MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Naltrexone Treatment for Opioid Use Disorder: Training for Clinicians
Part 3

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Adam Bisaga, MD, Disclosures

- Received free medication from Alkermes to support NIDA research
- Site PI on a multi-site clinical trial sponsored by Alkermes

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose thisinformation.

Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Describe the chronic disease model of opioid use disorder and the need for long-term pharmacological treatment
  - Discuss common and serious side-effects that may occur during treatment with naltrexone
  - Discuss safety concern, particularly the risk for overdose, associated with naltrexone treatment
  - Identify common clinical challenges and strategies to manage patients during early stages of treatment
  - Demonstrate an understanding of logistics associated with XR-naltrexone treatment

Training Outline

Naltrexone Treatment for OUD

Section 1:
Introduction to treatment of OUD

- Treatment of OUD using medications
- Neurobiology of OUD and MAT
- Agonist vs. antagonist: advantages and limitations
- The evidence to support use of naltrexone

Section 2:
Patient selection and treatment Initiation

- Selection of patients: individualized treatment
- Treatment initiation scenarios
- Withdrawal management and NTX induction protocols
- Managing patients during early stages of treatment

Section 3:
Maintenance treatment and treatment logistics

- Long-term treatment and treatment termination
- Common clinical challenges
- Safety concerns
- Logistics of using injectable naltrexone
- Demonstration of medication preparation and administration

Section 4:
Special Populations

- Adolescents, dual diagnosis, medically ill, pregnancy
- Naltrexone in criminal justice setting
- Behavioral strategies to augment effectiveness of NTX
- Discussing NTX and recovery with patients and with families
- Integrating MAT with 12-step principles and fellowship

Section 3:

Maintenance Treatment and Treatment Logistics

Long-term Treatment and Treatment Termination

Treatment Termination

- For many patients opioid use disorder is a chronic and relapsing condition
  - Necessitates long-term treatment with duration and intensity commensurate with disease severity
- Duration of treatment with naltrexone positively correlates with favorable outcome (relapse prevention)
  - It is not known what (if any) duration of treatment will reduce the risk relative to that of a general population
  - Ongoing psychosocial treatment and linking with long-term recovery-support services is necessary to sustain benefits of MAT
- Recommended duration of treatment with naltrexone in patients who achieved full remission and abstinence
  - Minimum: 6 months
  - Optimal: 1 year, but longer duration prevents relapse risk in the long run

Common Clinical Challenges

Serious Side Effects

- Injection site reactions (inflammation, tissue damage)
  - Local tenderness and a small “bump” are common, usually resolve within 1-3 days
  - Serious site reaction are more likely to occur if medication is administered into the fat tissue

- Rare
  - Depressed mood with suicidal behavior
  - Allergic (eosinophillic) pneumonia
  - Systemic allergic reactions

Common Side Effects

- Occur infrequently outside of the first month of treatment when majority of side effects are related to opioid withdrawal
  - nausea
  - tiredness
  - headache
  - dizziness
  - vomiting
  - decreased appetite
  - painful joints
  - muscle cramps
  - insomnia

Clinical Challenges: Testing the Blockade

- Approximately a third of patients will “test” blockade, often within 1-2 days after receiving XR-naltrexone
  - As blood level may be low the first 24hrs, oral supplementation may be considered on the first day
- Most commonly, patients will “test” 1-2 times with small amounts of opioid during the first week of treatment, after which they are “reassured” that blockade works and do not continue use
- Some patients will use large amounts, for 1-3 weeks, but very few will persist in the use if they receive full blocking doses of the medication
  - Very few patients try intentionally to “override the blockade”

“Blocked” vs. “unblocked” use

- The narcotic “blockade” wears off 2-3 days after oral and 5-6 weeks after injectable doses of naltrexone
  - Patients who use while still “blocked” (3-5 weeks post-injection) most often do not become re-dependent and can receive subsequent naltrexone doses and remain in treatment
  - Many patients who use while “blocked” prefer to remain on the medication
  - “Unblocked use” will rapidly progress to relapse and puts patient at risk for overdose
- Continuous blockade prevents patients from relapsing to physical dependence

Clinical Challenges: Managing Relapse (1)

- Occasionally patients report increased craving 3-4 weeks after the injection
  - It may be a pharmacological effect (blood level of the medication drops below a therapeutic level) or the expectancy effect (knowing that the blockade may be ”wearing off”)

- In patients who report increase in craving before the next scheduled dose may consider more frequent injections (e.g., every 3 weeks – off label) or supplementation with oral naltrexone (in weeks 3-4)

Clinical Challenges: Managing Relapse (2)

