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Pharmacological treatment of opioid use disorder in pregnancy

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ABSTRACT

Pharmacotherapy, or medication-assisted treatment (MAT), is a critical component of a comprehensive treatment plan for the pregnant woman with opioid use disorder (OUD). Methadone and buprenorphine are two types of opioid-agonist therapy which prevent withdrawal symptoms and control opioid cravings. Methadone is a long-acting mu-opioid receptor agonist that has been shown to increase retention in treatment programs and attendance at prenatal care while decreasing pregnancy complications. However methadone can only be administered by treatment facilities when used for OUD. In contrast, buprenorphine is a mixed opioid agonist-antagonist medication that can be prescribed outpatient. The decision to use methadone vs buprenorphine for MAT should be individualized based upon local resources and a patient-specific factors. There are limited data on the use of the opioid antagonist naltrexone in pregnancy. National organizations continue to recommend MAT over opioid detoxification during pregnancy due to higher rates of relapse with detoxification.

Introduction

For the vast majority of pregnant women with opioid use disorder (OUD), the use of pharmacotherapy as part of a comprehensive treatment plan is recommended. Pharmacotherapy, commonly referred to as medication-assisted treatment or MAT, has strongly become the method of choice for treatment of OUD for pregnant and non-pregnant people alike. Methadone became available first, and has been increasingly available for pregnant women since the 1970s.[1] Gradually over the last several years, buprenorphine has become more widely accepted and recommended for use in pregnancy as well.[1,2] Having access to both methods of opioid agonist therapy, methadone or buprenorphine, is critically important in order to tailor treatment to the unique needs of an individual pregnant woman. Pharmacotherapy, combined with individual counseling, behavioral therapy, and group therapy gives pregnant women the best opportunity to achieve and maintain sobriety through pregnancy, immediately postpartum, and beyond.

Methadone and buprenorphine are two types of pharmacotherapy referred to as opioid agonist therapy. The use of an opioid agonist to treat an opioid use disorder typically raises questions in the mind of the provider learning about this treatment modality for the first time. The rationale for the use of an opioid agonist to treat an opioid use disorder has as much to do with the ways in which methadone and buprenorphine are similar enough to, yet importantly different, from typical opioids of misuse. One of the important ways in which treatment opioids for agonist therapy are different

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from typical opioids of misuse is in their duration of action. Methadone and buprenorphine are both extremely long acting opioids, with half-lives 4–5 times, and sometimes longer, those of typically misused opioids. Oxycodone, for example, has a short half-life (approximately 3–4 h in plasma for those with an average rate of hepatic metabolism), necessitating frequent dosing to achieve a continued state of efficacy (i.e., relief of pain or euphoria). One of the properties that predisposes an opioid to be more or less likely to be misused is half-life, with shorter acting opioids being more commonly misused. This has to do with the reward pathways in the brain, as well as the frequency of the withdrawal state necessitating repetitive use.[3] In contrast, methadone has a half-life of at least 24 h, and typically closer to 36 h for the average metabolizer.[3] Once a person is stabilized at an effective dose, once daily administration of methadone is sufficient to relieve all withdrawal symptoms and block cravings for additional opioids. Methadone, and buprenorphine, will be discussed in greater detail later in this chapter.

The greatest benefits of agonist therapy, however, are the much more important and person-centered outcomes related to reduced risk of acquiring infectious diseases such as hepatitis B and C, HIV, skin and soft tissue infections, and endocarditis.[4] People who receive opioid agonist therapy for the treatment of opioid use disorder have significant reductions in involvement with the criminal justice system, as well as reductions in recidivism when they have the opportunity to access or maintain MAT during periods of incarceration.[5] Most importantly, people who are receiving MAT have lower rates of opioid overdose and death.[6,7]

Opioid agonist therapy has particular benefit for pregnant women suffering with OUD. Pregnant women who receive methadone or buprenorphine have higher rates of retention in treatment programs, as well as increased receipt of prenatal care. Pregnant women who receive both opioid agonist treatment and prenatal care have fewer obstetrical complications.[8] All providers who care for pregnant women should familiarize themselves with local, regional, and national resources for treatment. A searchable database that provides locations of treatment centers for opioid use disorder may be found at the Substance Abuse and Mental Health Services Administration's website: https://findtreatment.samhsa.gov.

