DRUG & ALCOHOL FINDINGS *Review analysis*

This entry is our analysis of a review or synthesis of research findings considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original review was not published by Findings; click Title to order a copy. The summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.





## Maintenance agonist treatments for opiate dependent pregnant women.

**Minozzi S., Amato L., Bellisario C. et al.**

**Cochrane Database of Systematic Reviews: 2013, 12, Art. No.: CD006318.**



*Is it better to prescribe pregnant opioid-dependent women methadone, buprenorphine or oral morphine? Just four randomised trials have addressed this issue and their findings are inconclusive, suggesting greater holding power for methadone but less severe neonatal withdrawal with buprenorphine.*

**SUMMARY** *[An updated version of the featured review was published in 2020. The authors found no new studies to incorporate, and consequently did not change their conclusions. However, important information has been added to the Drug and Alcohol Findings commentary (below) in order to set the findings in context.]*

Heroin crosses the placenta and pregnant, opiate-dependent women experience a six-fold increase in maternal obstetric complications such as low birth weight, toxaemia, third-trimester bleeding, malpresentation, puerperal morbidity, foetal distress and meconium aspiration. Neonatal complications include withdrawal, postnatal growth deficiency, microcephaly, neuro-behavioural problems, increased neonatal mortality and sudden infant death syndrome.

Among women and babies facing these risks, this review aimed to assess the effectiveness of treatments for the expectant mother as methadone maintenance compared to no intervention, or compared to another pharmacological or psychosocial intervention. Impacts considered were child health, neonatal mortality, retaining pregnant women in treatment, and reducing their substance use. Studies had to have randomly allocated opiate-dependent pregnant women to a maintenance treatment versus an alternative procedure.

Four such trials were found involving 271 women. Two involved outpatients in Austria, one inpatients in the USA, and one was an international study conducted in Austria, Canada and the USA. In all the trials the alternative procedure was itself a different maintenance treatment. Three trials compared methadone with buprenorphine and one methadone with oral, slow-release morphine. All the included studies ended immediately after the baby was born.

**Key points**
**From summary and commentary**

This review aimed to assess the effectiveness of maintenance treatments such as methadone maintenance for the treatment of pregnant women and the welfare of their babies.

Four trials were found which randomly allocated women to maintenance versus alternative procedures. Three compared methadone and buprenorphine.

Evidence was insufficient say which treatment is superior overall or to conclude they are equivalent.

However, while methadone seems superior at retaining patients in treatment, buprenorphine seems to lead to less severe neonatal abstinence syndromes.

## Main findings

Across the three trials which compared methadone with buprenorphine, retention was best when women had been offered methadone; the proportion of women who dropped out of treatment with methadone was about two-thirds that of women allocated to buprenorphine. However, across the two studies which provided this data, there was no statistically significant difference in the proportions of women who continued to use their primary problem drug, though the results favoured buprenorphine. Across the two studies whose data could be pooled, birth weight was higher in the buprenorphine group; the third study found no statistically significant difference. APGAR scores indicative of neonatal health did not significantly differ in the two studies to report this. Many measures were used in the studies to assess neonatal abstinence syndrome. The number of newborns treated for neonatal abstinence syndrome, the most critical outcome, did not differ significantly between babies born to mothers allocated to methadone versus buprenorphine. Only one study reported side effects; for the mothers there was no statistically significant difference but newborns in the buprenorphine group suffered significantly fewer serious side effects.

The single study to compare methadone with oral, slow-release morphine found no drop-out in either group. Mothers were over twice as likely to be abstinent from heroin if allocated to morphine. No side effects were reported for the mother, whereas one child in the methadone group had central apnoea (a temporary interruption in breathing) and one child in the morphine group had obstructive apnoea.

## The authors' conclusions

There were insufficient significant differences between methadone and buprenorphine or slow-release morphine to permit conclusions about which treatment is superior to another across all relevant outcomes. Even though a multi-centre, international trial with 175 pregnant women has recently been completed and included in this review, the body of evidence is still too small to permit the opposite conclusion – that the treatments are equivalent. However, while methadone seems superior in terms of retaining patients in treatment, buprenorphine seems to lead to less severe neonatal abstinence syndromes. No severe complications were noted.

The major flaw in the studies was that three out of four had a high drop-out rate (30% to 40%) and this differed between the women allocated to maintenance versus those allocated to alternative procedures.

