CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES & HEALTH INFORMATION DESIGNS

Connecticut Medical Assistance Program Quarterly Newsletter

The March newsletter is the second in a two-part series on Opioid Use Disorder (OUD). The first newsletter covered the history of opioid use in the U.S., actions leading up to the current epidemic, and measures taken to combat opioid use in our country. This newsletter will cover the epidemiology of OUD within the Connecticut Medical Assistance Program, management of opioid withdrawal, and Medication Assisted Treatment (MAT) options for OUD.

During 2019, approximately 41,000 unique Connecticut Medicaid recipients received a diagnosis of an opioid related disorder while approximately 29,000 received MAT with methadone, buprenorphine, or naltrexone (figure 1). While there have been signs of progress in Connecticut: opioid prescribing has declined nearly 50% from 2015 to 2019 and buprenorphine prescribing has increased by almost 80% (figure 2), there remain patients who are not receiving treatment for OUD. Evidence shows that maintenance MAT decreases the risk of relapse, overdose, and death associated with a return to opioid abuse.[1] OUD negatively impacts every part of an individual's life from unemployment, legal issues, estrangement from friends and family, to financial problems and homelessness. Identification of the disorder, management of withdrawal, and starting and maintaining treatment is paramount. Additionally, establishing preventative measures will help to stop this epidemic from reaching future generations. Coordination of care, adequate prevention, and treatment are required to respond effectively to this public health crisis.

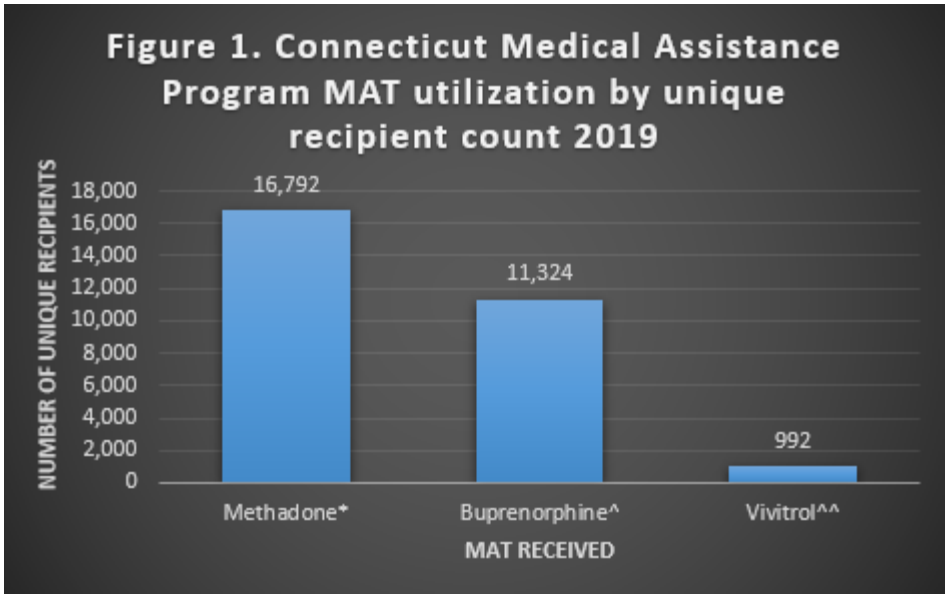
Managing Opioid Withdrawal

Treatment for OUD begins with tapering and cessation of opioids, management of opioid withdrawal and medication assisted withdrawal (or detox) which occurs in the first week after cessation of opioids.[2]

Symptoms of opioid acute withdrawal include: piloerection, nausea, diarrhea, and runny nose. Short acting opioids have shorter duration of acute withdrawal, about 7-10 days, whereas long acting opioids are associated with longer durations.[3] Scales such as the Clinical Opiate Withdrawal Scale (COWS) or the Subjective Opiated Withdrawal Scale (SOWS) can be used to help measure and assess a patient's acute withdrawal and guide symptom management appropriately.[3] A protracted withdrawal syndrome often occurs in patients with OUD after the acute withdrawal phase. Symptoms of protracted withdrawal last longer than the acute phase and include hyperalgesia, insomnia, dysphoria, and craving.[3]