As opioid agonist therapy is the treatment of choice for pregnant women with OUD, methadone and buprenorphine will now be discussed in greater detail. Naltrexone (an opioid antagonist) and detoxification (under medical supervision) must also be examined, as these are two additional modalities about which those treating pregnant women with OUD should be informed.

Methadone

Methadone has been used for more than 55 years in the treatment of opioid use disorders. Methadone was first approved by the FDA as an analgesic and antitussive on August 13, 1947. During that time period, its primary role in addiction medicine was in the detoxification of patients addicted to heroin. In 1962 it was first used as a maintenance therapy for those with intractable heroin addiction in research trials. By the early 1970s there was rapidly increasing interest in treating addiction with opioid maintenance therapy, but there were concerns about prescriptions leading to drug trafficking. Thus, the US legislature passed laws creating a regulatory framework for the use of methadone in the treatment of opioid addiction. These regulations required methadone treatment facilities to monitor daily medication administration as well as provide counseling, rehabilitation, and social services.[9]

Ideally, complete cessation of opioids would be the goal for anyone with an opioid use disorder. However, in practice this results in high rates of relapse. Substance use disorders are now understood in the context of chronic illnesses, and thus people remain at risk for relapse for the rest of their lives.[10] A more effective and durable treatment for these patients is thought to be medically-assisted therapy (MAT) with one of the opioid agonist or partial agonist medications. Goals of MAT include decreasing risks of transmitting infectious diseases such as HIV or Hepatitis C from contaminated needles, providing stability for interpersonal relationships and availability to work, and decreasing criminal activity associated with obtaining illicit substances.[10]

Methadone is a Schedule II synthetic opioid which acts as a potent agonist at the μ-opioid receptor (Fig. 1). It is metabolized through several CYP450 pathways, most importantly CYP2B6 and CYP3A4 isoforms in the liver. Additionally it blocks NMDA receptors and monoaminergic reuptake transporters.[11] At an appropriate therapeutic dose, methadone will produce cross-tolerance with shorter-acting opioids, which suppresses withdrawal symptoms and reduces cravings. Methadone has a long duration of action with half-life of 25–52 h. The long half-life provides for a smooth delivery of μ-opioid stimulation, stabilizing the physiologic effects of repeated stimulation and withdrawal caused by shorter-acting opioids. The half-life can be quite variable between people, and methadone may accumulate in the slow metabolizers.[11] Methadone has the potential to interact with several other medication classes that are metabolized by similar pathways, for instance anti-retrovirals. Increased systemic levels of methadone can lead to catastrophic side effects such as respiratory depression or rare prolonged QT-based cardiac arrhythmias (Torsade de Pointes). Methadone-related deaths are more likely to occur in the first four weeks of induction, yet those in methadone maintenance treatment programs still have overall reduction in all-cause mortality.

Methadone has high bioavailability and is available in many oral forms including oral solution, liquid concentrate, tablets, or powder. Opioid treatment programs primarily administer methadone orally in liquid form.

Methadone is generally considered safe in pregnancy with no clear association with congenital anomalies. Animal studies show conflicting results with no teratogenic effects in rats and rabbits, but large doses caused central nervous system (CNS) defects in pigs, hamsters, and mice. One human study suggested a small increase in congenital anomalies, but with no pattern of anomalies to suggest biologic plausibility.[12] Importantly, human studies are extremely limited.

Only SAMHSA-certified opioid treatment programs are permitted to dispense methadone for daily administration on site or at home. While methadone may be prescribed outpatient to treat chronic pain, it is illegal for physicians to

