DRUG & ALCOHOL FINDINGS *Review analysis*

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Buprenorphine versus methadone for opioid dependence in pregnancy.

Noormohammadi A., Forinash A., Yancey A. et al.

Annals of Pharmacotherapy: 2016, 50(8), p. 666–672.

Among pregnant women, substitute prescribing is preferable to continued illicit opioid use and supervised withdrawal. Buprenorphine has different properties to the dominant treatment option methadone, but both stand to improve pregnancy and infant outcomes.

SUMMARY In pregnant women dependent on opioids, the continuous cycle of intoxication and withdrawal can have adverse effects on their pregnancy as well as their general health. For example, during opioid use risks to the foetus include depleted levels of oxygen, increased acidity in the body, slow or halted growth and stillbirth, and during withdrawal from opioids, effects can include miscarriage and premature labour.

Opioid use while pregnant is also associated with 'neonatal abstinence syndrome', where after birth infants exposed to drugs during pregnancy experience withdrawal. Symptoms include wakefulness, irritability, tremors, rigidity and tension in the muscles, a very high fever, diarrhoea, weight loss, seizures, sneezing, and skin mottling. As these symptoms can also indicate other illnesses, the infant's urine and meconium can be tested to confirm the presence of opioids before diagnosing neonatal abstinence syndrome.

The featured paper compared the maternal and infant safety outcomes of two opioid substitution therapies (methadone and buprenorphine) in populations of pregnant women dependent on opioids. The aim of these treatments is to maintain a level of opioids in the body that prevent cravings and symptoms of withdrawal. This approach, as opposed to supervised withdrawal from opioids, is recommended during pregnancy by the American College of Obstetricians and Gynecologists.

Key points
From summary and commentary

The mainstay of treatment for pregnant women dependent on opioids is opioid substitution therapy, and specifically methadone. However, emerging evidence supports the use of buprenorphine.

The featured paper compared the maternal and infant safety outcomes of methadone and buprenorphine in populations of pregnant women.

Based on a review of five studies, buprenorphine significantly improved on or had similar outcomes to methadone on a range of measures.

Buprenorphine is available in two formulations – as a single agent and combined with naloxone. Only buprenorphine is considered suitable during pregnancy because of concerns about prenatal exposure to naloxone and its risk of inducing immediate foetal withdrawal.

Over the search period 2005–2016 there were a limited number of English-language studies published testing the efficacy and safety of opioid substitution therapies with pregnant women. These included five critical studies – four of which involved randomly allocating patients to methadone versus buprenorphine treatment, and one of which looked back at the data of patients treated with methadone versus buprenorphine. [The following summary also draws details from the source papers.]

Main findings

Buprenorphine significantly bettered or had similar outcomes to methadone on a range of measures including gestational period at delivery, length of infant hospital stay, development of neonatal abstinence syndrome, and total amount of morphine needed to treat neonatal abstinence syndrome (indicative of the severity of withdrawal the infants were experiencing).

In Austria, 18 women (24–29 weeks pregnant on enrolment) were maintained on oral slow-release morphine while being screened for the study, after which they were randomly allocated to receive either an oral methadone solution (40–100 mg/day) or buprenorphine tablets (8–24 mg/day) and admitted to the clinic for a minimum of three days in order for them to have access to 24-hour care. Food vouchers were given as compensation (to a maximum equivalent of €1,000 for 20 weeks' participation) to patients who completed all assessments regardless of their medication use or non-use. Six patients in the methadone group and eight in the buprenorphine group completed the trial. Methadone was significantly more effective

than buprenorphine based on maternal urine samples testing positive for the presence of opioids. However, there was no difference in relation to birth weight, infant health scores, or the average cumulative dose required to manage neonatal abstinence syndrome.

