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Maintenance agonist treatments for opiate dependent pregnant women (Review)
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Maintenance agonist treatments for opiate dependent pregnant women

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ABSTRACT

Background

The prevalence of opiate use among pregnant women ranges from 1% to 2% to as much as 21%. Heroin crosses the placenta and pregnant opiate dependent women experience a six fold increase in maternal obstetric complications such as low birth weight, toxaemia, 3rd trimester bleeding, malpresentation, puerperal morbidity, fetal distress and meconium aspiration. Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neurobehavioral problems, increased neonatal mortality and a 74-fold increase in sudden infant death syndrome.

Objectives

To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions on child health status, neonatal mortality, retaining pregnant women in treatment, and reducing use of substances

Search strategy

We searched Cochrane Drugs and Alcohol Group’ Register of Trials (June 2007), PubMed (1966 - June 2007), CINAHL (1982- June 2007), reference lists of relevant papers, sources of ongoing trials, conference proceedings, National focal points for drug research. Authors of included studies and experts in the field were contacted.

Selection criteria

Randomised controlled trials enrolling opiate dependent pregnant women

Data collection and analysis

The authors assessed independently the studies for inclusion and methodological quality. Doubts were solved by discussion.

Main results

We found three trials with 96 pregnant women. Two compared methadone with buprenorphine and one methadone with oral slow morphine. For the women there was no difference in drop out rate RR 1.00 (95% CI 0.41 to 2.44) and use of primary substance RR
2.50 (95% CI 0.11 to 54.87) between methadone and buprenorphine, whereas oral slow morphine seemed superior to methadone in abstaining women from the use of heroin RR 2.40 (95% CI 1.00 to 5.77)

For the newborns in one trial buprenorphine performed better than methadone for birth weight WMD -530 gr (95% CI -662 to -397), this result is not confirmed in the other trial. For the APGAR score both studies didn't find significant difference. No differences for NAS measures used. Comparing methadone with oral slow morphine no differences for birth weight and mean duration of NAS. The APGAR score wasn't considered.

Authors' conclusions

We didn't find any significant difference between the drugs compared both for mother and for child outcomes; the trials retrieved were too few and the sample size too small to make firm conclusion about the superiority of one treatment over another. There is an urgent need of big randomised controlled trials.

**Plain Language Summary**

Some women continue to use opiates when they are pregnant. Yet heroin readily crosses the placenta. Opiate dependent women experience a six-fold increase in maternal obstetric complications and give birth to low-weight babies. The newborn may experience narcotic withdrawal (neonatal abstinence syndrome), have development problems, increased neonatal mortality and a 74-fold increased risk of sudden infant death syndrome. Maintenance treatment with methadone provides a steady concentration of opiate in the pregnant woman’s blood and so prevents the adverse effects on the fetus of repeated withdrawals. Buprenorphine is also used. They reduce illicit drug use, improve compliance with obstetric care and improve birth weight but are still associated with neonatal abstinence syndrome. The present review found few differences in newborn or maternal outcomes for pregnant opiate-addicted women who were maintained on methadone, buprenorphine or oral slow morphine from a mean gestational age of 23 weeks to delivery. Only three randomised controlled trials satisfied the criteria for the review, two from Austria (outpatients) and one from the USA (inpatients). The trials continued for 15 to 18 weeks. Two compared methadone with buprenorphine (48 participants) and one compared methadone with oral slow morphine (48 participants). The number of women who dropped out from treatment and the use of primary substance appeared to be the same for methadone and buprenorphine. Oral slow morphine seemed superior to methadone for the number of women who used heroin in their third trimester but without a clear improvement in infant birth weight or duration of neonatal abstinence syndrome.

The number of participants in the trials was very small and may not be sufficient to detect differences. Only one study reported on the number of cigarettes the women smoked, a mean of 29 cigarettes per day at enrolment and 14 cigarettes per day at delivery. All the included studies ended immediately after the baby was born. No severe complications were noted.
BACKGROUND

The estimate prevalence of opiate use among pregnant women ranges from 1% to 2% to peak at 21% (Brown 1998), the availability of more recent data on prevalence is extremely limited: the sources searched (EMCDDA, Office of National Drug Control Policy (ONDCP), United Nations Office on Drug and Crime - World Drug Report 2007) do not report details of opiate use by sub-groups of population; the most recent data are from the 2006 National Survey on Drug Use and Health (http://oas.samhsa.gov/nhsda) reporting that in the USA the 4% of pregnant women (aged 15-44) reported use of illicit drugs, not specifying the type of drug.

Heroin readily crosses placenta and untreated opiate dependence in pregnant women is associated with many environmental and medical factors that contribute to poor maternal and child outcomes, and cause a six fold increase in obstetric complications such as low birth weight, toxaemia, 3rd trimester bleeding, malpresentation, puerperal morbidity, foetal distress and meconium aspiration. Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neurobehavioral problems, increase in neonatal mortality and a 74 fold increase in sudden infant death syndrome (Dattel 1990; Fajemirokun 2006; Ludlow 2004).

All of the commonly used opioids, including heroin and methadone, can produce neonatal abstinence syndrome in infants born to opiate dependent mothers. The neonatal abstinence syndrome combines all the symptoms of the adult withdrawal syndrome with irritability, poorly coordinated sucking and, in the most severe cases, seizures and death. (Kaltenbach 1998).

Since the early 1970, treatment with methadone has been the standard of care for pregnant women addicted to opiates. Despite its ability to induce fetal dependence and withdrawal, maintenance treatment provides a steady concentration in maternal blood plasma and thus prevent the adverse effects of repeated withdrawal on the fetus (Jarvis 1994).