**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, and abscesses. The featured review found few differences in newborn or maternal outcomes for pregnant women who were prescribed methadone, buprenorphine or oral slow-release morphine for their opioid dependence from an average gestational age of 23 weeks to birth. While methadone seemed superior in terms of retaining patients in treatment, buprenorphine seemed to lead to less severe neonatal abstinence syndrome. When the review was repeated in 2020, the findings and conclusions remained unchanged. With no additional studies to analyse, the reviewers maintained that there was insufficient evidence to draw conclusions about either the superiority or equivalence of different maintenance treatments among pregnant women with opioid dependence. However, for clinicians, UK treatment guidelines say the broad direction of travel is clear – 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. …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."*

### A 'birds eye' view of the evidence base

Many questions remained unanswered according to the 2013 and 2020 appraisals of the evidence base, including:

> *Which is the most effective drug treatment and at what dosage?*
>
> *What is the most appropriate type of setting?*
>
> *Is it useful to combine any type of psychosocial intervention with pharmacological treatment?*

The pool of research was limited because of the relative neglect of pregnant women in research, but also because of the parameters the reviewers set for inclusion. Four studies were analysed: three comparing methadone with buprenorphine (223 participants); and one comparing methadone with oral slow-release morphine (48 participants). Many others were excluded because they did not meet the 'gold standard' randomised controlled trial format for determining that an intervention *caused* the desired changes. This, for example, prohibited studies that retrospectively analysed the outcomes of women treated with opioid substitutes during pregnancy (unfold the supplementary text to see an example).

> Close supplementary text
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> A retrospective study in the United States analysed the outcomes of 62 patients prescribed buprenorphine–naloxone (a different formulation to buprenorphine alone) versus methadone 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, however, no differences between the two medications 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.
>
> This study showed an example of the results of opioid-substitute prescribing in real-life clinical practice, as opposed to practice manipulated for the purposes of research. However, it did not necessarily represent *typical* practice outside of that US treatment setting or *recommended* clinical practice. A Canadian review of the primary care management of opioid use disorders reported that pregnant women taking buprenorphine–naloxone should be switched to buprenorphine alone without naloxone because the safety of naloxone in pregnancy has not been confirmed, although preliminary evidence has found that it is safe (1 2 3 4). Furthermore, the study focused on the outcomes of the child versus the mother, which the authors of the Canadian review put in the following context: "…Neonatal abstinence syndrome is treatable and is not associated with long-term consequences. In contrast, treatment dropout can have devastating consequences, such as loss of child custody or death from overdose."
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> Close supplementary text

There is a cogent argument for applying this strict criterion. Without randomising participants to an intervention group versus a control group, the reviewers would not have been able to rule out the prospect that factors outside of treatment influenced the outcomes. For example, participants may have had different levels of motivation, readiness to change, self-efficacy, and access to resources. Randomisation helps to limit the effect that differences in participants will have on the outcomes. However, random allocation also represents a major departure from prescribing under real-life circumstances, and therefore the findings may not reflect the potential of buprenorphine, methadone or oral morphine if they had been *chosen* by patients and clinicians – important because there are critical differences between the two main options. Buprenorphine works in a different way to methadone, setting a 'ceiling' on opiate-type effects. This will not appeal to everyone who is dependent on opioids. People wanting to divorce themselves from opioids in general (ie, to do without opiate-type effects) are more likely to choose buprenorphine. This perhaps inconvenient dimension for researchers of patients having a strong preference one way or another was hinted at in data about the rate of drop-out in different treatment groups.

There was a high rate of dropout in studies comparing methadone and buprenorphine. While the researchers found that, overall, there was "probably little or no difference [between the two groups] in the number of women who dropped out of treatment", the MOTHER trial *did* find a marked and statistically significant difference – 18% in the methadone group discontinued treatment before birth versus 33% in the buprenorphine group. Furthermore, dissatisfaction with the study medication was reported as the reason for discontinuation by 71% of participants in the buprenorphine group, compared with only 13% of those in the methadone group.

Greater patient dissatisfaction with buprenorphine than with methadone has also been reported in trials with non-pregnant patients. Contextualising the greater 'holding power' of methadone than buprenorphine, authors of a 2014 Cochrane review which excluded pregnant women said:

> *"…It may well be that buprenorphine, being a partial agonist, does not retain people because it does not have a full opioid effect and is less satisfying to those allocated to it. Another possibility is that people in the initial stages of dosing who have recently ingested heroin suffer a mild withdrawal syndrome by virtue of buprenorphine (a partial agonist) displacing heroin (a full agonist) from opioid receptors in the central nervous system, and this mild withdrawal may lead to*

*leaving treatment. A further possibility is that buprenorphine is simply easier to withdraw from and, on that basis, those using it are more at liberty to leave treatment without the severe withdrawal syndrome that can accompany methadone withdrawal."*

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."

On this decision, UK treatment guidelines say the following:

*"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.

Last revised 22 January 2021. First uploaded 16 April 2015



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