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A Comparison of Pharmacologic Interventions in Pregnant Women with Opioid Use Disorder

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By

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Abstract

The purpose of this research and systematic literature review is to determine which pharmacotherapeutic agent, methadone or buprenorphine, leads to better outcomes in cases of pregnant mothers with opioid use disorder (OUD). Outcomes considered are maternal compliance, neonatal abstinence syndrome severity, and neonatal length of hospital stay. In the review, PubMed, Clinical Key, Cochrane Database of Systematic Reviews, and DynaMed Plus were searched. Key terms searched were "methadone, buprenorphine, pregnancy", "opioids, pregnancy", "neonatal abstinence syndrome" and "medication assisted treatment, pregnancy". Articles were narrowed with applications of filters for articles in the past fifteen years and by use of the English language. Selection criteria for research articles, original research, and meta-analysis included peer review. Other articles were found from the bibliographies of pertinent review and original research articles. Several studies were excluded, as their study population was not specified to have diagnosed OUD in pregnancy. The drawbacks to many of the studies is the inconsistencies in study conditions, and very small sample sizes. Much of the research presented shows evidence for the use of buprenorphine in the treatment of OUD in pregnancy. Buprenorphine seems to be a better medication assisted treatment (MAT) for the neonate in terms of reduced neonatal abstinence syndrome (NAS) and reduced length of hospital stay postpartum, while methadone still performs better for adherence for the mother. More research still needs to be done in order to demonstrate buprenorphine's superior efficacy compared to methadone use in pregnant patients with OUD.

Keywords: MAT, methadone, buprenorphine, pregnancy, OUD, opioid, addiction, NAS, neonate

Introduction

Opioid addiction in the United States has become a major public health crisis. The Centers for Disease Control and Prevention (CDC) estimates that 134 people die from opiate overdose each day. Unfortunately, addiction impacts people in all phases of life, including pregnant women. Neonates who are heavily exposed to opiates in utero often experience withdrawal upon parturition, a condition called neonatal abstinence syndrome (NAS). NAS increased by 500% in the US between 2000 and 2012. Treatment protocol supports the use of medication-assisted treatment (MAT) to prevent NAS. Currently, the drug methadone is administered to prevent pregnant women from abusing opiate substances, namely heroin or prescription opiates. However, a growing body of evidence supports other MAT drugs, most notably buprenorphine, for use in pregnant patients. The purpose of this study is to determine whether methadone or buprenorphine is more effective in preventing NAS, reducing length of hospital stay for the neonate of an opiate addicted mother, and ensuring maternal compliance.

A review of the literature shows that buprenorphine is as effective or more effective in reducing NAS and length of neonatal hospital stay compared to methadone. The literature also points towards methadone as a more effective agent for ensuring maternal compliance.

Statement of the Problem

Methadone is the current standard of care for the use of MAT in pregnant women with OUD. Studies are needed to show the safety and efficacy of other treatment options such as buprenorphine for this patient population.

Statement of the Research questions

In pregnant patients with OUD, how effective is methadone compared to buprenorphine in the reduction of NAS?

In pregnant patients with OUD, how effective is methadone compared to buprenorphine in the reduction in length of hospital stay for neonates?

In pregnant patients with OUD, how effective is methadone compared to buprenorphine in retention on MAT and prevention of relapse?

Review of Literature

A search was conducted using PubMed, Clinical Key, and DynaMed Plus using MeSH terms “methadone, buprenorphine, pregnancy”, “opioids, pregnancy”, “neonatal abstinence syndrome” and “medication assisted treatment, pregnancy”. Articles were narrowed with applications of filters for articles in the past fifteen years and by use of the English language. Selection criteria for research articles, original research, and meta-analysis included peer review. Other articles were found from the bibliographies of pertinent review and original research articles. A Cochrane Library search was also performed using the search term “methadone, buprenorphine, pregnancy” and “MAT” which revealed pertinent systematic reviews. Some articles were used to provide background information on pathophysiology of opioids and opioid use disorder. Several studies were excluded as their study population was not specified to have diagnosed opioid use disorder in pregnancy. The drawbacks to many of the studies is the inconsistencies in the different study conditions, and very small sample sizes.

US Opioid Epidemic, Pharmacologic and Physiologic Basis of Opiates, and Maintenance Therapy Drugs

Background information of opioids.

Opioids are endogenous peptides that bind to one of three G protein-coupled receptors in the body; mu (μ), kappa (κ), and delta (δ). These receptors can also be activated by exogenous administered opiates, both natural and synthetic. Full agonists of these receptor sites lead to

analgesia and euphoria, the desirable effects of these medications. Unfortunately, full agonists also cause respiratory depression and inhibition of gastrointestinal transit. Mu and delta receptors are selective for analgesia and reward, while the kappa receptor activation causes dysphoria (Waldhoer, Bartlett, & Whistler, 2004). Providing analgesia using exogenous opiates is a mainstay in modern medicine, especially when treating cancer patients or following surgery or injury.

US opioid epidemic.