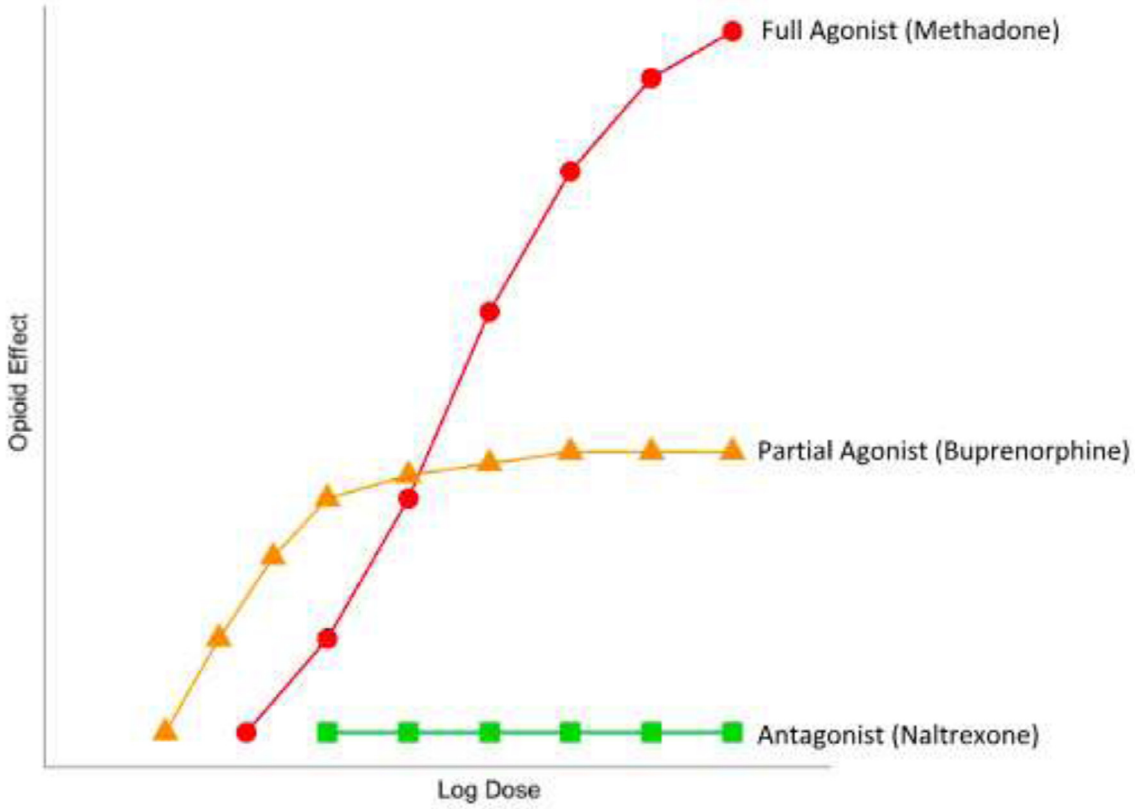

Fig. 1 – Opioid effect of medications utilized for medication-assisted therapy by log dose.

prescribe methadone as an outpatient for treatment of a substance use disorder.[13]

Methadone dosing is dependent on the intention for use. When methadone is used in the treatment of chronic pain, dosing is more frequent at 3–4x/day. In medication-assisted treatment of opioid use disorders, methadone dosing is typically once per day. The goals of treatment in this setting are to prevent opioid withdrawal symptoms, reduce cravings, and block euphoria caused by illicit or misused opioids. A typical starting dose may be 20–30 mg per day, gradually increasing in 5–10 mg increments until the optimal dose is reached (Fig. 1). In a retrospective review of 144 women treated with methadone during pregnancy, the mean initial maintenance dose was 69 mg (range 8–160 mg); mean dose at delivery was 93 mg (range 12–185 mg).[14] Goals of therapy are to give a sufficient dose that controls withdrawal symptoms and cravings while minimizing sedative side effects. Because of the physiologic changes of pregnancy including an increased volume of distribution and increased renal clearance, split dosing may be necessary to control withdrawal symptoms.[15] As such, the daily dose is typically divided into 12 h intervals for pregnant women.

The most common side effects of methadone are constipation, nausea/vomiting, diaphoresis, sedation/respiratory depression, decreased libido, and prolonged QT interval. It is recommended to obtain an electrocardiogram at time of initiation of therapy or with modification of medication dose.[16]

Care needs to be taken with the prescription of methadone in certain populations to minimize the possibility of adverse outcomes. Patients at risk for development of prolonged QT should be monitored closely. Prescribers should use caution if a patient is using benzodiazepines or other CNS depressants. Finally, there is a risk of abuse or diversion of methadone, which is mitigated by the rules surrounding methadone treatment programs.

In randomized controlled trials of methadone maintenance therapy in nonpregnant individuals versus nonpharmacological methods of treatment, methadone has been established as an effective means of retaining patients in treatment and decreasing heroin use.[17] Maintenance therapy has been shown to be effective at reducing relapse to opioid misuse, increasing retention in prenatal care and decreasing pregnancy complications. Early involvement in methadone maintenance programs increases attendance in antenatal care and decreases the risk of prematurity compared with pregnant women with untreated opioid use disorder.[18]

The primary drawback of using methadone for maintenance is that many women have difficulty accessing a methadone treatment facility. Additionally some patients may be unable to comply with daily visits, and in some states Medicaid does not cover methadone. Finally, neonatal abstinence syndrome is an expected, possible outcome of a pregnant woman receiving MAT. Studies have shown that decreasing the dose of methadone does not necessarily decrease the frequency or duration of NAS. In contrast to the usual dogma of minimizing medication exposures in pregnancy, prescribers should use the dose necessary to achieve treatment goals and resist attempts to minimize the methadone dose.