Methadone maintenance given during pregnancy reduces maternal illicit opiate use and fetal exposure, enhances compliance with obstetrical care, and is associated with improved neonatal outcomes like heavier birth weight (Fajemirokun 2006; Kaltenbach 1998). Additional benefits include a potential reduction in drug-seeking behaviours, including commercial sex to gain money to raise money for drug. This reduction may decrease the woman’s chance of acquiring sexually transmitted diseases such as human immunodeficiency virus (HIV) and hepatitis. For all these reasons, methadone treatment has become the “gold standard” for the management of pregnant heroin users (NIH 1998), and many guidelines in UK (UK Guidelines 2007), USA (CSAT 2005) and Australia (Dunlop 2003) support the use of methadone during pregnancy.

Earlier studies were performed in centres which offered methadone and comprehensive services, including obstetric, health, psychiatric care, individual, group and family therapy. Consequently, is difficult valuating the results of these studies to distinguish the benefits of methadone itself from measures of social and obstetric care (Wang 1999).

Buprenorphine also has been administered to opioid dependent pregnant women as maintenance treatment. Placental transfer of buprenorphine may be less than methadone, reducing fetal exposure and development of neonatal abstinence syndrome (Rayburn 2004). The available clinical literature suggests that buprenorphine maintenance is associated with reduced maternal illicit opiate use and fetal exposure, enhanced compliance with obstetrical care, and improved neonatal outcomes like heavier birth weight (Johnson 2003; Lejune 2006).

The Cochrane Drugs and Alcohol Group has conducted several systematic reviews on maintenance treatment: methadone (Faggiano 2003; Martick 2003 a), heroin (Ferri 2005), LAAM (Clark 2002), buprenorphine (Martick 2008), naltrexone (Minozzi 2006), psychosocial treatment alone (Mayet 2005) and psychosocial treatment combined with maintenance treatment (Amato 2004) but all these reviews do not include studies on pregnant opiate dependent women.

In the published literature we found two narrative reviews which discusses risk and benefits of maintenance treatment (Rayburn 2004; Wang 1999); none of them specified the inclusion criteria of the studies, described the studies and the results in a very generic way and do not draw firm conclusion about the superiority of one drug treatment over another. We also found two out of date reviews, both including observational studies in their meta analysis, which assessed the relationship between maternal opiate use and infant birth weight (Hulse 1997); eighteen studies included and neonatal mortality (Hulse 1998), seven studies included. The risk estimate for infant low birth weight was lower for women receiving methadone compared to heroin users: RR 1.36 (95% CI 0.83 to 2.2) and RR 4.61 (95% CI 2.78 to 7.65) respectively whereas the risk of neonatal mortality did not differ significantly: RR 1.47 (95% CI 0.88 to 2.33) for heroin and RR 1.75 (95% CI 0.60 to 4.59) for methadone.

Considering that few studies will be retrieved on opiate pregnant women and that the majority will be on methadone treatment alone or in combination with psychosocial interventions, we choose to include in our review any type of maintenance treatment alone or in combination with psychosocial intervention. The studies on different pharmacologic treatments will be analysed separately.

OBJECTIVES
To assess the effectiveness of any opioid agonist maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions on child health status, neonatal mortality, retaining pregnant women in treatment, and reducing the use of substances

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**
Randomised controlled trials and quasi randomised controlled trials enrolling pregnant women. Studies started after the delivery will be excluded.

**Types of participants**
Opiate addicts pregnant women of any age irrespective of duration of pregnancy. No restriction for women with physical or psychological illness

**Types of interventions**

*Experimental intervention:*
Any pharmacological interventions (methadone, buprenorphine, LAAM, heroin, morphine, codeine, alone or combined with psychosocial intervention for maintenance treatment

*Control intervention:*
No intervention,
Other pharmacological interventions
Psychosocial interventions alone

**Types of outcome measures**

**Primary outcomes**

*For the woman*
(1) drop out from treatment as measured by:
- number of women dropped out at the end of the intervention

(2) use of primary substance as measured by:
- number of women using heroin at the end of treatment confirmed by urine analysis

(3) results at follow up as measured by:
- number of women using heroin at the end of follow up (after the childbirth)
- drop out from treatment at the end of follow up (after the childbirth)

*For the child*
(4) health status measured as:
- birth weight
- APGAR score (Activity, Pulse, Grimace, Appearance, and Respiration score)
- Neonatal Abstinence Syndrome (NAS)
- prenatal and neonatal mortality

**Secondary outcomes:**
(5) any problem of pregnancy
(6) nicotine consumption
(7) use of other substances
(8) side effects for the mother
(9) side effects for the child

**Search methods for identification of studies**

**Electronic searches:**
Relevant trials were obtained from the following sources:
(1) Cochrane Drugs and Alcohol Group’ Register of Trials (June 2007)
(2) PubMed (from 1966 - June 2007)
(3) CINAHL (1982- June 2007)
We compiled detailed search strategies for each database searched to take account of differences in controlled vocabulary and syntax rules, see Appendix 1; Appendix 2; Appendix 3. There were no language or publication year restrictions.

**4) Additional searches**
We searched:
1) the reference lists of all relevant papers to identify further studies.
2) some of the main electronic sources of ongoing trials (National Research Register, meta-Register of Controlled Trials; Clinical Trials.gov, Agenzia Italiana del Farmaco)
3) conference proceedings likely to contain trials relevant to the review (College on Problems of Drug Dependence -CPDD)
4) National focal points for drug research (e.g., National Institute of Drug Abuse (NIDA), National Drug & Alcohol Research Centre (NDARC))
Authors of included studies and experts in the field in various countries were contacted to find out if they know any other published or unpublished controlled trials

**Data collection and analysis**

(1) **Study selection:**
One author (Minozzi) inspected the search hits by reading titles and abstracts. Each potentially relevant study located in the search have been obtained in full text and assessed for inclusion independently by three authors (Minozzi, Amato, Vecchi). Doubts have been solved by discussion between the authors.