Recently, there has been a surge in the prescribing of opioid medications for chronic pain. Americans do not report significantly more pain than in the past, but the amount of prescription opioids purchased in the US has increased since the 1990s. In 2012, the number of opiate prescriptions sold peaked at more than 225 million, at 81.3 prescriptions per 100 persons (U.S. Opioid Prescribing Rate Maps, 2018). Accidental overdose or drug-drug interactions with benzodiazepines or other sedating medications can occur, even in patients who take their medications as prescribed. In addition, there has been an increase of illicitly-made synthetic opioids that are mixed with other drugs like cocaine or methamphetamine, leading to unpredictable outcomes and overdose.

Naloxone affects mu, delta, and kappa opioid receptors non-selectively and reverses and competitively blocks the effects of other opioids. Within seconds, it can restore normal breathing in a person who has overdosed from opioid medication caused (NIDA, 2017). The Surgeon General of the United States Public Health Service has stated the importance of naloxone, stating: “for patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl… knowing how to use naloxone and keeping it within reach can save a life.” (Adams, 2018).

As many as 26% of patients who are prescribed long term opioid therapy in primary care suffer from opioid addiction (Boscarino et al., 2010). Unfortunately, some patients lose their ability to legally obtain opioid medication and look to illegal opioid medications to avoid withdrawal symptoms. Heroin is one such drug that is rampant in the United States. People who are addicted to prescription opioids are 40 times more likely to also be addicted to heroin (Jones, Logan, Gladden, & Bohm, 2015). According to the Center for Disease Control (CDC), between 2010 and 2016, the rate of heroin related overdose death increased by five times in the US (Opioid Overdose, 2017). This issue has become a public health epidemic, as opioid-related fatalities and infectious diseases like HIV and hepatitis C have increased. Dr. Nora Volkow's testimony to the Senate Judiciary Committee clearly outlined the need to consider evidence-based approaches to rules and regulations that are formulated against prescription opiates (Attacking America's Epidemic of Heroin and Prescription Drug Abuse, 2016).

Opioid use disorder.

Opioid use disorder (OUD) is a diagnosis included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published in 2013. For diagnosis, a person should experience two or more symptoms within a 12-month period and no dependence diagnosis. Severity is determined by a criteria count; mild (2-3), moderate (4-5) or severe (6+) (Hasin et al., 2013). Patients taking chronic opioids for medically indicated treatment can experience withdrawal when medications are stopped abruptly, but this is not an automatic diagnosis of OUD.

Symptoms for OUD diagnosis.

- Taking more opioid than intended
- Wanting to control opioid use without success

- Spending time obtaining, taking, or recovering from the effects of opioids
- Craving opioids
- Failing to carry out important roles at home, work, or school because of opioid use
- Continuing to use opioids, despite it causing relationship or social problems
- Giving up or reducing other activities because of opioid use
- Using opioids even when physically unsafe
- Knowing that opioid use is causing a physical or psychosocial problem, but continuing to take the drug anyway
- Tolerance for opioids
- Withdrawal symptoms when opioids are not taken

Medication Assisted Treatment.

Medication-assisted treatment (MAT) is a common strategy for combating OUD. MAT has become a therapeutic standard, as it is highly successful in retaining patients in treatment and reducing illicit drug use, and reduces morbidity, mortality, and the spread of infectious disease in addition to improvements in social functioning. MAT works by maintaining a lower level of opioid in the body than with illicit use (Tran, Griffin, Stone, Vest, & Todd, 2017). Opiate agonists are used to prevent withdrawal symptoms, drug craving, and relapse to drug use.

Methadone.

Methadone is a safe and effective drug used in maintenance therapy. It is a full opioid agonist at the mu opioid receptor, with a half-life of 24-36 hours (Johnson & Jones, 2018). Unfortunately, overdose is still possible with this drug, and most commonly occurs during the induction phase of its use. Methadone is typically provided in regulated treatment programs that dispense daily medication doses (Johnson & Jones, 2018). Over several weeks, the dose is

increased to reach therapeutic level. The pitfalls of methadone include respiratory depression, overdose risk, interaction with antiretroviral agents, and prolonged QT intervals (Blanco-Gandia, & Rodriguez-Arias, 2018). As an opiate agonist, methadone itself can be addicting, but can be preferable to heroin or other illicit sources of opiate. It is considered a pregnancy category C medication and there are no controlled studies of methadone use in pregnant women that can be used to establish safety.

A Cochrane review evaluated eleven randomized clinical trials (n=1969) concerning methadone maintenance therapy compared with placebo maintenance or nonpharmacologic therapy for OUD. Methadone was significantly more effective than non-pharmacological approaches in retaining patients in treatment and suppression of heroin use as measured by self-report and urine or hair analysis (RR = 0.66, 95% CI 0.56-0.78) (Mattick, Breen, Kimber, & Davoli, 2009).

Buprenorphine.