Buprenorphine

Buprenorphine was originally used as a treatment for moderate to severe pain. On October 8, 2002, the FDA approved

buprenorphine for medical maintenance treatment and medically supervised withdrawal. The medication qualified for prescribing in an outpatient setting by certified physicians, thus allowing access to medication-assisted treatment outside of the federally regulated opioid treatment centers. Physicians, and now nurse practitioners and physician assistants, who meet certain qualifications are able to obtain a waiver from SAMHSA to prescribe buprenorphine, with the goal of increasing access to medication-assisted treatment for patients who are unable to access methadone treatment clinics.

Buprenorphine is a Schedule III, mixed opioid receptor agonist-antagonist. It is a partial μ-opioid agonist, δ- and κ-receptor antagonist.[11] As a partial agonist with high affinity for the μ opioid receptor, it is able to displace and antagonize full μ agonists such as morphine, which can lead to a syndrome of acute (precipitated) withdrawal (Fig. 1). It has a long duration of action as it slowly dissociates from receptors. The partial agonist effects also mean that the medication has a ceiling effect for pain relief and respiratory suppression, making buprenorphine relatively safe with regards to risk for overdose when compared to full agonist opioids.

Buprenorphine is dosed daily and comes in a film or tablet to allow sublingual administration. Due to poor oral bioavailability, it must be administered sublingually rather than orally.[11] Buprenorphine is also formulated in a slow release transdermal patch, buccal film, as well as a parenteral injection; however these formulations are only FDA approved for the treatment of pain and not for the treatment of opioid use disorder. The FDA has approved a subdermal implant that provides continuous buprenorphine therapy for six months, which can be used in patients already stabilized on a sublingual dose, however there are no data on the use of this formulation in pregnancy.[20] The newest formulation of buprenorphine to receive FDA approval for the treatment of opioid use disorder is a once-monthly subcutaneous depot injection (brand Sublocade™). Typical doses of buprenorphine are 8–16 mg daily, with a typical max daily dose of 24 mg, and dose requirements may increase modestly during pregnancy.[19] To prevent diversion and illicit use, buprenorphine is also available in a combination product with naloxone, in which the latter only becomes active if injected intravenously.

Outside of pregnancy the combination buprenorphine/naloxone product is preferred. Traditionally the monoproduct buprenorphine has been recommended for use in pregnancy because of concerns about injection of naloxone and the effects of withdrawal on the fetus, however the buprenorphine monoproduct is higher risk for diversion and misuse.[21]

One of the major benefits of buprenorphine is that it can be prescribed in an outpatient setting. This provides a degree of privacy and confidentiality that is sometimes not available at methadone treatment programs. Additionally, the medication visits can be combined with prenatal care or addiction counseling.[20] As opposed to methadone, any pharmacy can fill a prescription for buprenorphine products. This can significantly increase availability to patients who may not have ready access to an outpatient treatment facility for methadone or are unable to attend a clinic on a daily schedule.

Like methadone, prescribers should use caution when considering buprenorphine for the treatment of patients who use other CNS depressants. The use of buprenorphine may be inappropriate for those patients who concurrently use alcohol, sedatives, hypnotic or anxiolytic medications because of the risk of adverse events such as respiratory depression.[13] It is generally well-tolerated, but possible side effects of the medication include headache, anxiety, constipation, perspiration, fluid retention in lower extremities, urinary hesitancy, and sleep disturbance.[13]

If a transition needs to be made between medications, some changes can be more problematic than others. Transitioning from buprenorphine to methadone is usually easy and there is no time delay required. Switching from buprenorphine to naltrexone takes longer (usually 7-14 days after last dose) because the patient needs to not be physically dependent when starting the pure antagonist. Switching from methadone to buprenorphine has a similar problem with a long half-life of opioid receptor stimulation. Sometimes this transition can be made easier by first transitioning to shorter-acting oral opioids prior to starting the buprenorphine. The patient should be experiencing mild to moderate opioid withdrawal before the first dose of buprenorphine is administered, to prevent precipitated withdrawal.[13]

