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Pregnancy and opioid use: strategies for treatment

Abstract: Illicit opioid consumption is associated with a sixfold increase in obstetric complications in pregnant women. Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neurobehavioural problems, increase in neonatal mortality and a 74-fold increase in sudden infant death syndrome. The primary goal of treatment for opioid dependence in pregnant women is to stabilise the patient, in order to avoid the permanent fluctuation of plasma levels and related foetal consequences, such as foetal distress and preterm birth. Psychosocially assisted opioid substitution treatment is the first-line treatment for opioid dependence in pregnant women, and several combinations of substitution medicines and psychosocial approaches are available. The pharmacological interventions studied in this overview were methadone, buprenorphine and slow-release oral morphine; the psychosocial interventions were cognitive behaviour approaches and contingency management. The observed differences between the three substitution approaches did not show a homogeneous and comprehensive pattern to conclude that one treatment is superior to the others for all relevant outcomes. While methadone seems superior in retaining patients in treatment, buprenorphine seems to yield to less severe neonatal abstinence syndrome and higher birth weight.

Keywords pregnancy opioids treatment systematic review

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Background

The true prevalence of drug use among pregnant women in Europe is difficult to ascertain, and differences across countries or in certain areas may exist. In reality, data on the prevalence of illicit drug use among pregnant women are not available for most European countries. Information made available by the EMCDDA's Reitox network ([1]) in a 2012 data collection exercise comes from isolated studies using various methodologies, and the results are not readily comparable. For example, a study conducted in an inner-city maternity hospital in Dublin, Irelandn found that 4 % of antenatal and 6 % of postnatal women tested positive for drug metabolites. The proportion of urine samples that tested positive for drug metabolites was higher among women admitted for labour than among women attending scheduled antenatal visits. One reason for this may be that women who use drugs are less likely to receive antenatal care than women who are drug free.

In a recent study, also using biological specimens, hair analysis showed that 16 % of women giving birth in a hospital in Ibiza, Spain, had used some type of illicit drug during the third trimester of their pregnancy (Friguls et al., 2012), although only 2 % of women reported drug use during their pregnancy. In Latvia, women reported drug use in 0.2 % of live births and 0.8 % of stillbirths. In this country, antenatal care is received before the twelfth week of pregnancy by 90 % of expectant women in the general population, compared with 70 % of those who had ever used drugs (EMCDDA, 2012). The National Registry of Mothers at Childbirth in the Czech Republic reported a prevalence of 1.8 % of illicit drug use among over 1 million mothers between 2000 and 2009.

Although it is difficult to estimate the real prevalence, the problem of pregnant drug users is known by those working in the field and it is important to accurately address it for several reasons. Firstly, pregnant women may shy away from health services for fear of the consequences on their parental rights; secondly, they may wish to quit drugs and treatment in an uncontrolled way, which can be riskier than remaining in pharmaceutically assisted treatment; and, finally pregnancy has been described as a 'window of opportunity' for drug users to take care of their health (Daley et al., 1998).

Risks of opioid use during pregnancy

All psychoactive drugs, including alcohol, tobacco and some prescribed medications, may have adverse effects on the pregnancy, the unborn child and the newborn. However, different drugs may act differently (Table 1). This may be a result of not only the drug itself, but also the poor overall health and nutritional status of the drug-using expectant woman. The degree of the impact of drug use during pregnancy largely depends on the intensity of drug use, which is complicated by the fact that patients frequently abuse more than one licit or illicit substance (Goel et al., 2011; Havens et al., 2009) and up to 97 % of opioid-dependent pregnant women are smokers (Jones et al., 2011).

TABLE 1

Health harms associated with substance use during pregnancy

	Alcohol	Tobacco	Cannabis	Amphetamines	Cocaine	Opioids
Low birth weight	+	+	+	+		+
Miscarriage	+	+	+	+	+	
Perinatal mortality	+	+				+ ([1])
Developmental problems in childhood	+		+		+	
Foetal morbidity	+		+	+	+	
Premature birth	+			+		+
Decreased foetal growth	+					
Impaired intrauterine growth	+					+
Neonatal withdrawal symptoms	+					+
Premature rupture of membranes, placental abruption				+	+	
Preterm delivery	+					
Respiratory depression						+

([1]) Related to withdrawal.
NB: The effect of these drugs may be confounded by polydrug use and/or other health and lifestyle factors associated with drug use.
Source: *A summary of the health harms of drugs,* The Centre for Public Health, Faculty of Health & Applied Social Science, Liverpool John Moores University, on behalf of the Department of Health and National Treatment Agency for Substance Misuse (2011).

