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CME Review Article

Keeping Up with Clinical Advances: Opioid Use Disorder

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- Differentiate the options available for medication-assisted treatment (MAT) of opioid use disorder (OUD)
- Increase adherence to MAT by optimizing strategies to reduce withdrawal symptoms
- Reduce relapse by applying maintenance treatment strategies for opioid use disorder

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REVIEW ARTICLE

Keeping Up with Clinical Advances: Opioid Use Disorder

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Opioid use disorder (OUD) is a disorder that can lead to several negative outcomes, including overdose and death. A variety of opioids can be abused by individuals including both prescribed and non-prescribed opioids. Continued opioid use can be driven by negative affective states associated with opioid withdrawal. Several treatments exist in the field including medication assisted treatments such as methadone, buprenorphine, and naltrexone. Treatments such as clonidine and lofexidine can also be used to assist with decreasing withdrawal symptoms. Increasing adherence to treatment can further improve patient outcomes and promote continuation with treatment. A variety of methods to reduce relapse can also be utilized such as opioid agonists and maintenance therapy. According to the Centers for Disease Control, opioid overdoses contributed to 67.8% of overdose deaths in 2017.

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Introduction

Opioid use disorder (OUD) is a complex disorder. According to the most recent data from the Substance Abuse and Mental Health Services Administration (SAMSHA), approximately 11.4 million individuals (4.2% of the total United States population) aged 12 or older misused opioids in 2017 with 11.1 million misusing prescription pain relievers.[1] Among the 886,000 individuals who used heroin, 562,000 misused both prescription opioids and heroin. Prescription opioids include hydrocodone, morphine, oxycodone, codeine, tramadol, buprenorphine, methadone, and fentanyl. The abuse of opioids has been well documented and can lead to increased emergency room (ER) visits,[2] health complications such as HIV or hepatitis C,[3] decreased social functioning,[4] overdose, and death.[5] While all of these conditions increase costs in health care and society, the opioid overdoses are the most concerning. Out of 63,632 overdose deaths in the United States in 2016, 66.4% of them involved opioids.[6]

The misconception of opioids as being a safe treatment for pain and subsequent overprescribing of opioids led to increased availability of prescription opioids. Opioid prescriptions increased in the United States from 76 million in 1991 to roughly 215 million in 2016.[7] Many individuals who had used prescription opioids in the early 2000's became dependent, and by 2014 they started turning to heroin as it was cheaper and prescription opioids became less available.[8] An example of decreased availability involved hydrocodone, which due to its increased abuse, was reclassified from schedule III to II on October 6, 2014. This lead to decreased prescribing of hydrocodone containing prescriptions particularly in Emergency Room settings.[9] Thus, prescription opioids were more regulated and less available, but another wave of opioid misuse began with heroin abuse increasing from 2014 to 2017.[10]

Continued opioid use is driven through a neurobiological process in which patients have a binge/ intoxication stage, withdrawal stage, and a preoccupation/ anticipation stage.[11] When used chronically, such as to treat chronic pain, tolerance will develop. This results in patients requiring higher doses in order to achieve the same effects. The chronic use of opioids can also cause hyperalgesia, or the amplification of minor pain.[12] Thus, during the initiation phase of opioid misuse, intoxication is often desired to relieve pain and dysphoria. Other rewarding effects of intoxication can be driven through dopamine release in the nucleus accumbens, which has been detailed in other publications and will not be elaborated in this review.[5]

The withdrawal stage follows from physiological dependence, which can be another driving force for continued substance use. Dependence can occur with chronic use of opioids, and withdrawal symptoms begin

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when opioids are abruptly discontinued. These withdrawal symptoms include nausea, vomiting, diarrhea, worsening pain, body aches, and worsening depressive and anxiety symptoms.[11] Patients can experience negative reinforcement of withdrawal symptoms with the improvement of withdrawal symptoms with subsequent use of opioids.