Buprenorphine and buprenorphine/naloxone products have been demonstrated to effectively reduce the use of opiates as well as decrease craving for opiates in those with opioid use disorder.[22] In conjunction with pharmacologic treatment, it is recommended that patients be offered comprehensive, integrated psychosocial treatment to optimize their chance at successful stabilization and recovery.[13]

Methadone has been the standard medication-assisted treatment in pregnancy because it has been used for over 50 years and has a larger body of literature. However, there are increasing data published regarding the safety of buprenorphine as well as the combination product buprenorphine/naloxone during pregnancy. A Cochrane review on the subject of opioid agonist therapy during pregnancy concluded that the overall body of evidence is small, but that there were no significant differences between methadone and buprenorphine to identify one as a superior therapy. The largest problem identified in the trials which limits their interpretation was attrition, which was as high as 30-40% in some trials, with the methadone groups having lower dropout rates than the buprenorphine groups.[23] The study that contributed the most patients to this review was the MOTHER trial, which is a randomized, placebo-controlled trial of buprenorphine versus methadone and evaluated maternal and neonatal outcomes of 175 pregnancies across 8 international sites. The primary results of this trial showed no difference in maternal outcomes except significantly higher patient drop out from buprenorphine than methadone group (33% vs 18%, $p = 0.02$). Regarding neonatal outcomes, the buprenorphine group required 89% less morphine and spent 43% less time in the hospital.[24]

While there appear to be some potential benefits to buprenorphine therapy, data are still somewhat limited on the combination therapy buprenorphine/naloxone in pregnancy.[20] More long-term data on infant and child effects after buprenorphine exposure are needed to aid in clinical decision-making. As with all new medication use in pregnancy, the patient should be included in shared-decision making to determine the best modality of medication-assisted treatment.

Pharmacotherapy selection

Methadone maintenance has long been considered the standard of care for treatment of opioid use disorder in pregnancy; however a growing body of data supports the consideration of buprenorphine as a treatment option.[9] The major benefits of buprenorphine products are that they are more widely available as outpatient prescriptions as opposed to methadone, which requires access to a federally-regulated treatment program. Additionally there is less potential for overdose, fewer drug interactions, and a potentially less severe neonatal abstinence syndrome. A recent systematic review and metanalysis by Zedler and colleagues compared randomized controlled trials and observational studies that evaluated pregnancy outcomes in buprenorphine-exposed and methadone-exposed pregnancies. Their findings indicate buprenorphine may be associated with less risk of preterm birth, higher birthweight and neonatal head circumference. The data are limited, but they saw no difference in spontaneous fetal death, congenital anomalies, and maternal adverse events.[25]

There are no absolute indications to direct a patient toward methadone maintenance or buprenorphine maintenance. The decision between treatment modalities is based largely on available local resources. If access is available to both agents, then the treatment should be individualized to patient characteristics such as medical comorbidities, concomitant medications, and severity of opioid use disorder.

Naltrexone

Naltrexone is an opioid antagonist. In the United States, naltrexone is available in an oral tablet form or in a once monthly extended-release injectable product (brand Vivitrol™). In other countries, there is an implantable formulation of naltrexone, which is typically utilized for 6 months at a time. There is not yet enough known about the use of naltrexone in pregnancy to recommend it as a first line therapy for opioid use disorder in pregnancy. There is also no expert consensus on whether naltrexone therapy should be initiated in pregnancy. Some experts agree that it is a reasonable consideration to continue naltrexone in pregnancy if a woman is already receiving this treatment, stable in her sobriety, and becomes pregnant. According to the American Society of Addiction Medicine National Practice Guidelines, if a woman becomes pregnant while receiving naltrexone therapy and she and her provider agree that her risk for relapse to opioid use is very low, it would be reasonable to discontinue the medication.[26] Because naltrexone is an opioid antagonist, there is no physical dependence to the medication and discontinuation of naltrexone does not result in any significant withdrawal symptoms. If the provider and patient remain concerned about relapse to opioid use should naltrexone be discontinued, it would be reasonable to consider either continuation of naltrexone, or change in pharmacotherapy to methadone or buprenorphine. A decision to continue naltrexone must include providing patient with information regarding risks, known or unknown, about naltrexone in pregnancy; consent to continue therapy should be obtained. If naltrexone is discontinued and a woman does in fact relapse to opioid use, the recommendation would be to offer buprenorphine or methadone.[26]