Buprenorphine is a first line medication for opioid dependence. It is a long-acting partial agonist of the mu opioid receptor, with slow dissociation, which allows for extended duration of action with just a single-dose (Blanco-Gandia, & Rodriguez-Arias, 2018). It also is an antagonist at the kappa receptor, which causes a ceiling effect for respiratory depression (Tran, Griffin, Stone, Vest, & Todd, 2017). Compared to methadone, there is less risk for overdose, less subjective euphoria, and reduced severity of withdrawal, leading to it being considered a safe alternative to methadone, as there is lower abuse potential and higher efficacy. Additionally, buprenorphine does not cause QT prolongation. Since it displaces stronger opioids already bound to the receptor, initiation should begin during mild withdrawal, not while the patient is still abusing opiates (Blanco-Gandia, & Rodriguez-Arias, 2018). Buprenorphine can be prescribed

through office-based maintenance therapy from a licensed provider. A newer implantable option has become available, making dosing and compliance even simpler (Johnson & Jones, 2018), as well as a subcutaneous injection that is administered monthly (Felberbaum, 2017). Buprenorphine is considered a pregnancy category C medication, indicating that the risk of adverse effects has not been ruled out.

A Cochrane review investigated randomized controlled trials regarding buprenorphine maintenance treatment versus placebo or methadone in the management of OUD. A total of 31 trials (n=5430) were included. Only high doses of buprenorphine (>16 mg) were more effective than placebo in suppressing illicit opioid use (3 studies, n=729, SMD -1.17, 95% CI -1.85 to -0.49), while buprenorphine in flexible doses was found to be less effective than methadone in retaining participants in treatment (5 studies, n=788, RR=0.83, 95% Cl 0.72 to 0.95) although there was no difference between medium-dose buprenorphine (7 - 15 mg) and medium-dose methadone (40 - 85 mg) in retention, (7 studies, 780 participants, RR 0.87; 95% CI 0.69 to 1.10) or in suppression of illicit opioid use as measured by urines, (4 studies, 476 participants, SMD 0.25, 95% CI -0.08 to 0.58) or self-report of illicit opioid use, (2 studies, 174 participants, SMD -0.82, 95% CI -1.83 to 0.19) (Mattock, Breen, Kimber, & Davoli, 2014).

Naltrexone.

Naltrexone is a competitive opiate antagonist available in oral, injectable, and implantable forms, which blocks euphoria if exogenous opioids are taken. It will cause withdrawal symptoms in patients who are dependent on opioids, and 7-10 days of abstinence are recommended before its initial use, so it can be challenging to initiate therapy. Its active metabolite has a half-life of up to 13 hours. It is used for detoxification and for management of

addiction but is less favorable (Blanco-Gandia, & Rodriguez-Arias, 2018). Johnson and Jones (2018) have shown that it can reduce the risk of relapse in patient with OUD.

A 2011 double blind, placebo-controlled, randomized 24-week trial was completed with 250 participants with OUD. Each participant was randomly assigned to injectable, once monthly extended release naltrexone group (n=126) or placebo (n=124). The median proportion of weeks of confirmed abstinence was 90.0% in the naltrexone group compared with 35.0% in the placebo group (p=0.0002). The mean change in craving was –10.1 in the naltrexone group compared with 0.7 in the placebo group (p<0.0001). Median retention was over 168 days in the naltrexone group compared with 96 days (95% CI 63–165) in the placebo group (p=0.0042) (Krupitsky et al., 2011).

Opiate addiction in pregnancy

Misuse of opioids crosses societal boundaries, and one such population is pregnant women. In 2012, the percentage of pregnant women entering treatment reporting prescription opioid misuse was 28%. Prescription opioid as the primary substance of abuse was 19%, up from 2% and 1% in 1992 (Tran, Griffin, Stone, Vest, & Todd, 2017). A combination of pregnancy and OUD presents a highly stressful situation. Many of these mothers experience anxieties and guilt about adverse effects on the neonate and feel pressured to stop opioids all together (McCarthy et al., 2017).

When a woman uses opioids through her pregnancy, the drug passes through the placenta to the fetus. OUD can cause complications in pregnancy for the mother, fetus, and neonate. When OUD goes untreated, the mother experiences increased risk for limited prenatal care, miscarriage, infectious exposure, preterm labor and delivery, opioid overdose, and subsequently death. The fetus is at risk for intrauterine growth restriction, preterm birth, and possibly

congenital abnormalities. The neonate is at increased risk for low birth weight, possible long-term developmental defects, and NAS (Johnson & Jones, 2018). Opioids taken during pregnancy, including MAT drugs, can lead to NAS. There is also increased neonatal mortality and a 74-fold increase in the risk of sudden infant death syndrome (Minozzi et al., 2013).

Despite the risks of opioid use in pregnancy, there is a high rate of opioid prescriptions given to pregnant women. Between 2000 and 2007 about 14.4% of pregnant women with private insurance and 21.6% of pregnant women enrolled in Medicaid filled prescriptions for an opioid during their pregnancy (Ailes et al., 2015). Many women are placed on long term opioid therapy for chronic pain or are addicted to opiates before achieving pregnancy (Johnson & Jones, 2018). When a woman with OUD reveals her use of opiates to healthcare providers, many women are met with stigma and poor medical management.

