation in patients who are not yet stable, because of the high rate of return to illicit opioid use and the increased chance of overdose death. Signs that a patient may be ready to cautiously explore the option of medication discontinuation include:

- Sustaining illicit drug abstinence over time.
- Having stable housing and income.
- Having no legal problems.

- Having substantially reduced craving.
- Attending counseling or mutual-help groups.[15]

Switching from an antagonist such as naltrexone to a full agonist (methadone) or a partial agonist (buprenorphine) is generally less complicated than switching from a full or partial agonist to an antagonist because there is no physical dependence associated with antagonist treatment and thus no possibility of precipitated withdrawal.

Patients being switched from naltrexone to buprenorphine or methadone will not have physical dependence on opioids and thus the initial doses of methadone or buprenorphine used should be low.

Patients should not be switched until a significant amount of naltrexone is no longer in their system, about 1 day for oral naltrexone or 30 days for extended release injectable naltrexone.

Patients who discontinue antagonist therapy and resume opioid use should be made aware of the increased risks associated with opioid overdose, and especially the increased risk of death.[16]

Any patients who want to transition from an antagonist to an agonist, or who wants to discontinue treatment, should be provided with overdose education and rescue naloxone (Narcan).

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[15] Medications for Opioid Use Disorder For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. (2018). *TREATMENT IMPROVEMENT PROTOCOL --Tip 63*,3-43 – 3-45.. doi:https://store.samhsa.gov/system/files/tip63_fulldoc_052919_508.pdf

HHS Publication No. (SMA) 19-5063FULLDOC First released 2018. Revised 2019. U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment

[16] National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. (pg-8) Available at: http://www.asam.org/docs/default-source/practicesupport/guidelines-and-consensus-docs/national-practice-guideline.pdf. Accessed: June 4, 2015

Federal guidelines on mandating counseling services, negative drugs screens, etc. to receive medication and rules about involuntary withdrawal

Relevant Selections from Federal OTP Guidelines – Code of Federal Regulations (SAMHSA, 2001)

Source: 66 FR 4090, Jan. 17, 2001, unless otherwise noted. Editorial Note: Nomenclature changes to part appear at 81 FR 44736, July 8, 2016.

https://www.samhsa.gov/medication-assisted-treatment/statutes-regulations-guidelines

(f) *Required services*—(1) *General.* OTPs shall provide adequate medical, counseling, vocational, educational, and other assessment and treatment services. These services must be available at the primary facility, except where the program sponsor has entered into a formal, documented agreement with a private or public agency, organization, practitioner, or institution to provide these services to patients enrolled in the OTP. The program sponsor, in any event, must be able to document that these services are fully and reasonably available to patients.

(5) *Counseling services.* (i) OTPs must provide adequate substance abuse counseling to each patient as clinically necessary. This counseling shall be provided by a program counselor, qualified by education, training, or experience to assess the psychological and sociological background of patients, to contribute to the appropriate treatment plan for the patient and to monitor patient progress.

(j) *Interim maintenance treatment.* **I.e., only providing medication while patients wait for a "spot" to get more comprehensive care

(1) The program sponsor of a public or nonprofit private OTP may place an individual, who is eligible for admission to comprehensive maintenance treatment, in interim maintenance treatment if the individual cannot be placed in a public or nonprofit private comprehensive program within a reasonable geographic area and within 14 days of the individual's application for admission to comprehensive maintenance treatment. An initial and at least two other urine screens shall be taken from interim patients during the maximum of 120 days permitted for such treatment. A program shall establish and follow reasonable criteria for establishing priorities for transferring patients from interim maintenance to comprehensive maintenance treatment.

(4) All requirements for comprehensive maintenance treatment apply to interim maintenance treatment **with the following exceptions:**

(i) The opioid agonist treatment medication is required to be administered daily under observation;

(ii) Unsupervised or "take-home" use is not allowed;

(iii) An initial treatment plan and periodic treatment plan evaluations are not required;

(iv) A primary counselor is not required to be assigned to the patient;

(v) Interim maintenance cannot be provided for longer than 120 days in any 12-month period; and

(vi) Rehabilitative, education, and other counseling services described in paragraphs (f)(4), (f)(5)(i), and (f)(5)(iii) of this section are not required to be provided to the patient.