- Most commonly, the first sign of relapse is new episode of opioid use and missing naltrexone doses/injections
- This warrants an immediate response to prevent de-stabilization:
  - Increase frequency and intensity of behavioral treatment and support groups
  - When appropriate, involving family/significant other/friends in treatment to improve adherence
  - Residential treatment/sober house
  - Patients who become re-dependent may require inpatient stabilization and another attempt at antagonist treatment
- If unable to stabilize, consider transition onto agonist

Clinical Challenges: Missing Doses

- Naltrexone non-adherence is often seen with oral preparation but also happens with injection and is a frequent reason for treatment failure
- Naltrexone non-adherence often occurs at treatment outset
  - Long-acting preparation should be chosen over oral preparation because it significantly reduces the risk of non-adherence
  - Injection naltrexone should be administered as soon as available; little/no advantage of an oral naltrexone “trial” prior to the injection
- If the patient is late for the next injection, contact the patient/family to advise oral doses (100-150 mg every 2-3 days)
  - Involve family in monitoring/supervising medication administration
- Verify that the patient is not physically dependent before administering “late” injection (similar to induction procedures)

Managing Severe Pain

- Commonly used prescription opioid analgesics will not be effective in patients on therapeutic doses of naltrexone
  - Patients should wear medical bracelet or carry a “wallet card”
- Alternative approaches to manage pain
  - Non-opioid therapies: acetaminophen, NSAID’s (ketorolac iv), ketamine, clonidine, muscle relaxants (baclofen), anticonvulsant (gabapentin)
  - Non-pharmacologic therapies: peripheral and neuraxial nerve blocks, local anesthetic infiltration
- High potency opioids (e.g., alfentanil) can override the naltrexone blockade but should be done under anesthesia monitoring

Safety Concerns

Naltrexone and Overdose

- Therapeutic doses of naltrexone protect against overdose however there is a significant risk of overdose if patient decides to stop taking naltrexone and resumes opiate use
  - Due to the absence of pharmacological blockade, absence of tolerance, and possibly increased sensitivity to opioids

- To mitigate this risk, provide a detailed description of risks at treatment outset (e.g., treatment agreement) and discuss it during treatment, especially in patients who continue use

Overdose Prevention Education

Example of treatment agreement language:

"I understand that after I stop naltrexone I may be more sensitive to the effects of heroin and any other narcotics. The amount of heroin or narcotics I may have been using on a routine basis before I started naltrexone, might now cause overdose and death. I fully understand the nature and seriousness of this possible consequence.

If I am not sure that I can avoid opiate use, I understand that I can be referred to alternative treatment programs, such as methadone maintenance, which is an effective treatment for heroin dependence and has a reduced risk of fatal overdose."

Overdose Risk

- Risk of overdose is present following completed opioid withdrawal or discontinuation of agonist maintenance.
- Treatment with agonist or antagonists reduces mortality as compared to drug-free treatment
- The risk of overdose is comparable among patients **in active** MAT (adherent to naltrexone oral/XR, buprenorphine, or methadone)
- Mortality rates differ among patients who **discontinue MAT**
  - Higher in patients treated with oral naltrexone as compared to methadone
  - higher in patients treated with oral as compared to XR-naltrexone
  - comparable in patients treated with XR-naltrexone and methadone
- The long “tail” on the serum XR-naltrexone curve may provide protection in patients who discontinue MAT, which is often marked by an elevated mortality

Depression and Suicide Risk

- There are concerns whether treatment with naltrexone increases risk of depression and suicidality through blocking of endogenous opioid activity
  - Though theoretically plausible, there is no systematic clinical evidence that naltrexone increases depression in this population
  - Depressive symptoms usually improve during early abstinence from opioids
  - However, some patients may have increased depressive symptoms, usually brief and occurring during the first few weeks of treatment
- Opioid Use Disorder is a risk factor for suicide: 10% vs. 1.3% in the general population
- Depression and suicidality warning is included in the package insert for Vivitrol
  - Suicidality was reported in 5% of patients treated with Vivitrol (10% in oral naltrexone) in open-label long-term US safety study
  - No such warning on buprenorphine package insert

Logistics of Using Injectable Naltrexone

Injectable Naltrexone: Ordering and Storage

- Medication needs to be ordered in advance through specialty pharmacy services
  - It is reimbursed under medical rather than pharmacy benefits
  - Medication is shipped directly to the medical office
  - Because it may take 1-2 weeks for the office to receive medication, patients may be treated with oral preparation until then
  - Most of the time patients with insurance do not have out-of-pocket expenses (vivitrolcopay.com)
- Once received, medication needs to be stored in the refrigerator (36-46^{o}F) but should not be frozen)
  - Medication has to reach room temperature prior to injection (30-40 min at RT)
  - Can be out of the fridge for up 7 days prior to injection, but it can be put back if not administered within this time