Medically supervised withdrawal begins with tapering of the opioid, either using methadone or buprenorphine as a substitute to the opioid of abuse, and/or using non-opioid medications to treat withdrawal symptoms. Tapering a patient may not be an easy task and can be complicated, especially in patients receiving long term high frequency opioids, as in cases of treatment for chronic pain. Patients who received shorter term opioids at lower doses or frequencies may tolerate tapering better than patients who were receiving long term opioids. Withdrawal hyperalgesia, or pain associated with opioid withdrawal, may return upon tapering making the withdrawal process more difficult. Physical and emotional pain due to opioid withdrawal can be experienced by patients during tapering, withdrawal, and protracted withdrawal causing a complex refractory withdrawal syndrome in some patients.[4]

Patients who choose medically supervised withdrawal without the support of methadone or buprenorphine risk relapse shortly following the supervised withdrawal. Medications (other than methadone and buprenorphine) used to treat withdrawal symptoms include: ondansetron for nausea, clonidine or lofexidine for anxiety and tachycardia, loperamide for



*Recipient count derived from procedure code billing for methadone administration.
^ Recipient count derived from pharmacy claims for buprenorphine products indicated for OUD.
^^Recipient count derived from pharmacy claims for Vivitrol administration in patients with a diagnosis of OUD.

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diarrhea, and benzodiazepines for anxiety.[3]

Medically supervised withdrawal is required for patients who opt to receive naltrexone as their medication of choice for MAT. Naltrexone is an opioid antagonist and if given to a patient who has opioids in their system, the patient will go into withdrawal.[3]

If methadone or buprenorphine are used to facilitate a patient's medically supervised withdrawal, continuation with either of those medications can and should continue.[3] Continuation of either medication is superior to no treatment and is associated with better outcomes compared to eventually tapering off the methadone or buprenorphine.[5,6]

Medication Assisted Treatment (MAT)

OUD is considered chronic due to the illness lasting well after the acute withdrawal phase.[8] Only about 20% of patients with OUD receive addiction treatment, with 6-month retention rates below 30-50% in most settings.[1,7] Patient barriers to OUD treatment include: cost and availability of treatment, not perceiving a need for treatment or not feeling ready to start treatment, location barriers to treatment centers, and the stigma surrounding drug addiction.[8]

Three FDA approved medications exist for MAT: methadone, buprenorphine, and naltrexone. MAT is the gold standard for treatment of OUD. When patients are engaged in treatment, the risk of relapse, overdose, death, infection, and incarceration all decrease compared to no treatment at all.