In the United States the PROMISE trial evaluated the safety and efficacy of methadone (flexible dosing of 20–100 mg) and buprenorphine (4–24 mg) with 30 patients who were 16–30 weeks pregnant on enrolment. More patients in the methadone group (11 patients, 73%) than the buprenorphine group (nine patients, 60%) completed the trial. There was a significantly greater reduction in the length of hospital stay for infants in the buprenorphine group, but no significant difference in outcomes related to peak score for neonatal abstinence syndrome or treatment for neonatal abstinence syndrome. This study laid the groundwork for the MOTHER trial (see below).

The MOTHER trial, which took place in the United States, Austria and Canada, extended the eligibility criteria of the PROMISE study to include women from six weeks (as opposed to 16 weeks) pregnant. Before being randomly allocated to receive either methadone (87 mg plus or minus 22 mg) or buprenorphine (14 mg plus or minus 6 mg), 175 patients were stabilised with rapid-release morphine on an inpatient basis. Higher numbers of patients dropped out of the buprenorphine group than the methadone group (28 versus 16), and of these patients a higher proportion said they were dissatisfied with their medication (71% versus 13%). There was no significant difference between methadone- or buprenorphine-exposed infants requiring treatment for neonatal abstinence syndrome or in their peak neonatal abstinence syndrome scores. A significant difference in the total amount of morphine needed for the treatment of neonatal abstinence syndrome was seen, with buprenorphine-exposed infants receiving 89% less. This group also had a significantly greater reduction in length of hospital stay and spent significantly less time in the hospital receiving medications for neonatal abstinence syndrome. The groups did not differ on serious maternal or infant adverse events. However, patients treated with methadone had higher rates of overall non-serious maternal adverse effects – specifically, maternal cardiovascular events such as rapid or slow heart rate, and hypotension or hypertension. Both the PROMISE and MOTHER studies found that buprenorphine is a safe and effective alternative to methadone in the treatment of opioid dependence during pregnancy.

To provide a real-world comparison, the Austrian site of the MOTHER trial compared patients receiving methadone (average 64 mg) and buprenorphine (13 mg) to those receiving the same treatments via standard care (an average of 74 mg and 10 mg respectively). Unlike in previous studies, the latter group included patients with current benzodiazepine and alcohol use and serious medical illnesses (ie, more representative of the population using opioid maintenance therapy during pregnancy), and methadone or buprenorphine was selected on the basis of medical judgment, previous experiences, and the patient's preference. In total 114 participants were included: 77 standard care (51 methadone and 26 buprenorphine, with no drop-outs) and 37 enrolled in the MOTHER trial (19 methadone and 18 buprenorphine, four drop-outs, three because of dissatisfaction with buprenorphine). There was no significant difference between the two cohorts of patients in the proportion of infants needing treatment for neonatal abstinence syndrome (47 infants or 63% in standard care vs. 28 or 76% in the trial). Infants in both groups exposed to methadone experienced significantly longer lengths of stay and durations of treatment, and their mothers delivered significantly sooner. Infants exposed to buprenorphine had significantly higher birth weights.

A retrospective study in the United States analysed the outcomes of 62 patients treated with buprenorphine–naloxone (14 mg plus or minus 7 mg) versus methadone (77 mg plus or minus 36 mg) for at least 30 days before delivery. Compared to methadone, buprenorphine–naloxone significantly improved the number of infants requiring treatment for neonatal abstinence syndrome, peak neonatal abstinence syndrome score, duration of neonatal abstinence syndrome treatment, and gestational age at delivery. There were no differences in the amount of morphine used to treat neonatal abstinence syndrome, hospital length of stay, birth weight, head circumference, neonatal length, preterm delivery, infant health scores, type of delivery, maternal weight gain, or use of analgesia during labour.

The authors' conclusions

Methadone remains the dominant opioid substitution therapy. While there is a growing body of evidence indicating that buprenorphine could be an equivalent option, larger studies would be needed to fully evaluate the safety and potential advantages of buprenorphine over methadone in obstetric populations.

Neither methadone nor buprenorphine are associated with major adverse consequences during pregnancy, although there are a limited number of published studies testing their effectiveness and safety, and even fewer involving their use during the first trimester (0–12 weeks). According to a small set of studies, buprenorphine may have a more favourable adverse event profile overall, including fewer drug-related interactions. However, in one study in particular, patients initially had higher dissatisfaction with buprenorphine. This finding could also be expected in real-life settings due to the longer induction phase of buprenorphine, its lower maximum potency, and the need for patients to be in mild to moderate withdrawal when initiating therapy.