Relevant Selections from Additional Federal OTP Guidelines (SAMHSA, January 2015)

https://store.samhsa.gov/system/files/pep15-fedguideotp.pdf

Involuntary Withdrawal from Treatment (i.e., "administrative withdrawal")

A major goal of an OTP is to retain patients for as long as they can benefit from and express a desire to continue treatment. Programs should make every effort to intervene productively in a patient's situation before resorting to administrative withdrawal. For example, patients with disruptive behavior should be screened and, if needed, referred for a full psychiatric evaluation. The type and quantity of behavioral services as well as the medical supervision for patients at risk for administrative withdrawal should be matched to address the degree of risk behavior. Involuntary "administrative withdrawal" requires OTPs to define and follow due process. The underlying goal is for involuntary medically supervised withdrawal to reflect a humane partnership between the patient and the treatment program. The program policies and procedures must take into consideration, on a case-by-case basis, all factors affecting the patient and all the steps involved in the process must be documented. Because of the risk of fatal overdose if relapse occurs, medically supervised withdrawal services should be accompanied by relapse prevention counseling, overdose prevention education as well as a naloxone prescription. The treatment and aftercare plans should always include a strategy to transition to medication assisted treatment including antagonist pharmacotherapy if needed.

42 CFR § 8.12 does not specify under what conditions administrative withdrawal is considered appropriate.

Standard practice regarding involuntary discharge among OTPs provide for the following situations:

- **Nonpayment of fees.** Remedies may include referral to a more affordable OTP or other forms of medication-assisted treatment.

• **Disruptive conduct or behavior.** Disruptive behaviors include dealing drugs, repeated loitering, or violation of treatment program rules resulting in documented observable, negative effect on the individual, program, staff, and/or other patients not successfully addressed by more conservative means. Clinical interventions should be aimed at retaining these patients in treatment and may include, as appropriate, intensified counseling opportunities, special treatment plans addressing the behavior, and/or referrals for mental health evaluation.

• **Violent conduct or threatening behaviors.** Violent conduct or threatening behaviors include assaults or attempted assaults and direct and credible threats of violence towards other patients, program staff members, or visitors. If practical under the circumstances and with due regard for patient and OTP staff safety, before administrative discharge, it is recommended that the OTP conduct a crisis assessment to address suicide risk, danger to self or others, urgent or critical medical conditions, and immediate threats. Please refer to SAMHSA's Suicide Prevention App for Behavioral Health and Primary Care Providers (http://store.samhsa.gov/apps/suicidesafe/)

• **Incarceration or other confinement** that does not permit medically supervised withdrawal for patients receiving maintenance therapy with an opioid agonist.

****NO MENTION OF MISSING COUNSELING OR CONTINUED DRUG USE AS GROUNDS FOR INVOLUNTARY WITHDRAWAL****

When a patient is administratively discharged from an OTP, the program must employ the same principles as those used for voluntary medically supervised withdrawal from medication. The goal is to follow a withdrawal schedule that is based on sound clinical judgment and close patient monitoring. A schedule for medically supervised withdrawal for administrative withdrawal from treatment is generally a minimum of 21 days, but the physician may adjust this timeframe depending on clinical factors. The patient's condition during this medically supervised withdrawal and all steps to address it should be documented in the patient's record.

Administrative withdrawal is usually involuntary and used only when all therapeutic options have been exhausted. Given the short timeframe in which administrative withdrawal occurs and the poor prognosis of patients who are involuntarily discharged, the preferred approach is for OTPs to refer or transfer patients to a suitable alterative treatment program. Because of the risks of relapse following detoxification, patients should be offered a relapse prevention program that includes counseling, naloxone and opioid antagonist therapy.

Substance Abuse Counseling

Appropriately trained, experienced, and certified or licensed substance abuse counselors should provide services at the intensity and for the duration required to meet each patient's needs as referenced in the individualized treatment plan. While there are no set patient-to-staff ratios specified in the federal regulations, states have set patient-to-staff ratios as high as 75:1 and as low as 30:1. States allow for an increase in the ratio under certain circumstances. Staff ratios should be sufficient to ensure that patients have reasonable and prompt access to counselors and receive counseling services at the required levels of frequency and intensity. An OTP's staffing of counselors is based on the characteristics and needs of particular patient populations and state requirements.

Relevant FAQ:

When a person in treatment for opioid addiction is abstinent from illicit opioids but tests positive for another drug, can we keep him or her in treatment?

Yes, a person who tests positive for drugs other than opioids may be kept in treatment. SAMHA encourages OTPs to ensure that the abuse of drugs other than opioids is addressed in treatment. The OTP should provide appropriate counseling and other treatment if it identifies abuse of other drugs or alcohol as a problem. When necessary, the OTP may refer the patient to another program for additional treatment services. For further information, please refer to TIP 43.