([1]) Reitox is the European information network on drugs and drug addiction.

Untreated opiate dependence in pregnant women is associated with many environmental and medical factors that contribute to poor maternal and child outcomes. Illicit opioid consumption is associated with a sixfold increase in obstetric complications such as low birth weight, toxaemia, third trimester bleeding, malpresentation, puerperal morbidity ([2]), foetal distress and meconium aspiration. Neonatal complications include narcotic withdrawal, postnatal growth deficiency, microcephaly, neurobehavioural problems, increase in neonatal mortality and a 74-fold increase in sudden infant death syndrome (Dattel, 1990; Fajemirokun-Odudeyi et al., 2006; Ludlow et al., 2004). Neonates born to mothers chronically abusing illicit opioids or provided with maternal medication-assisted treatment, such as methadone or buprenorphine, are frequently born with a passive dependency to those specific agents. Intrauterine exposition to all of the commonly used opioids, including heroin and methadone, but also prescription drugs (OxyContin, Percodan, Vicodin, Percocet and Dilaudid), sedative hypnotics such as benzodiazepines (e.g. Diazepam) and barbiturates can produce neonatal abstinence syndrome (NAS) after disruption of the trans-placental passage of drugs at birth. NAS is characterised by signs and symptoms of the central nervous system, hyperirritability, gastrointestinal dysfunction and respiratory and autonomic nervous system symptoms (Kaltenbach et al., 1998). However, with the current medical knowledge NAS is an easily treatable condition and no infant mortality should occur as a result of NAS.

It is important to note that, contrary to alcohol, benzodiazepines and nicotine, opioids do not have teratogenic potential ([3]). Thus, special attention needs to be paid to dependence and abuse of legal substances and prescription drugs that can have severe consequences for the foetus and newborn, such as foetal developmental disorders or sudden infant death syndrome (Fetal Alcohol Spectrum Disorders Center for Excellence, 2013; McDonnell-Naughton et al., 2012).

Description of the interventions

The primary goal of treatment for opioid dependence in pregnant women is stabilisation of the patient, in order to avoid the permanent fluctuation of plasma levels and related foetal consequences, such as foetal distress and preterm birth. Psychosocially assisted opioid substitution treatment (OST) is the first-line treatment for opioid dependence in pregnant women. Each dimension of this multicomponent intervention plays a different role. For example, although many women want to cease using opioids when they find out they are pregnant, they should be encouraged to start or, if this is already the case, remain in OST. This is because severe opioid withdrawal symptoms resulting from the abrupt interruption of opioids can lead to abortion in the first trimester of pregnancy or premature labour in the third trimester. Furthermore, a possible relapse to heroin use can result in obstetric problems.

Since the early 1970s, OST with methadone has been the standard treatment for opioid-dependent pregnant women. More recently, buprenorphine has been administered to this group for OST. Placental transfer of buprenorphine may be lower than methadone, reducing foetal exposure and the development of NAS (Rayburn and Bogenschutz, 2004). Promotion of compliance can be supported in a number of ways. Behavioural change techniques play a prominent role here.

In order to guarantee the effectiveness of cognitive behavioural interventions, treatment fidelity is important. Using standardised, manual-based interventions is an important tool here. The main approaches are based on motivational interviewing and motivational enhancement therapy (see box on page 4).

([2]) This refers to any illness occurring in the 10 days postpartum.
([3]) This means the potential to cause malformations to an embryo or a foetus.