Before starting treatment with either methadone or buprenorphine a number of factors need to be considered, including the patient's preference, previous experience, and access to maintenance therapy (as the requirements for providing methadone and buprenorphine can differ). It is important to ensure that patients are provided not only maintenance drug therapy but support to increase the

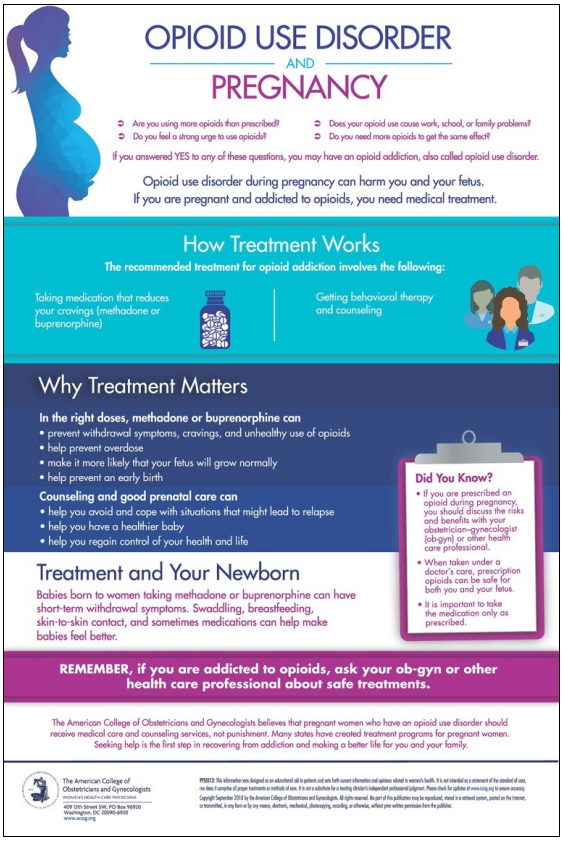
rate of success, as well as routine obstetric care.

There are contraindications around naloxone use in pregnancy, and consequently the combination treatment buprenorphine–naloxone is not recommended. However, in one study this formulation significantly improved neonatal outcomes compared with methadone treatment, and seemingly had an efficacy profile similar to that of single-agent buprenorphine.

FINDINGS COMMENTARY Unlike alcohol, cocaine and benzodiazepines, opioid use during pregnancy does not cause birth defects or damage foetal cells. However, fluctuating levels of opioids in the mother's blood can lead to withdrawal symptoms or overdose in the foetus, and those continuing to inject are at heightened risk of medical complications such as infectious diseases, endocarditis, abscesses, and sexually transmitted diseases.

Methadone and buprenorphine are effective treatments designated by the World Health Organization as essential medicines in the management of opioid dependence. While methadone is a 'full opiate agonist', meaning it produces greater opiate-type effects the higher the dose, buprenorphine is only a 'partial opiate agonist', creating a 'ceiling' of opiate-type effects – limiting the respiratory depression typically responsible for overdose deaths and attenuating the effect of 'on top' heroin use.

The featured review compared the impact of methadone and buprenorphine among women who were enrolled in the studies when between six and 30 weeks pregnant. It was not a requirement for constituent studies to have control groups where patients received no treatment or received supervised withdrawal from opioids – understandable as the former would be unethical and the latter against the recommendations of authoritative bodies including the American College of Obstetricians and Gynecologists (▸ educational aid). The implication of this design was that studies could not make pronouncements on the overall effectiveness of methadone or the overall effectiveness of buprenorphine, but rather their relative effectiveness.



An educational aid for patients in the United States, published in 2018 by the American College of Obstetricians and Gynecologists

Based on the studies identified, there was evidence that buprenorphine could be considered an equivalent option to methadone for use in pregnancy. However, the authors observed that methadone remains the dominant treatment and larger studies are still needed to fully evaluate buprenorphine's safety and potential advantages over methadone in obstetric populations.