The preoccupation/anticipation stage occurs after completion of acute physiological withdrawal and is often called "protracted" withdrawal, which can be a trigger for relapse. Cravings occur during this stage and are associated with neurochemical changes in the prefrontal cortex, orbitofrontal cortex, and hippocampus.[11] Patients can have cue induced relapse, drug induced relapse, or stress induced relapse during this stage. Examples of cues that can induce relapses include someone in recovery finding syringes or a previous dealer's phone number or visiting the place where they had purchased illicit opioids. Drug induced relapse can include beginning to use opioids again as well as inadvertent use by someone in recovery. An example can include someone who is prescribed opioid pain medication following an current medical or surgical procedure in which opioid medication would be warranted. Stress induced relapse can follow when the patient experiences psychosocial stress, which activates their hypothalamic-pituitary-adrenal (HPA) axis leading to relapse as a conditioned response.

This review article has three learning objectives that will teach you how to; (1) differentiate the options available for medication-assisted treatment (MAT) of OUD; (2) increase adherence to MAT by optimizing strategies to reduce withdrawal symptoms; and (3) reduce relapse to OUD by applying maintenance treatment strategies. In this article, the term OUD will be used in lieu of opioid abuse or dependence as a diagnostic criterion. This is in accordance with the updated *Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V)*. An OUD involves a problematic pattern of opioid use leading to clinically significant impairment/distress, manifested by at least 2 of 11 symptoms in a 12-month period. The symptoms discussed will include cravings, tolerance, and withdrawal symptoms.

Medication Assisted Treatments

Providers in the United States have many options for Medication Assisted Treatment (MAT) for OUD. These medications have various mechanisms of action. The four Food and Drug Administration (FDA) approved treatments include methadone, which is a full mu-opioid agonist and NMDA receptor antagonist. Buprenorphine is another option which is a partial mu-opioid agonist, kappa-opioid antagonist, and delta-opioid antagonist. The third is Naltrexone which is a mu-opioid antagonist and kappa-opioid antagonist. Lofexidine is a newly approved alpha-2 agonist, which is used to manage acute withdrawal symptoms.[13] These medications should be used along with a behavioral treatment program in order to improve medication adherence and abstinence from illicit opioids.

The first step in helping patients with OUD is managing their withdrawal symptoms when they abruptly stop using opioids. Several medications that have been used extensively for withdrawal symptoms include clonidine, guanfacine, and lofexidine. These medications can be used in a variety of settings for symptom relief. However, the appropriate level of care for using these medications varies based on the severity of the patient's opioid use and subsequent withdrawal severity. Settings include inpatient detoxification and subsequent rehabilitation, partial hospitalization programs, and outpatient treatment.

Acute withdrawal from opioids involves increased noradrenergic (NA-ergic) system activity, because continuous opioid exposure markedly inhibits this system's activity. When this opioid inhibition is removed, the NA-ergic activity then markedly increases, which is the source for many symptoms of opioid withdrawal. Withdrawal symptoms can include patient discomfort, autonomic changes (hypertension, tachycardia), joint and muscle aches/pain, gastrointestinal cramping, lacrimation, rhinorrhea, tremors, emesis, and drug cravings.[14] Managing withdrawal symptoms is important and patients who undergo severe withdrawals are able to have their symptoms treated with an alpha 2 agonist such as clonidine or lofexidine. These agonist medications reduce NA-ergic activity by binding to alpha-2 auto-receptors on these NA neurons, leading to feedback inhibition of the NA neurons' mimicking the previous opioid-induced inhibition.

Clonidine

Clonidine is an alpha 2 adrenergic agonist which is used off-label for symptoms of acute withdrawal from opioids. Typically, it is paired with the Clinical Opioid Withdrawal Scale (COWS) to assess symptom levels and judge adequate dosing of the clonidine. Clonidine can be given for symptomatic relief of gastrointestinal cramping, lacrimation, rhinorrhea, and hypertension. It can start with 0.1 mg doses at a time and ranges from 0.3 to 0.6 mg/day up until 1.2 mg per day for severe cases.[15] Double blind RCT's on patients maintained on methadone have demonstrated clonidine will also reduce cravings for heroin in response to stress related stimuli and reduce relapse to heroin in outpatients.[16] Some side effects to monitor with clonidine include hypotension, dizziness, sedation, and dry mouth.[15]