Recently, there have been criminalization efforts of maternal opioid dependence and coercion of pregnant women to undergo withdrawal. Sudden withdrawal poses risks of fetal hypoxia and adverse epigenetic programming related to catecholamine and corticosteroid surges that occur during withdrawal in utero. Medically assisted withdrawal is not recommended in pregnant women with OUD before 14 weeks or after 32 weeks of gestation and should only be considered after pregnancy if clinically indicated or if requested by the patient. Otherwise, pregnant women should be encouraged to consider ongoing MAT before delivery (Substance Abuse and Mental Health Services Administration, 2015). In a survey of pregnant women with OUD starting MAT, 43% said that when they told their physician about their pregnancy and dependence, no referral or supportive advice was given. There are even reports of physicians advising women that withdrawal-precipitated miscarriage would be the best outcome for the

patient, despite current literature that supports good outcomes with MAT (McCarthy et al., 2017).

Current guidelines support the administration of a MAT drug for OUD in pregnant women: either methadone or buprenorphine. There is a need for careful consideration of risks and benefits of these medications, but there are no known teratogenic effects to the human fetus when taken as directed (Substance Abuse and Mental Health Services Administration, 2015). MAT therapy helps prevent withdrawal, prevent complications of illicit opiate use, improve compliance with obstetric care, improve neonatal birth weight, and reduce obstetric complications, but are still associated with NAS (Johnson & Jones, 2018). Maintenance treatment provides a steady concentration of opiate in the pregnant woman's blood and so prevents the adverse effects on the fetus of repeated withdrawals (Minozzi et al., 2013). In conjunction with psychosocial and cognitive behavioral therapy, MAT is endorsed over medically assisted withdrawal or abstinence for pregnant women with OUD by the Substance Abuse and Mental Health Services Administration and the American College of Obstetricians and Gynecologists Committee (Tran, Griffin, Stone, Vest, & Todd, 2017).

Neonatal Abstinence Syndrome.

After birth, the neonate is cut off from the mother's blood supply and therefore from the opiates the neonate received from the mother. This abrupt removal from opiate exposure can cause withdrawal symptoms. NAS is a collection of symptoms associated with opiate withdrawal in neonates and is seen usually within the first 72 hours postpartum but can be seen as late as 7 days postpartum (Gomez-Pomar & Finnegan, 2018). Symptoms of NAS include high pitched crying, tremors, hyperactive Moro reflex, irritability, diarrhea and vomiting, uncoordinated sucking and swallowing, tachypnea, poor sleep, and low-grade fevers (Tran, Griffin, Stone, Vest,

& Todd, 2017). These abstinence signs can be seen in 60-80% of opioid exposed neonates, and severity is dependent on many variables like total exposure, length of substance abuse, and drug metabolism (Gomez-Pomar & Finnegan, 2018).

NAS can be monitored several ways and there is no national consensus as which tool is the best. The most widely used is the Finnegan Neonatal Abstinence Scoring System (FNASS). The scoring system contains 21 items to identify neonates that may need treatment with medications; the cutoff points being 3 subsequent scores of ≥ 8 or two subsequent scores ≥12 (Gomez-Pomar & Finnegan, 2018). Morphine sulfate treatment is given on symptom-based dosing. There is a significant healthcare dollar burden to care for these infants, as it costs nineteen times more to care for a neonate affected by NAS compared to non-NAS neonates (Johnson & Jones, 2018).

Table 1: Pros and Cons of different MAT drugs

Medication specific issues: medication-assisted therapy in pregnancy

Treatment	Pros	Cons
Methadone	• Demonstrated safety and efficacy in pregnancy • Decreased medication diversion • More structured program • More effective for polysubstance abuse • Effective if failed buprenorphine treatment • Safe for breastfeeding	• Daily clinic treatment required • Higher risk of overdose • Interactions with other medication • Prolongation of QT interval • Neonatal abstinence syndrome
Buprenorphine	• Does not require proximity for daily clinic visits • Decreased overdose risk • Decreased interactions with other medications • Less severe, shorter neonatal abstinence • More discreet • Safe for breastfeeding	• Risk of precipitated withdrawal during initiation • Lack of long-term data on child outcomes • Increased diversion risk • Lower retention in treatment • Less effective if buprenorphine drug of abuse • Requires mild withdrawal to start treatment
Buprenorphine + naloxone	• Decreased diversion risk • Similar outcomes to buprenorphine alone • Limited breastfeeding data	• Severe withdrawal if used incorrectly (ie, injected) • Lack of long-term data on child outcomes
Naltrexone	• Requires completed opioid withdrawal to initiate • Limits overdose risk • No maternal withdrawal if treatment stopped • Minimal breastfeeding data	• Limited effectiveness of opioid treatment if required (eg, after a cesarean section) • Lack of long-term data on infant and child outcomes • Minimal data on pregnancy and breastfeeding • Minimal data on long-term maternal outcomes