(2) **Assessment of the methodological quality:**
Study quality have been assessed according to the criteria indicated in Cochrane Reviews Handbook 4.2 (Higgins 2005);
Two authors (Minozzi, Vecchi) assessed the included studies. Any doubt about how to rate the studies have been resolved by discussion between the authors.

Selection bias: empirical research has shown that lack of adequate allocation concealment is associated with bias (Chalmers 1993; Moher 1998; Moher 1999; Schulz 1995). Indeed, concealment has been found to be more important in preventing bias than other components of allocation, such as the generation of the allocation sequence.

Performance bias: systematic differences in the care provided to the participants in the comparison groups and the placebo effect could effectively take place in the addiction field. Blinding of providers avoids co intervention whereas blinding of participants avoids contamination, systematic differences in compliance, systematic differences in the placebo effect and detection bias.

Attrition bias: loss of follow up and drop out from the study is one of the bigger problem in the field of addiction; in fact the retention in treatment is very often the primary outcome measure in these trials; for these reason the information on people who left the study will not used as a validity criterion.

Detection bias: to keep blind the people who will assess outcomes is particularly important when subjective outcome measures are used; this is not the case for for mother outcomes, where the primary outcomes are the retention in treatment rate or the use of substances measured by Bioanalisis, but could be relevant for newborn outcomes, which are subjectively assessed by the physician.

Selection bias, performance bias and detection bias was assessed and rated as follow:

(1) Selection bias: allocation concealment
A: adequate allocation concealment, central randomizations (e.g. allocation by a central office unaware of subject characteristics), pre-numbered or coded identical bottles or containers which are administered serially to participants, drug prepared by the pharmacy, serially numbered, opaque, sealed envelopes, on-site computer system combined with allocations kept in a locked unreadable; computer file that can be accessed only after the characteristics of an enrolled participant have been entered or other description that contained elements convincing of concealment.;
B: unclear allocation concealment: when the authors either did not report an allocation concealment approach at all or report an approach that did not fall in the category A or C.
C: inadequate allocation concealment: alternation or reference to case numbers, dates of birth, day of the week. Any procedure that is entirely transparent before allocation, such as an open list of random numbers or other description that contained elements convincing of not concealment

(2) Performance bias: blinding of those providing and receiving the intervention
A: double blind
B: single blind (blinding of participants)
C: unclear
D: no blinding

(3) Detection bias: blinding of those who assessed outcomes
A: blinding assessment
B: unclear
C: un blinding assessment

Studies with adequate allocation concealment were classified as A: low risk of bias, studies with unclear allocation concealment were classified as B: moderate risk of bias and studies with inadequate allocation concealment were classified as C: high risk of bias

The methodological quality was not be used as a criterion for inclusion; we didn't find any class C study so we didn't perform a sensitivity analysis, either including or excluding the classes C ones from meta-analysis in order to assess the effect of the low quality studies

Data were extracted independently by two authors (Minozzi, Vecchi). Any disagreement was discussed.

Data synthesis:
Key findings were summarized narratively in the first instance and assessed for meta-analysis where possible. Dichotomous outcomes were analysed calculating the Relative risk (RR) for each trial with the uncertainty in each result being expressed by their confidence intervals. Continuous outcomes were analysed calculating the WMD or the SMD with 95%CI. For nicotine use we compared the difference of the mean number of cigarettes smoked from baseline to end of treatment in the experimental and control group. In case of missing standard deviation of the differences from baseline to the end of treatment, the standard deviation were imputed using the standard deviation of the mean at the end of treatment for each group. The outcome measures from the individual trials were combined through meta-analysis where possible (comparibility of intervention and outcomes between trials) using a fixed effect model unless there was significant heterogeneity, in which case a random effect model was used. A P-value of the chi-square test less than 0.05 indicates a significant heterogeneity.

We did not use data presented as number of positive urine tests over total number of tests in the experimental and control group as measure of substance abuse. This is because using tests instead of the participants as the unit of analysis violates the hypothesis of independence among observations. In fact, the results of tests done in each participant are not independent

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

We identified 75 reports, 64 were excluded on basis of title and abstract; 11 articles were retrieved in full text for more detailed evaluation, 8 of which were excluded, and 3 satisfied all the criteria to be included in the review.
We didn’t find any unpublished study. We wrote to the first authors of published studies. One replied. He confirmed that to his knowledge there are not unpublished trials and that the three articles included in this reviews are the only exiting randomised trials on pharmacotherapy for pregnant women. He gave us information about one ongoing randomised study. See Figure 1

For substantive descriptions of studies see 'Characteristics of Included studies' and 'Characteristics of excluded studies' tables.
Flow chart showing identification of included trials.

1. Potentially relevant references identified from Medline N=613
2. Potentially relevant references identified from Cinahl N=91
3. Potentially relevant references identified from CDBG Register N=33
4. References excluded on basis of title and abstract N=64
5. References retrieved for more detailed evaluation N=11
6. References excluded after reading N=8
7. References included in the review N=3
8. RCTs included in the meta-analysis N=3
Excluded studies

Eight studies did not meet the criteria for inclusion in this review. The grounds for exclusion were: study design not in the inclusion criteria: 6studies (Ebner 2007; Fisher 1998; Hulse 2004; Keiser-Marcus 2002; Gordon 2004; Laken 1997); type of participants not in the inclusion criteria (Jackson 2004), type of control intervention not in the inclusion criteria (Carroll 1995).

Included studies

Three studies with 96 participants met the inclusion criteria for this review.

Duration of trials:
The mean duration of the trials was 16.3 weeks (range 15 to 18 weeks), from a mean gestational age of 23 weeks to the delivery.