Lofexidine

Lofexidine is alpha 2 adrenergic agonist, which has been used widely in Europe for OUD. It recently achieved FDA

approval in the United States in 2018 for opioid withdrawal symptoms in adults.[6] Lofexidine has several advantages as it typically does not require dose titration, targets autonomic symptoms, and has fewer side effects, particularly orthostatic hypotension and associated fainting than clonidine.[17] Lofexidine has fixed dosing from 2.4 mg to 3.2 mg daily. This medication does not relieve the acute withdrawal symptoms of anxiety or diarrhea, which is a factor to consider. It also has similar side effects to clonidine of sedation, but substantially less orthostatic hypotension. Lofexidine is particularly useful for patients who are going to be treated with the MAT naltrexone, because naltrexone will precipitate opioid withdrawal if given to an individual with active OUD and ongoing physical dependence on opioids.

Naltrexone

Naltrexone is FDA approved for OUD in both oral tablet form and long acting injectable form. Naltrexone mechanism of action is as a competitive antagonist which is non-selective with higher affinity toward mu-opioid receptors. This mechanism of action blocks the mu-opioid site to prevent binding by other opioids, and thereby prevent the reinforcing and analgesic effects of most opioids.[13] Patient are typically initiated on an oral form after being opioid free for 7 days to minimize the risks for precipitating withdrawal symptoms. Once oral naltrexone is well-tolerated, the long acting injectable can be substituted for the oral naltrexone as a adherence enhancer compared to the oral form.[18] The long acting naltrexone depot injectable is dosed once a month at the 380 mg intramuscular dosing. Studies have revealed greater length of retention and more negative urine drug screens with the intramuscular form compared to the daily oral formulation.[19] The randomized controlled trial leading to FDA approval involved 250 opioid addicted patients over 6 months and reported significantly better abstinence rates with the naltrexone depot form compared to placebo. The depot naltrexone patients attained 90% opiate free weeks compared to 40% of the patients receiving placebo.[20]

Naltrexone depot formulation can have several side effects including up to 17% of individuals having transaminase elevations, but these enzyme elevations have not been associated with severe adverse effects.[21] Other important considerations are precipitation of withdrawal symptoms (if naltrexone started too soon after opioid discontinuation), injection site reactions, sterile abscess from injection into fatty tissue, and eosinophilic pneumonia.[22]

Methadone

Methadone was the first medication to be FDA approved and used for the treatment of OUD. Methadone acts as a full mu agonist at the mu opioid receptor and can provide withdrawal symptom relief as well as analgesia. It is beneficial for use in both acute withdrawal states as well as in maintenance treatment, which will be discussed later. Methadone has two formulations as an oral tablet and a liquid concentrate. This medication is available for outpatient medical withdrawal treatment only in specialized clinics, which are regulated by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) as well as state governments.[23] Clinics that can dispense methadone are known as opioid treatment programs (OTP) and include psychosocial evaluations, counseling, monitored daily administration of medication, urine drug screens for the methadone metabolite, and progression to "take-home" doses over weekends. As of 2017 there are only 1,317 OTP facilities that can prescribe methadone.[24] Any use of methadone for this outpatient detoxification purpose extending beyond 72 hours of methadone prescribing is only legal within these programs.

Methadone treatment for detoxification and maintenance has many positive outcomes that have been documented extensively in the literature. Methadone can also be used for acute withdrawal symptoms with planned taper to discontinuation. Short, rapid methadone tapers typically result in poor outcomes and rapid relapse to illicit opioid use and OUD.[25] Thus, tapering detoxifications need to last for several months in outpatients. Methadone maintenance treatment is superior to short term outpatient detoxification to prevent relapse and provide successful long term outcome.[26]

Methadone has side effects which can impact a patient's willingness to continue to participate in maintenance treatment. These include constipation, nausea, vomiting, sedation, and reduced libido.[27] Other medical side effects that can be observed with methadone include decreased luteinizing hormone, reduced testosterone, and cardiac corrected QT interval (QTc) prolongation.[28] Cardiac QTc prolongation can occur at a range of doses, but is more likely at the usual maintenance doses of 80–120 mg daily. Cardiac evaluation with an electrocardiography (ECG) is recommended before starting a patient on methadone, and if a prolonged QTc is already present, then methadone is relatively contraindicated.[29]