In 2014, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published "Pregnancy and opioid use: strategies for treatment" – an overview of the effectiveness of opioid substitution therapies, either alone or in combination with psychosocial interventions. The findings were based on three studies included in the featured review, and one additional study comparing methadone with slow-release morphine. EMCDDA researchers found that while methadone seemed superior in retaining patients in treatment, buprenorphine was associated with less severe neonatal abstinence syndrome and higher birth weight. Echoing the calls in the featured study for further research, they concluded:

> *"Many questions remain unanswered, such as which is the most effective drug treatment and at what dosage, what is the most appropriate type of setting and, especially, whether or not it is useful to associate any type of psychosocial intervention to pharmacological treatment."*

It is not uncommon for pregnant women to be excluded from clinical trials in general, and of those examining patient outcomes from methadone versus buprenorphine, very few have focused on or reported on pregnant women. A search for literature over an eleven-year period up to 2016 yielded only five studies (one of which did not meet the scientific 'gold standard' of a randomised trial). Cognisant of the limited adequacy of the evidence base for treating pregnant women with medication, and the way that the response to treatment can be complicated by overlapping problems, a team from the Medical University of Vienna sought to

develop recommendations to improve patient management from conception to postnatal follow-up by synthesising available research along with their own clinical experience. Broadly their advice was that in the short and longer term, mother and child do best if multi-disciplinary treatment is initiated as soon as possible, maintenance prescribing is permitted, and there is regular monitoring. Around the same time, another team provided a North American perspective and much more detailed guidance on opioid maintenance therapies – covering induction, stabilisation, preventing and managing relapse, medication during labour and delivery, pain relief, breastfeeding, the interactions of methadone and buprenorphine with other medications, and managing psychiatric conditions. This guidance concluded that "the advent of buprenorphine has brought both a new treatment option and unique challenges to treatment, not only in terms of dose induction and pain management but also the need for rational decisions about whether methadone or buprenorphine may be most appropriate for a given clinical situation."

British addiction treatment guidelines agree with the reviewers that substitute prescribing is preferable to continued illicit substance use:

> *"Substitute prescribing can occur at any time in pregnancy and carries a lower risk than continuing illicit use. Women whose babies were exposed to methadone and illicit drugs during pregnancy delivered earlier and had more severe neonatal withdrawal than those who were on methadone only… Substitute prescribing has the advantage of allowing engagement and therefore identification of health and social needs, as well as offering the opportunity for brief interventions and advice to improve outcomes."*
>
> *"The research evidence demonstrates no difference in adverse effects between methadone and buprenorphine with both having no adverse effects on the pregnancy or neonatal outcomes, with incidence of [neonatal abstinence syndrome] similar to methadone exposure… However, there is some evidence that buprenorphine use results in [neonatal abstinence syndrome] of lower severity. Therefore, in a pregnant woman who is informed of the risks it is reasonable to allow her to remain on methadone or buprenorphine. Transfer to buprenorphine during pregnancy is not advised because of the risk of precipitated withdrawal and the risk of inducing withdrawal in the foetus. If detoxification is unsuccessful and the patient's drug use becomes uncontrolled at any stage of pregnancy, reduction should be stopped or the opioid dose increased until stability is regained."*

Culturally, dependence on drugs carries a stigma and shame over and above most other health problems. This stigma and shame is compounded for pregnant women, and can have a knock-on impact on the substance use treatment they feel able to access, the treatment choices they make, *and* their engagement with basic antenatal care. For UK professionals, NICE guidelines support the provision of healthcare for pregnant women with co-occurring complex issues such as drinking and drug use problems, and this includes advice for overcoming barriers to care, for example by: (1) ensuring that the attitudes of staff do not prevent women from using services; (2) addressing women's fears about the involvement of children's services and potential removal of their child; and (3) addressing women's feelings of guilt about their substance use and the potential effects on their baby.

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