Treatment regimes and setting:
Two trials were conducted in Austria (Fischer 1999; Fischer 2006) and one in USA (Jones 2005).
Two trials compared methadone, dose between 40 and 100 mg/day with buprenorphine, dose between 8 and 24 mg/day (Fischer 2006, Jones 2005); one trial compared methadone (mean dose at delivery 53.48 mg.) with oral slow-morphine (mean dose at delivery 300.43 mg.) (Fischer 1999).
Two studies were conducted in outpatient setting (Fischer 1999, Fischer 2006) and one in inpatient (Jones 2005).

Participants:
96 opiate dependent pregnant women meeting DSM-IV criteria. Mean age 27.3 years. Mean gestational age: 23 weeks. Nicotine use during pregnancy was reported only in one trial (Fischer 1999) as mean number of cigarettes per day; it was 27.56 (SD 26.28) for the methadone group and 31.30 (SD 22.56) for the morphine group.

Rating instruments utilized in the studies:
All the included studies measured NAS using the Finnegan Score (Finnegan 1992).

Comparisons:
Comparison 01: methadone versus buprenorphine, two trials (Fischer 2006, Jones 2005) 48 participants
Comparison 02: methadone versus slow slow morphine: one trial (Fischer 1999), 48 participants

Risk of bias in included studies

All the studies were randomised controlled trials. The allocation concealment was adequate in two studies (Fischer 2006, Jones 2005) and unclear in the third study (Fischer 1999). Two studies were double blind (Fischer 2006, Jones 2005) and one was unblinded (Fischer 1999). The outcome assessor was blind in two studies (Fischer 2006, Jones 2005) and unblinded in the third study (Fischer 1999)

Sensitivity analysis excluding studies with inadequate allocation concealment was not performed because none of the included studies had an inadequate allocation concealment.

Effects of interventions

Comparison 01: Methadone versus buprenorphine

Meta-analysis was possible only for drop out rate and number of newborn treated for NAS because for the other outcomes the studies used different ways of reporting the results.

Primary outcomes

For the woman

1) drop out from treatment:
Number of participants who did not complete the treatment: Two studies, (Fischer 2006; Jones 2005). 48 participants, see Analysis 1.1, Relative Risk (RR) 1.00 (95% CI 0.41 to 2.44), the result is not statistically significant.

2) use of primary substance of abuse:
One trial (Jones 2005), 20 participants, see Analysis 1.2, outcome 02, RR 2.50 (95% CI 0.11 to 54.87), the result is not statistically significant.

3) results at follow up:
none of the studies considered this outcome

For the child

4) health status:
measured as:
birth weight: one study (Jones 2005) 19 participants (one mother in the buprenorphine group delivered twins, so twins data were not considered for this outcome because could be altered by twin status) see Analysis 1.3, WMD -530 gr (95% CI -662gr to -397gr), the results are in favour of buprenorphine. The second study (Fischer 2006) doesn't report data but refers that were not statistically significant difference in the birth weight between groups (mean: 2820 gr).

APGAR score (Activity, Pulse, Grimace, Appearance, and Respiration score) at 5 minutes: one study (Jones 2005) 21 participants see Analysis 1.4, WMD 0.00 (95% CI -0.11 to 0.11), the result is not statistically significant. The second study (Fischer 2006) doesn't report data but refers that were not statistically significant difference in the APGAR score between groups.

Neonatal Abstinence Syndrome (NAS): number of newborn treated for NAS, two studies (Fischer 2006; Jones 2005), 35 participants see Analysis 1.5 RR 1.28 (95% CI 0.58 to 2.85); the results are not statistically significant.

NAS peak score over all observation days: one study (Jones 2005), 21 participants: methadone: 4.9, buprenorphine: 6.8; the result is not statistically significant.

Mean duration of treatment for NAS: one study (Fischer 2006), 14 participants, see Analysis 1.6, WMD 0.50 (95% CI -1.84 to 2.84); the result is not statistically significant.

Total number of morphine drops administered: one study (Jones 2005) 21 participants: methadone:93.1, buprenorphine:23.6; the result is not statistically significant.

Mean cumulative dose of morphine required to manage NAS: one


Secondary outcomes

(5) any problem of pregnancy:
In one study (Fischer 2006) one woman in the methadone group required vacuum extraction due to a prolonged delivery. Three children were delivered prematurely in the methadone group and 2 in the buprenorphine group (one at week 34, one at week 35 and three at week 36). In the second study (Jones 2005) there was one preterm birth in the methadone group (week not reported).

(6) nicotine consumption:
No data were reported in both studies

(7) use of other substance of abuse
One study (Jones 2005) reported the percentage of urine positive for each substance during the study period for the methadone and buprenorphine group respectively: cocaine: 15.6% and 16.7%; benzodiazepines: 0.4%, 2.5%; amphetamine: 0%, 0%; marijuana 7.5%, 0%. The other study (Fischer 2006) reported the median number of urine samples positives for methadone and buprenorphine respectively: Cocaine: 0.00, 0.00; benzodiazepines: 7.82, 5.36.

(8) side effects for the mother:
No side effects for the mothers were reported.

(9) side effect for the child:
No side effects for the children were reported in both studies.

Comparison 02: Methadone versus oral slow morphine

Primary outcomes

For the woman

(1) drop out from treatment:
There were no participants drop out in both groups.