There are several medical and social reasons that interest in naltrexone (and interest for use in pregnant women with opioid use disorder) endures, despite less robust data compared to methadone or buprenorphine for the prevention of relapse to opioid use and retention in treatment. Since naltrexone in an opioid antagonist, there is no physical dependence, tolerance, nor risk for misuse. When the extended-release injectable formulation of naltrexone is used, there is virtually no risk for diversion. Concerning pregnant women with opioid use disorder, there is particular interest in naltrexone as a medication that would not carry the chance for neonatal abstinence in the infant after birth. Despite these potentially desirable characteristics of the medication, amassing safety and efficacy data for the use of naltrexone in pregnancy has been a slow process given the ethical considerations of a randomized, controlled trial with pregnant participants.[27] The limited pre-clinical and clinical data that do exist will be examined now.

There have been few animal model studies that examine the effect of prenatal exposure to naltrexone. At doses up to 50 times an equivalent human therapeutic dose, there were no changes in maternal rat health, nor in the duration of the pregnancy. There was, however, a clinically significant finding in pain sensitivity and neurobehavioral development in the rat pups exposed to naltrexone in utero, and the authors caution that the continuous antagonism of developing opioid receptors may interfere with the development of the endogenous opioid system.[28] Another study that examined pregnant rabbits and their offspring exposed to naltrexone at 200 times an equivalent human therapeutic dose did not find any impairment in fertility, nor did there appear to be any embryologic or fetal malformations. There has been report of increased early fetal loss in rats and rabbits exposed to naltrexone at these extremely high doses of naltrexone, which are on the order of hundreds of times greater than an equivalent human therapeutic dose.[29] However, given the limited data available regarding naltrexone's effect on fertility, pregnancy loss, and fetal and neonatal development, these animal model findings must be taken into consideration, and may give cause for caution.

The majority of data reporting on women with naltrexone use in pregnancy has come from Australia, where a 6-month implantable formulation of naltrexone is approved for treatment of opioid use disorder. Of more than 25 case reports and case series published, all have demonstrated overall reassuring maternal and neonatal outcomes, including no observed increase in preterm delivery, and Apgar scores, birth weights, and head circumferences within the typical range.[30–32] Although informative, the implantable naltrexone formulation is not available within the United States, and these data would have to be extrapolated to either oral or extended release injectable naltrexone which may not be equivalent. As such, further investigation is needed to evaluate naltrexone as a viable medication-assisted treatment for pregnant women with opioid use disorder.

Perhaps the most important factor regarding use of naltrexone in pregnancy, relates to the process of naltrexone

Table 1 – Medication assisted treatment medications comparison.

Medication	Mechanism	Route of administration	Dosage	Availability
Methadone	Full Agonist	Oral: Liquid, Pill or Wafer	Daily	Opioid Treatment Program
Buprenorphine	Partial Agonist	Sublingual: Pill or Film	Daily	Prescriber with waiver
		Implant	Every 6 months	
		Injectable	Every 4 weeks	
Naltrexone	Antagonist	Oral	Daily	Provider with prescribing authority
		Injectable	Monthly	

initiation, which differs from women who become pregnant already on naltrexone therapy. In order to safely start naltrexone in a pregnant, opioid-dependent woman, she must be completely detoxified from opioids. If naltrexone, or any opioid antagonist, is given to a person with full or partial opioid agonists occupying the opioid receptors, the agonist will be displaced, resulting in precipitated and profound opioid withdrawal. Thus, in order to start naltrexone, a person must be at least 5–7 days from last opioid use. This necessary detoxification is fraught with risk, the largest of which being relapse to opioid use. Not only would a woman be vulnerable to all of the usual risks of relapse to use, including acquisition of infection, overdose, and death, she could potentially be at higher risk due to the loss of tolerance associated with her attempt to become opioid free. Given this risk, the most robust indication for use of naltrexone appears to be in relapse prevention for the currently opioid-free person in a controlled environment (residential treatment facility, or leaving incarceration) when also paired with appropriate psychosocial supports.