Note. Adapted from "Opioid use disorders and pregnancy," by A. J. Johnson and C.W. Woods, 2018, Obstetrics and Gynecology Clinics of North America, 45, p 205. Copyright Elsevier Inc

Comparison of Buprenorphine and Methadone in Opiate Addicted Pregnant Patients and NAS

A study published in 2013 used a theoretical cohort of 1000 mother-baby dyads to compare buprenorphine versus methadone for MAT during pregnancy. Fowler et al. investigated

maternal retention in treatment, NAS, preterm birth, and quality adjusted life years (QUALYs). They found that buprenorphine led to better outcomes for neonates. Buprenorphine had 145 fewer cases of NAS, 44 fewer preterm births which is a cost savings of over $12.4 million healthcare dollars. Methadone had 888 remain in the treatment group compared to 694 remaining who used buprenorphine. Despite dropout rates of 56.4% with buprenorphine, it was still a more economical choice than methadone (Fowler et al., 2013).

A longitudinal study published in 2017 where data was collected from women with OUD on buprenorphine treatment at the Center for Addiction and Pregnancy examined the effects of maternal buprenorphine maintenance on infant outcomes. Only 41 of the original 127 pregnant women completed the protocol through delivery. Of the women who discontinued the trial, 42 of the women switched to methadone treatment. Jansson et al. (2017) found that 59% of neonates that experienced NAS required pharmacologic management NAS severity (total morphine required to treat NAS in mg) on buprenorphine dose showed a statistically significant relation between maternal buprenorphine dose and NAS severity ($p=0.03$). Total length of hospitalization of neonates was 14.7 days on average (SD=9.0, Range 5-44) (Jansson et al., 2017).

A Cochrane review of maintenance agonist treatment for pregnant women with OUD assessed four randomized controlled trials to assess the effectiveness of maintenance treatment. This review found that mothers that are on methadone therapy are less likely to drop out of the study (RR 0.64, 95% CI 0.41 to 1.01, three studies, n=223) compared to those on buprenorphine. There was no significant difference in the number of newborns treated for NAS, but evidence is considered very low (RR 1.22, 95% CI 0.89 to 1.67, three studies, n=166) (Minozzi et al., 2013).

The MOTHER (Maternal Opioid Treatment: Human Experimental Research) study was a large double blind, double dummy, randomized, stratified, flexible-dosing, parallel group clinical

trial that compared 175 pregnant women with OUD on methadone versus buprenorphine maintenance treatment. Neonates were evaluated for NAS using the 28-item modified Finnegan scale (Jones et al., 2012). Both mother and infant outcomes were measured. Discontinuation of treatment occurred in 18% of women in methadone treatment and 33% of women in buprenorphine treatment ($p=0.02$). It was found that 71% of women who left the buprenorphine group reported their reason for discontinuation to be dissatisfaction, compared to only 13% in the methadone group. Only 131 women completed the study, $n=73$ in the methadone group and $n=58$ in the buprenorphine group. The number of neonates requiring NAS treatment was not significantly different between groups ($p=0.26$) and peak NAS score was not significantly different ($p=0.04$). Neonates from the buprenorphine group needed 89% less morphine than those exposed to methadone ($p<0.0091$) and spent 43% less time in the hospital ($p<0.0091$) (Jones et al., 2010).

Coyle et al. (2012) took data from three sites of the MOTHER study, a double blind, double dummy, randomized clinical trial, to determine the effects of in utero exposure to methadone or buprenorphine on infant behavior. They included 39 full term infants either exposed to buprenorphine ($n=18$) or methadone ($n=21$) from the study. In this subset, days of infant hospital stay were 18.7 ($SD=15.5$) for methadone group and 11.8 for the buprenorphine group ($SD= 4.0$). NAS treatment was looked at in terms of days medicated and total amount of morphine. In the methadone group, 13.8 ($SD=2.9$) days with 21.5g ($SD=49.9$) of morphine was used for NAS treatment. In the buprenorphine group, 7.2 days ($SD=3.1$) with 2.5g ($SD=3.5$) of morphine was used for NAS treatment. The buprenorphine-exposed infants required less morphine to treat withdrawal than infants in the methadone-exposed condition, and both groups

had a significant linear ($p<0.02$) and curvilinear ($p<0.03$) trajectory over days of assessment (Coyle et al., 2012).

Unger et al. (2011) analyzed the data from three mothers from the MOTHER study who had two consecutive pregnancies. This allowed for control in differences in maternal metabolism, and other environmental variables that may impact data. The women were treated with either methadone or buprenorphine during the first pregnancy and the respective opposite medication in the second pregnancy. All 6 neonates did experience NAS for some length of time. The mean total NAS score was 119.7 (SD=30.7) and NAS medication needed was 2.5 mg (SD=1.6) for methadone and 86.7 points (SD= 28.8) and NAS medication needed was 1.2mg (SD=1.1) for buprenorphine. Buprenorphine exposed neonates tended to have less NAS and need less medication than those exposed to methadone. However, those exposed to methadone in utero were 400 grams heavier than those exposed to buprenorphine (Unger et al., 2011).