(2) use of substance:
Number of participants who used heroin in the third trimester: one study (Fischer 1999), 48 participants, see Analysis 2.1, RR (fixed) 2.40 (95% CI 1.00 to 5.77); the results are in favour of oral slow morphine

(3) results at follow up:
The study did not consider this outcome

For the child

(4) health status measured as:

DISCUSSION

We found few differences in neonatal or maternal outcome in women who received methadone compared to either buprenorphine or oral slow morphine. Only three trials with 96 pregnant women satisfied the criteria to be included in the review. Two (Fischer 2006; Jones 2005) compared methadone with buprenorphine (48 participants) and one (Fischer 1999) compared methadone with oral slow morphine (48 participants).
For the women there was no difference in drop out rate and use of primary substance between methadone and buprenorphine, whereas oral slow morphine seemed superior to methadone in abstaining women from the use of heroin during pregnancy.

For the newborns in one trial buprenorphine seemed better than methadone for birth weight, but this result is not confirmed in the other trial. For the APGAR score both studies which compared methadone with buprenorphine didn't find significant difference. For NAS none of measures used by studies found a statistically significant difference between the two treatments.

The study which compares methadone with oral slow morphine didn't find any statistically significant difference for birth weight and mean duration of NAS. The APGAR score wasn't considered by the study.

The difficulty of determining whether opioid substitution is associated with better outcome for the newborns always needs to be considered in relation to the direct effects of cigarette smoking. Only one study (Fischer 1999) reported data on cigarette consumption at the start of the study and at delivery. Women smoked a mean of 29 cigarettes per day at enrolment in the study and a mean of 14 cigarettes per day at delivery. There was no statistically significant difference between groups in the reduction of cigarettes smoked. This seems to be a relevant outcome not considered by the majority of the included studies. The level of nicotine exposure during pregnancy does affect birth weight and could affect NAS.

The methodological quality of included studies is good for the two studies comparing methadone with buprenorphine whereas the study which compares methadone with morphine has some methodological flaw. The sample size are very small in all studies, so we can't exclude the possibility that the non significant results could be done to second type error.

Furthermore, we did not find any unpublished study despite a big effort done in contacting all the first authors of the included studies and the search of Conference proceedings. We found an ongoing study (Jones 2007) that enrolls 370 women, as soon as it will be published we will update the review with the new results.

All the included studies ended the follow up immediately after the delivery, while could be useful to know, both for the mother and for the child health, if after the delivery the mothers continued to use maintenance treatments.

**Authors' conclusions**

**Implications for practice**

Overall, we didn't find any significant difference between the drugs considered (methadone vs buprenorphine or oral slow morphine) both for mother and for child outcomes; however the trials included were too few and the sample size too small to make any firm conclusion about the superiority of one treatment over another.

**Implications for research**

There is an urgent need of big randomised controlled trials comparing different pharmacological maintenance treatments with longer follow up periods (ideally until one year) which consider as relevant outcomes also the level of nicotine exposure, the concomitant use during pregnancy of other prescribed medications (like SSRIs, benzodiazepines) and non-prescribed drugs like cocaine, alcohol, marijuana. The MOTHER-Study, an ongoing study where over 300 patients will be enrolled, will have the power to present the main topics in this field. Moreover studies assessing the effectiveness of psychosocial treatments realised in adjunct to pharmacological treatments versus pharmacological treatments alone should be conducted.

**References**

**References to studies included in this review**

Fischer 1999 (published data only)

Fischer 2006 (published data only)

Jones 2005 (published data only)

**References to studies excluded from this review**

Carroll 1995 (published data only)

Ebner 2007 (published data only)
Fisher 1998  {published data only}

Gordon 2004  {published data only}

Hulse 2004  {published data only}

Jackson 2004  {published data only}

Keiser-Marcus 2002  {published data only}

Laken 1997  {published data only}

References to ongoing studies

Jones 2007  {unpublished data only}

Additional references

Amato 2004

Brown 1998

Chalmers 1993

Clark 2002

CSAT 2005

Dattel 1990

Dunlop 2003

Faggiano 2003

Fajemirokun 2006

Ferri 2005

Finnegan 1992

Higgins 2005

Hulse 1997

Hulse 1998

Jarvis 1994

Johnson 2003

Kaltenbach 1998
Lejuene 2006

Ludlow 2004

Mattick 2003 a

Mattick 2008

Mayet 2005

Minozzi 2006

Moher 1998

Moher 1999

NIH 1998

Rayburn 2004

Schulz 1995

Uk Guidelines 2007

Wang 1999

* Indicates the major publication for the study

**CHARACTERISTICS OF STUDIES**

**Characteristics of included studies**  [ordered by study ID]
### Fischer 1999

**Interventions**

(1) oral methadone (24 participants) versus (2) oral slow-morphine (24 participants) after an induction period of 10 days. At delivery mean methadone dose was 53.48 mg, mean morphine dose was 300.43 mg. Outpatient. Follow up mean: 15 weeks. Country of origin: Austria

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Retention; Fetal distress; Birth weight; NAS (Finnegan scale); Cocaine and benzodiazepine consumption (urinalysis); opioid use (identification of injection sites for morphine-maintained group and urinalysis for methadone-maintained group)</th>
</tr>
</thead>
</table>

**Notes**

<table>
<thead>
<tr>
<th>Risk of bias Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Fischer 2006

**Methods**


**Participants**

Participants: 18 pregnant adults; mean age 25.9 years; 66.6% single; 61.1% completed 9 years of education; duration of heroin consumption: mean 20.6 months. Mean gestational age at entry: 24 weeks. Inclusion criteria: opioid-dependent pregnant females meeting DSM-IV criteria. Exclusion criteria: severe somatic or other severe psychiatric diseases, high risk pregnancy

**Interventions**

(1) oral methadone (9 participants) versus (2) oral buprenorphine (9 participants). Dose of methadone between 40 and 100 mg/day; dose of buprenorphine between 8 and 24 mg/day. Outpatient. Follow up: mean 16 weeks. Country of origin: Austria