Buprenorphine

Buprenorphine is a partial mu agonist that was developed for the treatment of OUD. This medication is a partial agonist, which results in a ceiling effect at opioid receptors. This helps to prevent the risk of overdose and respiratory depression in patients who may use more than directed.[30] This medication is available in many forms with the FDA having approved a buccal film, sublingual film, implantable form, long acting subcutaneous injectable, and sublingual tablet forms. This medication is

often combined with naloxone in a 4:1 ratio of buprenorphine to naloxone. This naloxone addition is to prevent diversion of this medication by injected use, because naloxone is not absorbed sublingually, but by injection it will precipitate opioid withdrawal symptoms.

Buprenorphine is easily prescribed in routine outpatient office-based practice compared to methadone, which requires specially regulated clinics. The only prerequisite for the prescribing of buprenorphine is that a provider completes an approved course by either the American Academy of Addiction Psychiatry, American Society of Addiction Medicine, or the American Osteopathic Academy of Addiction Medicine.[31] Once a physician has completed the course, which is typically 8 hours in duration, he or she can apply for a waiver from SAMHSA. Physicians who have successfully obtained the waiver can initially treat 30 patients in their first year and then apply for a waiver to treat 100 patients. After one year of treating 100 patients another waiver can be applied for which increases the limit to 275.[32] Patients are typically assessed by their provider and can be induced on buprenorphine in the office-based setting, while monitoring for any acute side effects such as nausea, vomiting, acute withdrawal symptoms, fainting, or dizziness.[33] The patients can then be followed on an outpatient basis by their outpatient provider. Medication providers should collaborate with psychosocial treatments including individual/group counseling, social work intervention, and community resources to continue to help treat the patient.

Buprenorphine can be used for both acute detoxification and maintenance treatment. When used for detoxification, individuals on extended tapers (4 weeks) tend to have less withdrawal symptom severity and better sleep than those on shorter taper courses.[34] Patients may also benefit from other psychosocial supports or psychopharmacologic treatments if planning to complete an acute taper.

Buprenorphine has some side effects and other limitations in its effectiveness. One side effect is mild increases in liver function tests among patients with hepatitis.[35] Buprenorphine can also lead to overdose if combined with other sedating medications such as benzodiazepines.[33] The partial agonism of the mu receptor typically can offset full agonists such as morphine, hydrocodone, and heroin. However, it can be over-ridden by high potency opioid agonists such as fentanyl and carfentanil, which stimulate a different part of the mu opioid receptor rather than the typical G-protein site that binds morphine and hydrocodone compounds. Another limitation is the availability of providers who can prescribe buprenorphine in the United States. A 2015 study revealed approximately 90.3% of the population lived in a county had a physician who could prescribe buprenorphine. This resulted in 9.7% of the population, or approximately 30 million people, who resided in a county without a provider who could prescribe buprenorphine.[36] The majority of these counties tended to be rural and many rural counties only had one provider, which could affect a patient's access to these resources, since any provider will need to have a local back-up provider for vacations and emergencies.

Buprenorphine has abuse potential even with the inclusion of naloxone. Several controlled laboratory studies have revealed the abuse potential of buprenorphine in intravenous and intranasal heroin abusers, although it is less reinforcing in the buprenorphine/naloxone combination.[37] In Finland, buprenorphine mono-formulation displaced heroin as the number one abused substance, but this abuse eventually decreased with its replacement by the buprenorphine/naloxone combination.[38,39] Another concern is diversion amongst patients and their social contacts, as a survey of injection drug users from Baltimore in 2008 revealed. They found 23% obtained buprenorphine illicitly and 13% from friends.[40] The overall prevalence of illicitly obtained buprenorphine in the past 3 months was 9%, and the majority of respondents were using it to manage withdrawal symptoms. Providers need to be conscious about possible misuse or diversion and can monitor patients by using urine drug screens, buprenorphine confirmatory screens, film counts, and state prescription monitoring programs.