A retrospective study published in 2012 by Pritham, Paul and Hayes reviewed charts of 152 pregnant women with OUD and taking either methadone or buprenorphine maintenance therapy. Length of hospital stay was 21.3 days (SD=12.6) in the methadone group compared to 13.7 days (SD= 11.9) in the buprenorphine group ($p=0.05$). In the methadone group, 84.6% of neonates were treated for NAS, compared to only 68.8% of buprenorphine group neonates ($p=0.11$) (Pritham, Paul, & Hayes, 2012).

Lacroix et al. (2011) investigated the effects of exposure to buprenorphine compared to methadone in pregnancy. Through this prospective multicenter study, women exposed to buprenorphine (n=90) and methadone (n=45) were included. NAS, monitored with the Finnegan score six times per day, occurred more frequently in the methadone group (62.5% vs. 41.2%, $p=0.03$). After adjustment for illicit opiate exposure in the 3rd trimester, rates of NAS were not

different between groups. Treatment for NAS with opiates was needed in 84% of neonates in the methadone group versus only 57% of those in the buprenorphine group (p=0.03) (Lacroix et al., 2011).

Pregnant women addicted to intravenous heroin were studied in a five-year randomized prospective comparative study by Binder and Vavřinková (2008). In the first trimester of pregnancy women addicted to heroin (n=47), methadone (n=32), and buprenorphine (n=38) were enrolled. NAS was evaluated with the Finnegan score scale at six-hour intervals, but if the score was greater than eight, scoring was done every four hours. Opium tincture was used for NAS treatment in a symptom dosing regimen. The degree of NAS severity was 9.2 in the buprenorphine group, 11 in the heroin group, and 17.8 in the methadone group (buprenorphine to methadone $p<0.000001$, heroin to methadone $p<0.00001$) (Binder & Vavřinková, 2008).

A randomized, double dummy, double blind, flexible dosing comparison study was completed by Fischer et al. (2005) to investigate the efficacy and safety of methadone versus buprenorphine in pregnant women with OUD. A very small sample size of 18 was used, and after drop outs six women were maintained with methadone and eight with buprenorphine. Urine toxicology data indicated that methadone was more effective than buprenorphine in preventing additional opioid consumption in the pregnant women (p=0.029). Of the 14, three neonates exposed to methadone and three exposed to buprenorphine had NAS scores that did not exceed 8, and therefore did not require treatment. For the other 8 neonates, there was no difference in the mean total dose of morphine required to treat NAS in the two groups (methadone: 2.71 ± 1.68 mg; buprenorphine: 2.00 ± 2.00 mg; p = 0.640). The mean duration of treatment for NAS was statistically insignificant, at 5.3 (range 4–7; SD 1.5) in the methadone group and 4.8 days (range 1–8; SD 2.9) in the buprenorphine group (p = 0.766) (Fischer et al., 2005).

One study by Jones et al. (2005) looked at NAS in neonates exposed to methadone and buprenorphine from pregnant women dependent on opioids. The study was designed to provide preliminary data for safety and efficacy for a larger trial. It was a randomized, double blind, double dummy, flexible dosing, parallel group-controlled trial that included 10 neonates exposed to buprenorphine and 11 neonates exposed to methadone in utero. It was found that 20% of buprenorphine-exposed and 45.5% methadone exposed neonates were treated for NAS (p=0.23). Total amount of morphine used for NAS treatment in methadone-exposed neonates was three times greater than for buprenorphine-exposed neonates (93.1 mg versus 23.6 mg; p=0.13). Length of hospitalization was shorter for buprenorphine-exposed neonates (6.8 days, SE = 0.86) than for methadone-exposed neonates (8.1 days, SE = 0.78) (p = 0.021) (Jones et al., 2005).

Discussion

Although buprenorphine is not the standard of care for pregnant women with OUD, it should be considered as an alternative to methadone maintenance therapy. NAS is reduced with buprenorphine compared to methadone treatment, though more women sustain MAT with methadone. Because NAS is less severe with buprenorphine MAT compared to methadone MAT, length of stay (LOS) is less with buprenorphine exposed neonates and thus is a more effective way to spend the very limited healthcare dollars that exist for these patients. In addition, MAT drug choice should be individual. Finally, if one MAT drug is failed, another should be initiated.

In pregnant patients with OUD, how effective is methadone compared to buprenorphine in the reduction of NAS?

NAS can be considered several different ways. Some studies considered the number of days neonates were treated for NAS, while others looked at the average NAS score from the Finnegan scale, while some considered the amount of morphine needed to treat NAS. Each study may have used different parameters on when to treat NAS, and how often to look for signs and symptoms. Such inconsistencies between studies make true comparison difficult.

NAS severity.

One study shows that buprenorphine treatment in mothers with OUD leads to less severe NAS compared to methadone (Fowler, et al., 2013). But, in one of the most extensive and thorough studies, the MOTHER project, neonates requiring NAS treatment was not significantly different between mothers maintained on buprenorphine vs methadone. Furthermore, peak NAS score was not significantly different (Jones et al., 2010).