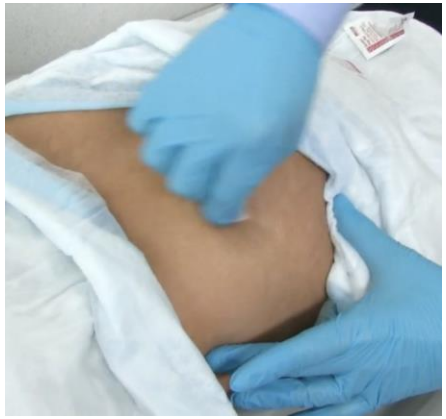
Injectable Naltrexone: Office Based Logistics

- Medication comes with a syringe and two sets of needles (different lengths)
- Additional supplies needed: alcohol/betadine swabs, gauze, band aids, medical pads (chux), sharps container
- Injection technique: standing up vs. lying down vs. bending over
  - Lying down is preferred to minimize muscle tension
- It is preferable, but not essential, to have nurse or other staff present, as the patient is partially undressed for the injection

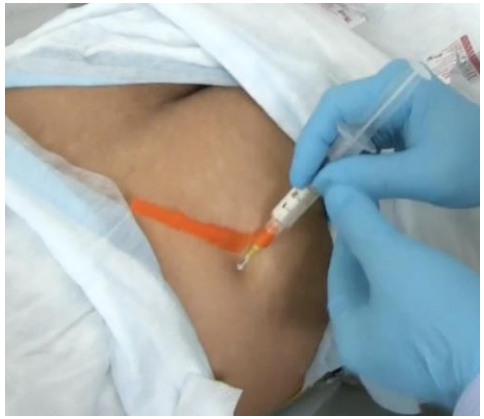
Injectable Naltrexone: Injection Logistics (1)

- Medication powder and diluent have to be mixed (by hand or with a vortex shaker) and suspension should be injected immediately to minimize the risk of needle clogging
  - Occasionally the needle clogs, if that happens, withdraw the syringe and change the needle (included in the set)
- The recommended dose of VIVITROL is 380 mg or 4 mL of the suspension to be delivered as a single deep IM injection into the gluteal muscle every 4 weeks or once monthly
  - Alternate site (L/R) with each injection
- Dorsogluteal side is preferred for injection but providers may consider a ventrogluteal injection side (from the side) if it provides better access to the muscle

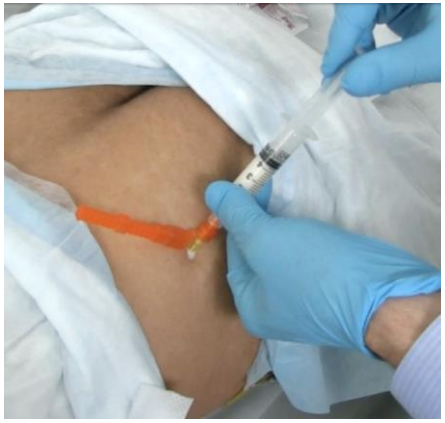
Injectable Naltrexone: Injection Logistics (2)



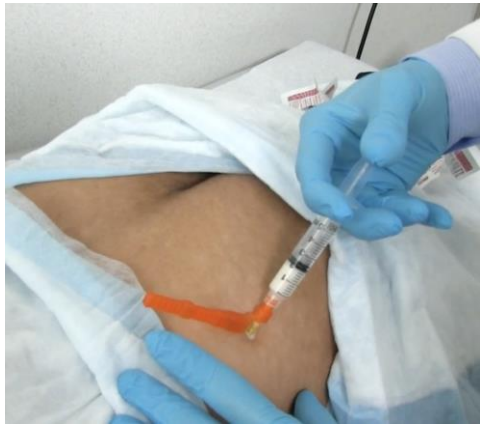
1. Using the circular motion clean the injection site with the alcohol swab



2. Quickly insert the full length of the needle

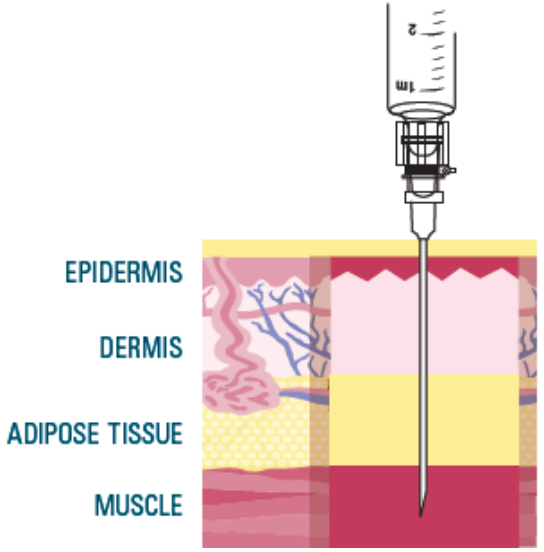


3. Aspirate for blood before injecting the suspension



4. Inject the suspension in a smooth and continuous motion (approx. 30s)

- Administer injection into the outer upper quadrant of a gluteal muscle
- Administer deeply into the muscle tissue, avoid injecting to adipose tissue
- Alternate site (L/R) for each injection