**Outcomes**

Retention; Maternal withdrawal symptoms (Wang Withdrawal Questionnaire); illicit drugs use: opioid, cocaine, benzodiazepine (urinalysis); Birth weight; NAS (Finnegan scale); child health status APGAR score

**Notes**

<table>
<thead>
<tr>
<th>Risk of bias Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>
### Jones 2005

| Methods | Randomized controlled trial.  
| Allocation concealment: adequate  
| Double blind.  
| Blinding of outcome assessor: yes |
| Participants | Participants: 30 pregnant adults; mean age 30.1 years; 75% African-American, 20% white, 5% other; 55% unemployed seeking, 40% unemployed not seeking, 5% homemaker; mean years of education 10.2; use cocaine: past 30 days 75%; opioid use: >4x/day 55%; mean gestational age at entry: 23 weeks  
| Inclusion criteria: estimated gestational age of 16-30 weeks; opioid-dependent pregnant females meeting DSM-IV criteria. Exclusion criteria: current diagnosis of alcohol abuse or dependence; self-reported use of benzodiazepines; serious medical illness; diagnosis of pre-term labor; evidence of fetal malformation; positive HIV test |
| Interventions | (1) oral methadone (15 participants) versus (2) oral buprenorphine (15 participants). Dose of methadone: mean 60 mg/day; dose of buprenorphine: mean 12 mg/day. Setting: Inpatient. Follow up mean: 18 weeks  
| Country of origin: USA |
| Outcomes | Retention; Illicit drug use (urinalysis); N° of neonates treated for NAS; peaks of NAS score; length of neonatal hospitalisation; birth weight, child health status; APGAR score |
| Notes | |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Adequate</td>
</tr>
</tbody>
</table>

DSM: Diagnostic and statistical Manual of Mental Disorders  
NAS: Neonatal Abstinence Syndrome  
VAS: Visual Analogue Scale  
HAD: Hamilton Depression Scale  
WWQ: Wang Withdrawal Questionnaire

### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carroll 1995</td>
<td>Excluded as the type of control intervention was not in the inclusion criteria: both group received methadone at the same dose</td>
</tr>
<tr>
<td>Ebner 2007</td>
<td>Excluded as the study design was not in the inclusion criteria: not randomised controlled trial</td>
</tr>
<tr>
<td>Fisher 1998</td>
<td>Excluded as the study design was not in the inclusion criteria: not randomised controlled trial</td>
</tr>
<tr>
<td>Study</td>
<td>Exclusion Reason</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gordon 2004</td>
<td>Excluded as the study design was not in the inclusion criteria: not randomised controlled trial</td>
</tr>
<tr>
<td>Hulse 2004</td>
<td>Excluded as the study design was not in the inclusion criteria: not randomised controlled trial</td>
</tr>
<tr>
<td>Jackson 2004</td>
<td>Excluded as the type of participants was not in the inclusion criteria: newborn randomised to receive different treatment after the delivery</td>
</tr>
<tr>
<td>Keiser-Marcus 2002</td>
<td>Excluded as the study design was not in the inclusion criteria: not randomised controlled trial</td>
</tr>
<tr>
<td>Laken 1997</td>
<td>Excluded as the study design was not in the inclusion criteria: not randomised controlled trial</td>
</tr>
</tbody>
</table>

**Characteristics of ongoing studies**  
*ordered by study ID*

**Jones 2007**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>370 opioid dependent pregnant women</td>
</tr>
<tr>
<td>Interventions</td>
<td>methadone vs buprenorphine for maintenance</td>
</tr>
</tbody>
</table>
| Outcomes                    | For the child: NAS intensity, n. treated for NAS, amount of medication needed to treat NAS, head circumference, length of hospital stay.  
For the mother: retention in treatment, use of substance of abuse, |
| Starting date               | 2005                                                                |
| Contact information         | Jones HE, Ph.D., Department of Psychiatry, Johns Hopkins University School of Medicine; hejones@jhmi.edu |
| Notes                       | multicenter double blind randomised controlled trial               |
## DATA AND ANALYSES

### Comparison 1. methadone vs buprenorphine

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 drop out</td>
<td>2</td>
<td>48</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.01 [0.41, 2.44]</td>
</tr>
<tr>
<td>2 use of primary substance</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.06 [0.11, 54.87]</td>
</tr>
<tr>
<td>3 birth weight</td>
<td>1</td>
<td>19</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-530.01 [-662.78, -397.22]</td>
</tr>
<tr>
<td>4 APGAR score</td>
<td>1</td>
<td>21</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5 N. treated for NAS</td>
<td>2</td>
<td>35</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.28 [0.58, 2.85]</td>
</tr>
<tr>
<td>6 mean duration of NAS treatment</td>
<td>1</td>
<td>14</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.06 [-1.84, 2.84]</td>
</tr>
<tr>
<td>7 length of hospital stay</td>
<td>1</td>
<td>21</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>1.30 [0.60, 2.00]</td>
</tr>
</tbody>
</table>

### Comparison 2. methadone vs oral slow morphine

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 use of substance</td>
<td>1</td>
<td>48</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.05 [1.00, 5.77]</td>
</tr>
<tr>
<td>2 birth weight</td>
<td>1</td>
<td>48</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>124.00 [-186.94, 434.94]</td>
</tr>
<tr>
<td>3 NAS mean duration</td>
<td>1</td>
<td>48</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-5.01 [-10.97, 0.97]</td>
</tr>
<tr>
<td>4 nicotine consumption</td>
<td>1</td>
<td>48</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>4.43 [-1.47, 10.33]</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1 methadone vs buprenorphine, Outcome 1 drop out.