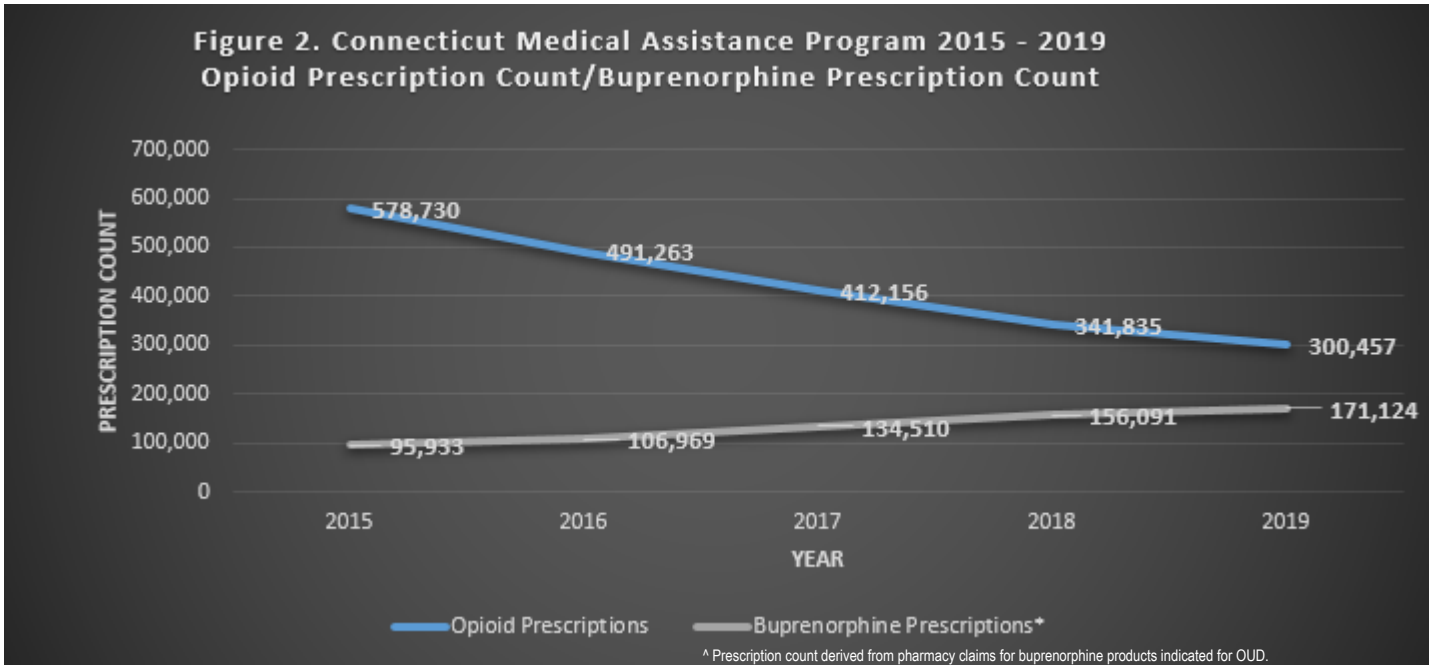
Methadone

Methadone, a μ-opioid agonist Schedule II prescription medication, treats OUD while reducing illicit opioid use and retaining patients in treatment better than placebo or no medication at all.[6,9] Methadone works by competitively binding to μ-opioid receptors while blocking the effects of other opioids. The World Health Organization (WHO) lists methadone as an essential medication to treat OUD.

When used to treat OUD, methadone is only available through federally certified OTPs (Opioid Treatment Programs). There are approximately 1,500 OTPs in the U.S. that offer methadone maintenance to patients. Some also provide buprenorphine and Vivitrol (sustained release naltrexone IM) but their status as a federally qualified OTP provides authority to dispense methadone.[10] Other services that OTPs provide to patients include: treatment oversight and daily medication administration, drug testing, and counseling.

Because methadone is a μ-opioid agonist, it has no ceiling effect and risk of overdose is associated when used above a patient's tolerance level. Initiation of methadone dosing should be individualized, started low, and slowly titrated due to patient variability. The half-life of methadone is 24-36 hours and steady state is not reached until about 4 days after the first dose, providing an opportunity for accumulation of the medication even at very low doses. The first dose for patients who are opioid tolerant is typically 10 – 20 mg orally with subsequent doses of 5-10 mg given at two-hour intervals if the patient is still having signs/symptoms of opioid withdrawal until a total of 40mg has been given on the first day. Pregnant patients may require a higher dose of methadone as the placenta can metabolize a significant amount of the drug. Opioid withdrawal can be life-threatening to the fetus. Dose titration may occur over the next 2-4 weeks usually stabilizing around 60 – 120 mg/day.[10] Higher doses are associated with better outcomes, and a recent Cochrane review found that flexible dosing of methadone resulted in higher patient retention in treatment compared to buprenorphine.[3,11] The main goal of methadone dose titration is to avoid sedation and eliminate withdrawal symptoms until the next dose. The caveat is finding the individual maintenance dose as each patient is different.

Methadone's adverse events are similar to other opioid agonists: constipation, nausea, sexual dysfunction (decreased estrogen, testosterone, osteoporosis, amenorrhea, infertility, compression fractures), sedation, weight gain, and edema. Additionally, methadone can cause QTc prolongation. High doses of methadone and certain concurrent medications can increase that risk; however,



most occurrences are nominal.[12,13] Methadone has the most drug - drug interactions compared to the other MAT therapies. Because methadone is a 3A4 substrate, its metabolism is affected by cytochrome P450, 3A4 inducers and inhibitors. For a complete list of drug-drug interactions, refer to methadone's package insert. Although there is a risk of adverse events when taking methadone concurrently with benzodiazepines or other CNS depressants, the FDA recommends the benefit of MAT to outweigh the risk of adverse events associated with concurrent therapy.[14]

Federal regulations allow OTP consideration for patients to take home doses of methadone. The longer the patient remains in treatment with clean urine toxicology screens and good behavior, the greater the take home dose opportunities become.[10]