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PCSS-MAT Mentoring Program

- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
- PCSS-MAT Mentors are a national network of providers with expertise in **medication-assisted treatment and addictions**.
- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
- No cost.

For more information visit:

pcssmat.org/mentoring

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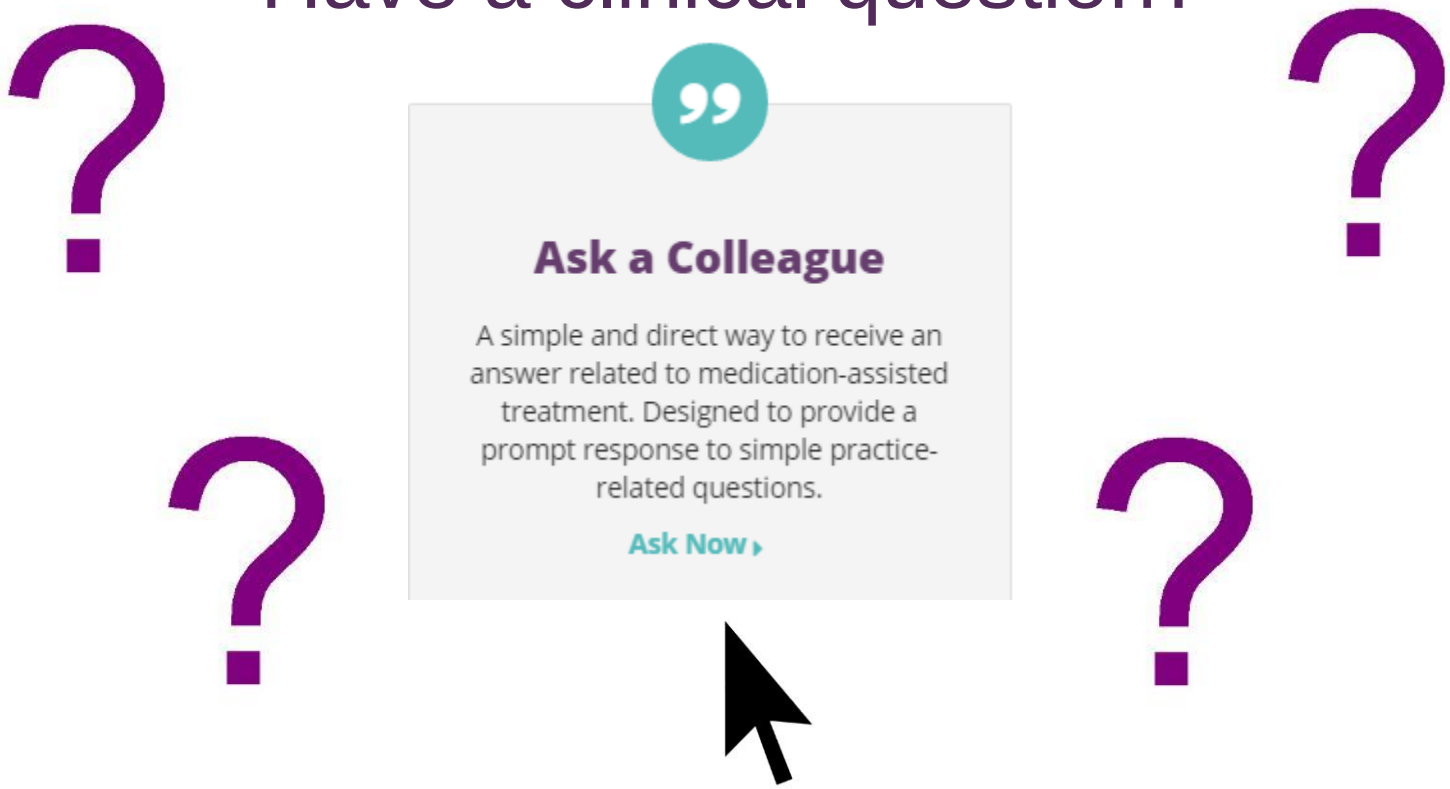
PCSS Discussion Forum

Have a clinical question?



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For more information: www.pcssmat.org

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