Review: Maintenance agonist treatments for opiate dependent pregnant women

Comparison: 1 methadone vs buprenorphine

Outcome: 1 drop out

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone n/N</th>
<th>buprenorphine n/N</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
<th>Weight</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer 2006</td>
<td>3/9</td>
<td>1/9</td>
<td>1.01 [0.41, 2.44]</td>
<td>14.3 %</td>
<td>3.00 [0.38, 23.68]</td>
</tr>
<tr>
<td>Jones 2005</td>
<td>4/15</td>
<td>6/15</td>
<td>1.00 [0.41, 2.44]</td>
<td>85.7 %</td>
<td>0.67 [0.23, 1.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>24</td>
<td>24</td>
<td>100.0 %</td>
<td>1.00</td>
<td>1.00 [0.41, 2.44]</td>
</tr>
</tbody>
</table>

Total events: 7 (methadone), 7 (buprenorphine)
Heterogeneity: $\chi^2 = 1.67, df = 1 (P = 0.20); I^2 = 40\%$
Test for overall effect: $Z = 0.0 (P = 1.0)$
Analysis 1.2. Comparison 1 methadone vs buprenorphine, Outcome 2 use of primary substance.

Review: Maintenance agonist treatments for opiate dependent pregnant women

Comparison: 1 methadone vs buprenorphine

Outcome: 2 use of primary substance

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone</th>
<th>buprenorphine</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Jones 2005</td>
<td>1/11</td>
<td>0/9</td>
<td>100.0 %</td>
<td>2.50 [0.11, 54.87 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>11</td>
<td>9</td>
<td>100.0 %</td>
<td>2.50 [0.11, 54.87 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (methadone), 0 (buprenorphine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

Analysis 1.3. Comparison 1 methadone vs buprenorphine, Outcome 3 birth weight.

Review: Maintenance agonist treatments for opiate dependent pregnant women

Comparison: 1 methadone vs buprenorphine

Outcome: 3 birth weight

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone</th>
<th>buprenorphine</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Jones 2005</td>
<td>11</td>
<td>3000 (120)</td>
<td>8</td>
<td>3530 (162)</td>
<td>*</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>11</td>
<td>8</td>
<td>100.0 %</td>
<td>-530.00 [-662.78, -397.22 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 7.82 (P < 0.00001)
Analysis 1.4. Comparison 1 methadone vs buprenorphine, Outcome 4 APGAR score.

Review: Maintenance agonist treatments for opiate dependent pregnant women
Comparison: 1 methadone vs buprenorphine
Outcome: 4 APGAR score

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone</th>
<th>buprenorphine</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Jones 2005</td>
<td>11 8.9 (0.09)</td>
<td>10 8.9 (0.15)</td>
<td></td>
<td>100.0 %</td>
<td>0.0 [ -0.11, 0.11 ]</td>
</tr>
</tbody>
</table>

Total (95% CI) 11 10 100.0 % 0.0 [ -0.11, 0.11 ]

Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)

Analysis 1.5. Comparison 1 methadone vs buprenorphine, Outcome 5 N. treated for NAS.

Review: Maintenance agonist treatments for opiate dependent pregnant women
Comparison: 1 methadone vs buprenorphine
Outcome: 5 N. treated for NAS

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone</th>
<th>buprenorphine</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Fischer 2006</td>
<td>3/6 5/8</td>
<td></td>
<td>0.80 [ 0.31, 2.10 ]</td>
<td>67.2 %</td>
<td></td>
</tr>
<tr>
<td>Jones 2005</td>
<td>5/11 2/10</td>
<td></td>
<td>2.27 [ 0.56, 9.20 ]</td>
<td>32.8 %</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 17 18 100.0 % 1.28 [ 0.58, 2.85 ]

Heterogeneity: Chi² = 1.57, df = 1 (P = 0.21); I² =36%
Test for overall effect: Z = 0.61 (P = 0.54)
### Analysis 1.6. Comparison 1 methadone vs buprenorphine, Outcome 6 mean duration of NAS treatment.

**Review:** Maintenance agonist treatments for opiate dependent pregnant women

**Comparison:** 1 methadone vs buprenorphine

**Outcome:** 6 mean duration of NAS treatment

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone</th>
<th>buprenorphine</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV/Fixed,95% CI</td>
<td>IV/Fixed,95% CI</td>
</tr>
<tr>
<td>Fischer 2006</td>
<td>6</td>
<td>5.3 (1.5)</td>
<td>8</td>
<td>4.8 (2.9)</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>6</td>
<td>8</td>
<td>100.0 %</td>
<td>0.50 [-1.84, 2.84]</td>
<td></td>
</tr>
</tbody>
</table>

- Heterogeneity: not applicable
- Test for overall effect: Z = 0.42 (P = 0.68)

### Analysis 1.7. Comparison 1 methadone vs buprenorphine, Outcome 7 length of hospital stay.

**Review:** Maintenance agonist treatments for opiate dependent pregnant women

**Comparison:** 1 methadone vs buprenorphine

**Outcome:** 7 length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone</th>
<th>buprenorphine</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV/Fixed,95% CI</td>
<td>IV/Fixed,95% CI</td>
</tr>
<tr>
<td>Jones 2005</td>
<td>11</td>
<td>8.1 (0.78)</td>
<td>10</td>
<td>6.8 (0.86)</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>11</td>
<td>10</td>
<td>100.0 %</td>
<td>1.30 [ 0.60, 2.00 ]</td>
<td></td>
</tr>
</tbody>
</table>

- Heterogeneity: not applicable
- Test for overall effect: Z = 3.62 (P = 0.00030)
## Analysis 2.1. Comparison 2 methadone vs oral slow morphine, Outcome 1 use of substance.