Another study found that the degree of NAS severity was 9.2 in the buprenorphine group, 11 in the heroin group, and 17.8 in the methadone group (Binder & Vavřinková, 2008). This is certainly concerning, considering MAT therapy with methadone is found to cause worse NAS than heroin use.

Unger et al. (2011) found a mean total NAS score of 119.7 points for methadone and 86.7 points for buprenorphine, showing neonates exposed to buprenorphine tended to have less NAS than those exposed to methadone.

Additionally, a Cochrane review shows that there is no significant difference in the number of newborns treated for NAS when comparing mothers maintained on methadone versus buprenorphine (Minozzi et al., 2013). Although, this was considered low level evidence.

Morphine need.

Jones et al. (2010) found that neonates from the buprenorphine treatment group needed 89% less morphine than those exposed to methadone for NAS treatment. However, Fischer et al. (2005) found that there was no difference in the mean total dose of morphine required to treat NAS between methadone and buprenorphine exposed neonates. Unger et al. (2011) found that NAS medication needed was more than double for methadone neonates compared to buprenorphine. In contrast, Jones et al. (2005) found that total morphine need was triple in the methadone exposed neonates compared to the buprenorphine group. Coyle et al. (2012) found that the dose of morphine difference was significant and 21.5g of morphine was used for NAS treatment in the methadone group and only 2.5g of morphine was used for NAS treatment in the buprenorphine group.

NAS incidence.

Jansson et al. (2017) found that of mothers maintained on buprenorphine, 59% of their neonates experienced NAS and required pharmacologic management. In another study by Pritham, Paul, and Hayes (2012) 68.8% of neonates exposed to buprenorphine needed NAS treatment. In that same study, 84.6% of neonates exposed to methadone needed treatment for NAS (Pritham, Paul, & Hayes, 2012). Jones et al. (2005) found that only 20% of buprenorphine exposed and 45.5% methadone exposed neonates were treated for NAS. Lacroix et al. (2011) showed that treatment for NAS was needed in 84% of neonates in the methadone group versus only 57% of those in the buprenorphine group. Furthermore, it was shown that after adjustment for illicit opiate exposure in the 3rd trimester, NAS instance was not different between groups (Lacroix et al., 2011).

Duration of NAS treatment.

Fischer et al. (2005) found that the mean duration of treatment for NAS was statistically insignificant between groups, while Coyle et al. (2012) found that an average of 13.8 days in the methadone group and only 7.2 days in the buprenorphine group was needed for NAS treatment: nearly half the amount of time.

In pregnant patients with OUD, how effective is methadone compared to buprenorphine in the reduction in length of hospital stay for neonates?

Jansson et al. (2017) looked only at neonates exposed to buprenorphine and found that total length of hospitalization of neonates was 14.7 days on average but ranged from 5-44 days. Pritham, Paul, and Hayes (2012) found similar results, in that buprenorphine exposed neonates had an average LOS at 13.7 days. This was compared to methadone exposed neonates, who stayed an average of 21.3 days. This study had a very small sample size (Pritham, Paul, & Hayes, 2012). Coyle et al. (2012) found LOS to be 18.7 (SD=15.5) for the methadone group and 11.8 for the buprenorphine group, while Jones et al. (2005) found LOS to be much shorter in both groups, as buprenorphine exposed neonates stayed about 6.8 days compared to methadone exposed neonates at 8.1 days. This statistic was significantly different. The MOTHER project showed that neonates exposed to buprenorphine in utero compared to methadone spent significantly less time in the hospital, about 43% (Jones et al., 2010).

In pregnant patients with OUD, how effective is methadone compared to buprenorphine in retention on MAT and prevention of relapse?

Fowler et al. (2013) found that the maternal dropout rate 56.4% with buprenorphine, compared to only 11.2% in the methadone group. Another study that was principally studying buprenorphine MAT mothers noted 86 of 127 left the study protocol. Of those, 42 women

decided to switch to methadone MAT and 44 left drug treatment all together (Jansson et al., 2017). In the MOTHER project, discontinuation of treatment occurred in 18% of women in methadone treatment and 33% of women in buprenorphine treatment. They found that 71% of women who left the buprenorphine group reported their reason for discontinuation to be dissatisfaction, compared to only 13% in the methadone group (Jones et al., 2010).

In another very small study by Fischer et al. (2005), urine toxicology data indicated that methadone was more effective than buprenorphine in preventing additional opioid consumption in pregnant women.

A Cochrane review concluded that mothers that are on methadone therapy are less likely to drop out of the study compared to those on buprenorphine (Minozzi et al., 2013).