Buprenorphine

Buprenorphine, a partial μ-opioid agonist (weak kappa antagonist and delta agonist), is a Schedule III prescription medication. Naloxone is commonly paired with buprenorphine formulations as an abuse deterrent. Naloxone is minimally absorbed sublingual (SL) so it does not interfere with SL buprenorphine efficacy. The naloxone is present so that if an attempt is made to abuse the buprenorphine/naloxone by giving it IV or snorting, then the effects of the buprenorphine and any other opioids that may be taken will be blocked by the naloxone and withdrawal may be precipitated. Buprenorphine binds tightly to the μ-opioid receptors while blocking the effects of other opioids. This blockade can be overcome by giving higher doses of other opioids, especially hydromorphone. A common question is "Should buprenorphine products be continued when patients are admitted for surgery?" The consensus now is that the buprenorphine products should be continued just as methadone is continued when patients are admitted for surgery. In fact, buprenorphine itself can be a very effective analgesic when given SL, as an IV bolus every four hours as needed, or in a PCA (patient controlled analgesia) syringe. Buprenorphine being a partial agonist means that there is a ceiling to the respiratory depressant effects but not to the analgesic effects. It is effective for visceral, neuropathic and musculoskeletal pains. Buprenorphine and buprenorphine/naloxone formulations treat OUD in patients while reducing illicit opioid use and retaining patients in treatment better than placebo or no medication at all.[11]The WHO lists buprenorphine as an essential medication to treat OUD.

In order to prescribe buprenorphine, physicians must qualify for a federal waiver through the Substance Abuse and Mental Health Services Administration (SAMHSA) which includes 8 hours of training. An APRN may also obtain a waiver, however, they require 24 hours of training. Once providers receive the federal waiver, they can prescribe buprenorphine to a maximum of 30 patients in their first year. After one year, they can request to increase their buprenorphine patient base to a maximum of 100 patients and eventually increase to 275 patients if they specialize in addiction medicine, addiction psychiatry, or through additional practice requirements.[15]

Available formulations of buprenorphine used for OUD include:[10]

- Buprenorphine sublingual tablet (generic Subutex)
- Buprenorphine/naloxone sublingual films
- Buprenorphine/naloxone sublingual tablets (Zubsolv)
- Buprenorphine/naloxone buccal films (Bunavail)
- Buprenorphine implants (Probuphine)
- Buprenorphine extended release subcutaneous (SC) injection (Sublocade)

Available formulations of buprenorphine used for analgesia:

- Buprenorphine buccal tablet (Belbuca)
- Buprenorphine sustained release patch (Butrans)

Sublingual buprenorphine can be initiated at home by the patient, under specific prescriber's orders, or in the prescriber's office. Patients should be instructed to take their first dose of buprenorphine when they first start to experience opioid withdrawal and at least 12 hours after the use of a short acting prescription opioid or heroin. A dose of 2 – 4 mg is commonly started on day 1 of induction with a dose repeated every two hours, not to exceed 16 mg on day 1. The patient should stop taking buprenorphine once there are no signs of withdrawal/cravings or side effects such as sedation. On day 2, the patient may take 8 mg twice a day and then take a third dose of 8 mg if the patient is having overt signs of withdrawal or more subtle signs of withdrawal (cravings, dysphoria, restlessness). The majority of patients will stabilize on doses between 4 and 24 mg/day of buprenorphine with very little clinical benefit shown at doses above 24 mg/day.[10] Buprenorphine can be dosed once daily, divided into multiple daily doses or even dosed every other day once the patient is stabilized on a fixed dose. For example, a patient may take 8 mg of buprenorphine daily, they can take 4 mg every 12 hours, or they can take 16 mg of buprenorphine every other day.[16] Buprenorphine may be a better option for patients who want an office-based treatment setting with less structure compared to methadone OTPs.

Subdermal buprenorphine requires stabilization with a maximum of 8 mg/day of transmucosal buprenorphine. The implant will provide continuous therapy for 6 months, requiring patients to have a new implant placed twice a year. The buprenorphine extended release SC injection requires patients to be stabilized on 8 – 24 mg/day of transmucosal buprenorphine for at least 7 days prior to initiation. The injection will provide continuous therapy for 1 month, requiring patients to receive monthly injections.[10] Twenty-four hours after injection, there is a peak blood level which slowly declines over the month. There is a 50% decline from peak to trough over the month. The average trough is approximately 2 ng/ml which is still effective for treating OUD. When planning painful surgical procedures, it may be best to perform procedures at a trough buprenorphine concentration. Always consider using multimodal analgesic therapy (acetaminophen, NSAIDs, gabapentin, baclofen, or tizanidine).