### Review: Maintenance agonist treatments for opiate dependent pregnant women

### Comparison: 2 methadone vs oral slow morphine

### Outcome: 1 use of substance

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone</th>
<th>morphine</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer 1999</td>
<td>12/24</td>
<td>5/24</td>
<td>2.40 [ 1.00, 5.77 ]</td>
<td>100.0%</td>
<td>2.40 [ 1.00, 5.77 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>24</strong></td>
<td><strong>24</strong></td>
<td>2.40 [ 1.00, 5.77 ]</td>
<td>100.0%</td>
<td>2.40 [ 1.00, 5.77 ]</td>
</tr>
</tbody>
</table>

Total events: 12 (methadone), 5 (morphine)

Heterogeneity: not applicable

Test for overall effect: Z = 1.96 (P = 0.050)

## Analysis 2.2. Comparison 2 methadone vs oral slow morphine, Outcome 2 birth weight.

### Review: Maintenance agonist treatments for opiate dependent pregnant women

### Comparison: 2 methadone vs oral slow morphine

### Outcome: 2 birth weight

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>methadone</th>
<th>morphine</th>
<th>Mean Difference IV,Fixed,95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer 1999</td>
<td>24 3036 (470)</td>
<td>24 2912 (619)</td>
<td>124.00 [ -186.94, 434.94 ]</td>
<td>100.0%</td>
<td>124.00 [ -186.94, 434.94 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>24</strong></td>
<td><strong>24</strong></td>
<td>124.00 [ -186.94, 434.94 ]</td>
<td>100.0%</td>
<td>124.00 [ -186.94, 434.94 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.78 (P = 0.43)
### Analysis 2.3. Comparison 2 methadone vs oral slow morphine, Outcome 3 NAS mean duration.

**Review:** Maintenance agonist treatments for opiate dependent pregnant women  
**Comparison:** 2 methadone vs oral slow morphine  
**Outcome:** 3 NAS mean duration

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Methadone</th>
<th>Morphine</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Fischer 1999</td>
<td>24 16 (10.06)</td>
<td>24 21 (11.03)</td>
<td>100.0%</td>
<td>-5.00 [-10.97, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>24</td>
<td>24</td>
<td>100.0%</td>
<td>-5.00</td>
<td>[-10.97, 0.97]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable  
Test for overall effect: Z = 1.64 (P = 0.10)

---

### Analysis 2.4. Comparison 2 methadone vs oral slow morphine, Outcome 4 nicotine consumption.

**Review:** Maintenance agonist treatments for opiate dependent pregnant women  
**Comparison:** 2 methadone vs oral slow morphine  
**Outcome:** 4 nicotine consumption

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Methadone</th>
<th>Morphine</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Fischer 1999</td>
<td>24 -11.67 (12.24)</td>
<td>24 -16.1 (8.24)</td>
<td>100.0%</td>
<td>4.43 [-1.47, 10.33]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>24</td>
<td>24</td>
<td>100.0%</td>
<td>4.43</td>
<td>[-1.47, 10.33]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable  
Test for overall effect: Z = 1.47 (P = 0.14)

### Appendices

---

*Maintenance agonist treatments for opiate dependent pregnant women (Review)*

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Appendix 1. Cochrane Drugs and Alcohol Group' Register of Trials search strategy

diagnosis=opioid or opiate* and Pregnan* [TI, AB]

Appendix 2. Pubmed search strategy

1. exp opioid-related disorders/
2. (opioid* or opiate*) and (abuse* or addict* or dependen*)
3. (drug or substance) and ((abuse* or addict* or dependen* or disorder*))
4. 1 or 2 or 3
5. exp heroin/ or heroin
6. (opoid* or opiate*)
7. opium
8. exp methadone/ or methadone
9. 4 or 5 or 6 or 7 or 8
10. pregnan*
11. pregnancy/
12. Pregnancy complications/
13. mother*
14. 10 or 11 or 12 or 13
combined with the phases 1 & 2 of the Cochrane Sensitive Search Strategy for the identification of RCTs as published in Appendix 5b2, Cochrane Handbook for Systematic Reviews of Interventions:
15. randomized controlled trial.pt.
16. randomized controlled trials/
17. controlled clinical trial.pt.
18. random allocation/
19. double blind method/
20. single blind method/
21. 15 or 16 or 17 or 18 or 19 or 20
22. clinical trial.pt.
23. exp clinical trials/
24. (clin* and trial*).
25. ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*))
26. exp PLACEBOS/
27. placebo*
28. random*
29. Research Design/
30. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 21 or 30

Appendix 3. CINAHL search strategy

1. exp “Substance Use Disorders”/
2. ((drug or substance) and (addict* or dependen* or abuse*))
3. ((opioid* or opiate*) and (abuse* or addict* or dependen*))
4. 1 or 2 or 3
5. exp heroin/ or heroin
6. (opioid* or opiate*)
7. opium
8. exp methadone/ or methadone
9. 5 or 6 or 7 or 8
10. randomi*
11. (clin* and trial*)
12. (singl* or doubl* or tripl* or trebl*) and (mask* or blind*)
13. crossover*
14. allocate*
WHAT'S NEW

Last assessed as up-to-date: 7 January 2008.

HISTORY

Protocol first published: Issue 1, 2007
Review first published: Issue 2, 2008

CONTRIBUTIONS OF AUTHORS

Minozzi inspected the search hits by reading titles and abstracts; Minozzi, Amato, Vecchi independently assessed for inclusion each potentially relevant study located in the search; Minozzi, Vecchi extract data independently, Amato commented the draft of the review and Davoli supervised.
DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

• Department of Epidemiology, ASL RM E, Italy.

External sources

• No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Birth Weight [drug effects]; Buprenorphine [therapeutic use]; Infant, Newborn; Methadone [therapeutic use]; Narcotics [agonists; *therapeutic use]; Opioid-Related Disorders [*rehabilitation]; Pregnancy Complications [*rehabilitation]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Infant; Pregnancy