Applicability to Clinical Practice

North Dakota experiences opioid addiction across the state but faces challenges for patients to get the care they need due to a lack of specialists and a vastness of rural geography. Project ECHO or “Extension for Community Healthcare Outcomes” is a hub and spoke model used to train rural providers with the resources and information through video conferencing. This project is administered by the North Dakota Department of Human Services (NDDHS) in collaboration with the University of North Dakota School of Medicine and Health Sciences Center for Rural Health and has been in existence since fall 2017. Project ECHO is focused on the opioid epidemic in North Dakota and provides video sessions weekly from experts and specialists in academic or health care centers to primary care teams in rural parts of the state (Kusler, 2018). In the Management of Opioid Use Disorder series, Project ECHO has devoted two 1.5-hour clinic sessions on pregnant and lactating patients and neonatal abstinence syndrome

for which providers are able to get continuing education credit (Project ECHO, 2017). The 2015 federal guidelines for opioid treatment states "Although the level of evidence supporting buprenorphine maintenance during pregnancy is not as voluminous as that supporting methadone maintenance treatment, decisions need to factor in access and the specific needs and goals of the patient" (Substance Abuse and Mental Health Services Administration, 2015). It is crucial that this topic be addressed in project ECHO sessions, as well as in similar education programs for providers across the country. Adding buprenorphine as an acceptable alternative to methadone during pregnancy for women with OUD will increase access to better MAT treatment, and convenience and availability for the recipients.

Furthermore, the Champion Prescriber initiative expands access to MAT in North Dakota. Opioid Treatment Programs exist in Fargo, Minot, and Bismarck and serve as the "hubs". Office-based opioid treatment medical providers with buprenorphine waivers serve as the "spokes". These providers provide MAT treatment and overdose prevention education, collaborate with providers in project ECHO, and provide training on the use of Naloxone. Champion Prescribers should be aware that both methadone and buprenorphine are acceptable choices for MAT in pregnancy and should help the patient weigh risks and benefits when deciding which medication is right for that patient and their neonate.

The First Steps to Healthy Babies service provided by Sanford in Bemidji, MN aims to help women have safe and healthy pregnancies and encourages sobriety with support services. Alyssa Bruning, RN-BSN, is a passionate case manager for the clinic. In a personal interview with Alyssa, she explained that since March 2017, the clinic has been providing MAT for opioid-addicted pregnant women. As of the summer of 2018, treatment is provided for family members as well. The clinic uses buprenorphine exclusively for its pregnant patients on MAT, as there is

less “red tape” involved in starting treatment. Alyssa explains that training to prescribe the drug is much shorter and simpler than that of methadone. Furthermore, buprenorphine is safer, and she finds that neonatal length of stay is shorter than on babies exposed to methadone. Buprenorphine is more easily covered by insurance as well. At the clinic, the case managers focus on education of NAS, and non-pharmacologic methods mothers can use to soothe their babies during their withdrawal. They also successfully educated and trained obstetric nurses on the Finnegan NAS assessment, as well as reducing stigma and judgement toward the opiate addicted mothers. Alyssa has found that more empathetic patient care leads to more successful recoveries.

Alyssa says that the clinic feels affirmed in their policy and procedure, as it closely follows The American College of Obstetricians and Gynecologists (ACOG) 2016 guidelines. Primary care providers should be familiar with these guidelines, especially affirming the universal screening for drug abuse in pregnant women. She says it is so important to allow the woman to have the opportunity to self-disclose. The response of the provider should be proper case management and continuing to allow the patient to obtain proper prenatal care, though most of their patients are still coming from self-referral. Unfortunately, many women are afraid to disclose their drug use, and worry that child protective services will “take their baby away”. One of the missions of the clinic is to do just the opposite. They have seen a significant increase in the number of mothers who undergo MAT during pregnancy and are able to return home with their infant. Many mothers who never receive treatment do not get proper prenatal care, and often child protective services do get involved when the mother shows up in labor and withdrawal (A. Bruning, personal communication, December 11, 2018).

Proper education on OUD in pregnancy should be offered to all healthcare providers. Since stigma still exists with MAT, providers should be given the tools to screen, refer, and care for pregnant mothers with OUD. Withdrawal during pregnancy should be discouraged, and personal judgements withheld.

Prevention is also key in this problem. When prescribers more responsibly choose patients that need opiates for pain control, there will be a major impact on the number of patients that become addicted. This is shown in the decline of opioid prescribing nationally. After much awareness has been brought to the opioid crisis, the CDC shows that from 2012 to 2017 the rate declined to the lowest it had been in more than ten years, with 191 million opioid prescriptions written, a rate of 58.7 per 100 people. Unfortunately, hotspots still exist. In 2017, the North Dakota counties of Ramsey, Adams, and Foster had opioid prescription rates per 100 persons of 108.6, 100.8, and 88.7, respectively. These numbers are improved compared to 2007 though, as Ramsey's prescription rate was 165.79 and Adams' at 125.39 per 100 persons (Foster county did not report). As a state, North Dakota has improved its prescribing rates. The prescribing rate was 41.5 per 100 persons in 2017, compared to 56 per 100 persons in 2006 (U.S. Opioid Prescribing Rate Maps, 2018). When both providers and patients of the healthcare in the US and North Dakota are informed and educated, the opiate crisis can be tackled.

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