Buprenorphine, like methadone, is hepatically metabolized by cytochrome P450 3A4 and has similar drug - drug interactions to methadone, although less than methadone. For a complete list of drug-drug interactions, refer to a buprenorphine package insert. Although there is a risk of adverse events when taking buprenorphine concurrently with benzodiazepines or other CNS depressants, the FDA recommends the benefit of MAT outweighs the risk of adverse events associated with concurrent therapy.[14]

The goal of MAT with buprenorphine is to reduce or eliminate symptoms of opioid withdrawal while finding the right dose to limit sedation. In the event a patient requests to discontinue buprenorphine or methadone

treatment, a tapering schedule should be planned and patients informed of the risks of discontinuing treatment.[10] The longer a patient receives MAT, the less likely they will relapse. Once a patient stops MAT, there is a greater risk of relapse.[7,17]

Oral Naltrexone or Extended Release Injectable Naltrexone (XR-NTX)

Naltrexone is a μ-opioid receptor antagonist. It has affinity for opioid receptors but does not produce the same effects as opioid agonists. Naltrexone blocks the effects of opioid agonists and partial agonists. While oral naltrexone was not superior to placebo or no medication in retaining patients in treatment or reducing opioid use,[18] XR-NTX was found to be superior in treating patients while reducing illicit opioid use and retaining patients in treatment better than placebo or no medication at all.[19,20] It will not reduce cravings as both methadone and buprenorphine do.

Naltrexone requires a prescription for use, but no federal waiver or OTP is required to prescribe or dispense. The short acting oral formulation of naltrexone has poor treatment adherence and high discontinuation rates; therefore, it is not commonly used as MAT in current practice. The long acting IM depot formulation (XR-NTX) significantly improved treatment retention compared to placebo, as do methadone and buprenorphine, however, because it is relatively new compared to other forms of MAT, it has less data available with regard to use. Current studies comparing buprenorphine to XR-NTX show that patients who are initiated on either treatment option similar outcomes.[21,22]

Because naltrexone is a μ-opioid antagonist, it blocks the μ-opioid receptors and does not have the same effect as opioid agonists such as analgesia, euphoria, and sedation. It should be noted that while naltrexone has a high affinity for opioid receptors, if patients take high enough doses of opioid agonists, naltrexone blockade can be overridden, and risk of overdose can occur.[10]

XR-NTX is a once monthly depot formulation that contains 380 mg of naltrexone. The injection is administered in office and provides continuous therapy for 1 month, requiring patients to receive monthly injections.[10] One caveat with naltrexone initiation is the requirement that patients abstain from opioid use for approximately 1 week due to the ability of naltrexone to trigger withdrawal. Prior to administration, patients can be weaned from opioids with the use of a buprenorphine or methadone taper. A wash out period of 7-10 days is required from all opioids prior to the initiation of XR-NTX to avoid withdrawal.

Naltrexone has very few adverse effects and minimal drug-drug interactions. While methadone or buprenorphine MAT is recommended for women with OUD who are pregnant, naltrexone is not recommended for use during pregnancy due to the risk of adverse effects associated with withdrawal on the fetus.[23] When surgery is planned, it is best to try and schedule the surgery at the end of a month when naltrexone will be at its lowest concentration. XR-NTX has been found to be useful in settings that are reluctant to rely on opioid agonists, such as criminal justice settings.[24] Additionally, due to the requirement that patients remain abstinent from any opioid for about 1 week prior to initiating, incarceration provides an ideal setting for abstaining from opioids prior to treatment initiation. Considering that approximately 60% of incarcerated individuals have a substance use disorder (SUD), XR-NTX has become a popular option for treatment of OUD, particularly for inmates approaching release from incarceration when tolerance to opioids is low and the risk of relapse and overdose is high post release.[25,26] A current 5 year phase 3 study is underway to determine the outcome of XR-NTX treatment (1 month prior to release from prison followed by monthly injections post release) on treatment adherence, opioid use, re-arrest, and re-incarceration. Completion of this study is expected in 2021.[27]

Prior to starting any MAT providers should:[10]

- Check the state PDMP
- Take the patient's history
- Conduct a physical exam, assessing for signs and symptoms of intoxication or withdrawal
- Obtain lab tests (urine screens for drug and alcohol, pregnancy test – naltrexone is not recommended for use in pregnant patients, LFTs, hepatitis and HIV testing)
- Obtain informed consent

When considering the three treatment options for OUD, the American Society of Addiction Medicine recommends that MAT selection be a mutual decision between the patient and prescriber.[28] Additional factors to consider when selecting MAT therapy include patient preference for medication and treatment setting, treatment history, and any comorbidities. Information regarding the different options for MAT should be shared with patients. This should include accessing the different medications, side effects, mechanisms of action, and cost.

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