Naloxone

Naloxone, while FDA approved to reverse opioid overdose, is discussed as it is important for providers to be knowledgeable about its use. Naloxone is a non-selective mu opioid antagonist that has a higher affinity for the mu receptors over other opioids. It displaces prior bound ligands and can help reverse the effects of opioid overdose, including respiratory depression. Naloxone is available in three FDA approved forms, injectable, auto injectable, and nasal spray. Providers should become familiar with their state laws if naloxone is available without prescription and if patients have access to it. The Centers for Disease Control has recently published guidelines recommending prescribing of naloxone along with more regular follow up for patients treated for chronic pain with opioids at or above 50 morphine milli-equivalents a day, because of the overdose risk for these patients as well as anyone who might accidentally ingest this dosage of opioids.[41]

Early detection of opioid overdose is important, such as checking for a response from an individual. It is important to activate emergency services and administer Naloxone intranasally or intramuscularly. Typically, a 4 mg nasal spray is administered in one nostril and if no response within 2–3 minutes, another new 4 mg dose can be given in the other nostril.[42] For the injection,

0.4 mg is administered in the upper arm or thigh muscle and if no response within 3 minutes, another dose can be given.[43] Basic life support should be followed once the naloxone is administered. The opioids duration of action may last longer than the naloxone initial dosing and there could be a continued risk for respiratory depression.[42] It is important to ensure providers discuss this with their patients and their families.

Increasing Adherence to Medication Assisted Treatments

Providers can increase adherence to medication assisted treatment (MAT) by individualizing treatment including optimizing strategies to reduce protracted withdrawal symptoms. Protracted withdrawal symptoms include sleep disturbances, anxiety, and abnormalities related to persistent hypothalamic-pituitary-adrenal (HPA) axis over-activity leading to cue and stress induced craving.[44,45] Several medications which can assist with protracted as well as acute withdrawal include the full mu opioid agonists and partial agonists, as previously covered. Lofexidine might also have an off label use in combination with the antagonist naltrexone to reduce these protracted withdrawal symptoms and to reduce cue and stress induced craving.[46]

Methods to Reduce Relapse and Maintenance Treatment Strategies

Once a patient completes withdrawal and establishes sobriety from illicit opioids, the maintenance stage of treatment begins. Providers should have their goal to assist in reducing relapse by applying maintenance treatment strategies for OUD. There are several different pharmacological treatment options including a full mu-opioid agonist (methadone), partial mu-opioid agonist (buprenorphine), and a mu-opioid antagonist (naltrexone). Several psychosocial interventions are also beneficial and important components of comprehensive treatment including group and individual counseling, sober living centers, partial hospitalization programs, and residential long-term treatment.

Opioid agonists such as methadone and buprenorphine have been well studied in the literature for their use as maintenance treatment for OUD. Methadone has many benefits which were seen in a naturalistic study completed in 1991.[47] This study followed 388 male patients in 6 methadone clinics over an extended period of time. Of those who remained in the program after 4 years, the rate of IV drug use had declined from 81% to 29%. There were 105 individuals who left treatment and 82% returned to IV drug use within 1 year. Another finding was that there was a reduction in crime by 95% by participants over a 3–6 year period of treatment. Interim methadone maintenance, which includes methadone dosing without counseling or psychosocial services, has also been shown to reduce criminal activity and money spent on illicit drugs, but to a more limited extent.[48]

Once a patient is in the maintenance stage of treatment, methadone maintenance or office based buprenorphine therapy can help manage opioid cravings and prevent acute and reduce protracted withdrawal symptoms.[13] The benefits of methadone maintenance or buprenorphine treatment include improved effectiveness in maintaining sobriety compared to abstinence-based treatment[49] and improved maternal and fetal outcomes in pregnant women.[50] For inmates who are incarcerated, initiation of treatment during their incarceration can reduce risk of opioid overdose after release.[51] Methadone maintenance treatment programs have several limiting factors on a patient's overall ability to achieve sobriety from illicit opioids. These risk factors for relapse can include psychosocial factors that cannot be addressed by psychopharmacology alone such as unstable housing and lack of employment.[52] Other risk factors include current cocaine or alcohol use, and social factors such as living with a heroin user.[53] The importance of psychosocial interventions is to address the psychological and social stressors patients are facing.