Use of naltrexone for the treatment of opioid use disorder in pregnancy has special considerations as related to pain management during labor and post-partum. A person taking an opioid antagonist may require multidisciplinary intrapartum and postpartum pain management planning, particularly for women requiring operative vaginal delivery or cesarean delivery. From the general surgery literature, it appears that when an opioid antagonist is continued in the perioperative period, patients require higher doses of opioids and are at risk for less well controlled anesthesia and pain in the perioperative period.[33] Recommendations from this literature suggest that any planned surgeries be scheduled for 24–72 h after last dose of oral naltrexone, and 4 weeks from last extended release injectable naltrexone. For unplanned or emergent surgeries, recognition of the presence of the opioid antagonist is important along with close monitoring of patients with the knowledge that higher than usual doses of opioids that will be required for anesthesia and pain control.

A final consideration regarding use of naltrexone in pregnant women is breastfeeding. There are very limited data regarding use of naltrexone while breastfeeding, and as such, the FDA has cautioned use during lactation. One important case study describes the finding that although naltrexone and its metabolite 6,B-naltrexol does appear in human breast milk, infant testing demonstrated that infant's total exposure would be approximately 1% of maternal dose. This case study also noted that the infant had appropriate growth and development.[34] Given the limited data available, it would be reasonable to consider the risks and benefits to the mother-infant dyad regarding use of or foregoing naltrexone as part of an individual woman's treatment plan for prevention of relapse to opioid use while breastfeeding (Table 1).

Detoxification

Despite clear guideline recommendations from the World Health Organization, the Substance Abuse and Mental Health Services Administration, the American College of Obstetricians and Gynecologists and many others, that the recommended treatment of opioid use disorder in pregnancy is, and remains, the use of medication assisted treatment, many women—and providers—continue to attempt detoxification from opioids during pregnancy as a treatment intervention for OUD.[35–37]

This practice is in contrast to the historical fear of detoxification in pregnancy as harmful for mother and fetus. The fear of opioid detoxification –and initial recommendation for use of MAT—stemmed from two publications in the 1970s. The first was a case study published by Rementeria and Nunag of a women who very unfortunately delivered a term stillbirth infant in the setting of severe opioid withdrawal. In the second, Zuspan et al published their investigation of fetal stress during maternal detoxification, which was determined by the demonstrated increase in catecholamines in the amniotic fluid (obtained via repeated amniocentesis).[38,39] These two publications, coupled with ever-mounting data demonstrating improved maternal and neonatal outcomes for mothers who received methadone therapy in pregnancy, turned the tide strongly in favor of continued pursuit of MAT as the treatment of choice for opioid-dependent women in pregnancy.

The current opioid epidemic has rekindled interest in opioid detoxification. As more pregnant women are suffering with opioid use disorder, there has been a corresponding increase in the number of infants born at risk for neonatal abstinence syndrome (NAS) or neonatal opioid withdrawal syndrome (NOWS). Current treatment for NAS often includes extended hospitalizations for the infant, most often in the neonatal intensive care unit, which comes at a high cost. Although NAS is an expected, temporary, and treatable condition, it has contributed to the revived interest in the use of detoxification protocols for pregnant women with opioid use disorder. Bell et al and Stewart et al, have published data demonstrating that medically supervised detoxification from opioids *can* be done in pregnancy without significant increase in miscarriage, preterm labor, fetal distress, or fetal demise.[40,41] The question is not whether detoxification *can* be done, it is whether it *should* be done: opioid detoxification in pregnancy protocols typically have low completion rates,

high risk of relapse to use in pregnancy, and limited data regarding maternal and neonatal outcomes beyond delivery. And the risks of relapse cannot be overstated: relapse is not simply the return of the presence of an opioid. Relapse risks include exposure to HIV, hepatitis C, hepatitis B, skin and soft tissue infections, bacteremia and endocarditis, overdose, and death. When these risks are weighed against the possibility of temporary and treatable neonatal abstinence syndrome, overwhelmingly the recommendation continues to be the use of medication-assisted treatment over detoxification as the intervention of choice for the treatment of opioid use disorder in pregnant women.

Conclusion

In summary, medication assisted treatment remains the gold standard therapy for the treatment of opioid use disorder in pregnancy. Methadone or buprenorphine may be utilized, and the choice of pharmacotherapy is dependent upon both patient specific as well as provider level factors, and treatment availability in the patient's community. There continue to be some questions regarding the use of naltrexone in pregnancy for the indication of opioid use disorder, and more research is needed to further determine whether naltrexone should be offered to pregnant women as a third pharmacotherapy option. Detoxification alone as an intervention for the treatment of opioid use disorder in pregnancy should be avoided, as detoxification alone demonstrates lack of efficacy and also potentiates harm.

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