Maintenance therapy involving buprenorphine has been shown to be effective and well tolerated by patients. Buprenorphine can be used long term with less primary side effects (constipation, nausea) compared to methadone.[30] There is also no evidence of organ damage with chronic dosing, and less significant medication interactions compared to methadone.[35] Buprenorphine has a ceiling effect due to its partial agonism which prevents overdose from it and most other opioids, except for fentanyl and its derivatives. Buprenorphine use can lead to decreased heroin mortality, decreased emergency department utilization, improved overall quality of life, and improved psychosocial functioning.[30] Buprenorphine has been shown to be more effective than placebo on a range of short-term outcomes, particularly treatment retention and illicit opioid use.[13,54] Longer term buprenorphine, like methadone maintenance, also improves other areas including employment, criminal activity, and psychological adjustment (depression).[13,49] There can be cognitive impairment with buprenorphine which is a factor to consider.[55] Another important factor to consider is to note that leaving medication assisted treatment is associated with high mortality.[56] The risk for mortality is greatest in the first 4 weeks after discontinuation of methadone or buprenorphine.[57] Thus, providers have to engage patients to remain in treatment and have a variety of maintenance medications which can assist with maintaining sobriety.

Conclusion

Providers have many challenges and opportunities to help with the current opioid crisis. First, pain treatment providers must assess a patient's motivation for wanting and needing to continue opioid prescription treatment for pain and to determine if any misuse is occurring. Second, providers must use various methods to monitor for opioid misuse including utilization of statewide prescription monitoring programs, urine drug screens, and by assessing patients more regularly with shorter follow up periods.

When the provider determines that opioid misuse or lack of need for continued opioid prescribing has become evident, providers should be knowledgeable about current treatments and resources that are available in their area. Having information regarding residential treatment options for both insured and non-insured populations can help patients and their families. Providers can also refer to specialists such as in Addiction Psychiatry or Addiction Medicine, when they develop concerns about a patient's medication regimen developing into an OUD.

Providers must be vigilant about the direction that OUDs are progressing in the upcoming years. As more users of opioids are turning away from prescription opioids to heroin and fentanyl over the past 3 years,[10] this led to an increase of lethal overdoses. A critical contributing factor to the lethality of opioid overdoses include the emergence of synthetic opioids in the United States. Synthetic opioids such as fentanyl are 50–100 times more potent than traditional opioids such as morphine and pose additional risks for overdose, because they bind to activate a different signaling mechanism than do other opioids including our main treatment and overdose medications (naloxone).[58] Fentanyl and other non-pharmaceutical analogues of fentanyl have been found in heroin, which can pose additional risks, because patients may be unaware of the potency of this altered heroin that they are obtaining and using.

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Optional Posttest and CME Certificate

CME Credit Expires: July 31, 2022

Posttest Study Guide

The posttest can only be submitted online. The below posttest questions have been provided solely as a study tool to prepare for your online submission. **Faxed/mailed copies of the posttest cannot be processed** and will be returned to the sender. If you do not have access to a computer, contact NEI customer service at 888-535-5600.

1. The long acting naltrexone depot injectable is dosed once a month at _____intramuscular dosing:
   A. 120mg
   B. 380mg
   C. 90mg
   D. 220mg

2. What off-label medication, when used in combination with naltrexone can reduce withdrawal effects, and increase adherence for MAT:
   A. Buprenorphine
   B. Lofexidine
   C. Methadone

3. Which medication has a ceiling effect due to its partial agonism which prevents overdose from it and most other opioids, except fentanyl and its derivatives?
   A. Buprenorphine
   B. Naltrexone
   C. Methadone
   D. Naloxone

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1. Read the article
2. Complete the posttest and evaluation, available only online at www.neiglobal.com/CME (under "CNS Spectrums")
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