The different strategies for treating opioid dependence in pregnancy reviewed in this paper

Contingency management (CM): the premise behind CM is to systematically use reinforcement techniques to modify behaviour in a positive and supportive manner. It has been used in the treatment of substance abuse since the 1970s (Sitzer and Nancy, 2006). The most common form of CM has been the use of monetary vouchers, although prize reinforcers have been used as well. CM was first demonstrated to be efficacious in both treatment retention and substance abstinence in cocaine-dependent individuals (Higgins et al., 1991), but has subsequently been studied in relation to opioids, marijuana, cigarettes, alcohol, benzodiazepines and multiple drugs. Recently it has been used in populations of pregnant, illicit-drug-dependent women.

Cognitive behavioural therapy (CBT) focuses on altering the beliefs that contribute to substance use and providing training in coping and skills development (Galanter et al., 2007). Cognitive strategies (e.g. identifying distorted thinking patterns) are typically combined with behavioural strategies (e.g. coping with craving to use, communication, problem solving, substance refusal skill training) (Waldron and Turner, 2008). The Social Behaviour and Network Therapy approach uses a range of cognitive and behavioural strategies to build social networks supportive of change involving the client and other network members (family and friends) (UKATT research team, 2001).

Opioid substitution treatment (OST): Also called 'substitution therapy', 'agonist pharmacotherapy', 'agonist replacement therapy' or 'agonist-assisted therapy', OST is defined as the administration under medical supervision of a prescribed psychoactive substance that is pharmacologically related to the one producing dependence to patients with substance dependence, for achieving defined treatment aims. Substitution therapy is widely used in the management of nicotine ('nicotine replacement therapy') and opioid dependence.

Motivational interviewing (MI) and motivational enhancement therapy (MET): MI was initially developed for treating problem drinkers (Miller et al., 2003). It is a directive, client-centred counselling style for eliciting behaviour change by helping clients explore and resolve the ambivalence surrounding their substance use (Rollnick and Miller, 1995). It draws from the trans-theoretical model of change (DiClemente and Prochaska, 1998) in order to improve treatment readiness and retention. In the motivational approach (MI, MET), rather than confront the patient's resistance to abstinence in a direct, possibly aggressive, manner, the therapist 'rolls with resistance'. At the same time, he or she tries to help the patient develop more self-motivation to stop using via specified techniques (Woody, 2003).

How the interventions work

Methadone maintenance given during pregnancy reduces maternal illicit opiate use and foetal exposure, enhances compliance with obstetric care, and is associated with improved neonatal outcomes, such as increased birth weight (Fajemirokun-Odudeyi et al., 2006; Sutter et al., 2014). Additional benefits include a potential reduction in behaviours related to drug-seeking (for example, prostitution as a means to raise money for drugs). This reduction may decrease the woman's risk 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 national and international guidelines (UK: Department of Health (England) and the devolved administrations 2007; USA: CSAT, 2005; Australia: Dunlop et al., 2003; and WHO, 2009) support the use of methadone during pregnancy ([4]).

Studies conducted between 1988 and 1998 were performed in treatment centres offering methadone and comprehensive services, including obstetric, health and psychiatric care and individual, group and family therapy. Consequently, it is difficult to evaluate the results of these studies in order to distinguish the benefits of methadone in isolation from social measures and obstetric care (Wang, 1999).

The available clinical literature suggests that buprenorphine maintenance is associated with reduced maternal illicit opiate use and foetal exposure, enhanced compliance with obstetric care, and improved neonatal outcomes, such as increased birth weight (Johnson et al., 2003; Lejeune et al., 2006).

As already mentioned, pregnancy has been considered a 'window of opportunity' for drug treatment intervention (Daley et al., 1998). Maternal concern for the baby has been thought of as a motivator to seek treatment. Although qualitative studies have documented maternal motivation (Dakof et al., 2003; Murphy et al., 1999), they have also described the many structural and social barriers to both receiving and remaining in treatment (Boyd et al., 1999; Murphy et al., 1999).

([4]) An inventory of national treatment guidelines and international guidelines is available on the EMCDDA's Best practice portal, at emcdda.europa.eu/best-practice/standards/treatment

Why this review?

Systematic reviews of evidence are available for all the substitution treatment and psychosocial approaches to treat opioid dependence but only a few of them include studies on pregnant women. Furthermore, recent studies have enlarged the treatment options for pregnant opioid users. Therefore, an overview of the effectiveness of the available interventions is needed.

The objective of the present overview is to assess the effectiveness of any OST, either alone or in combination with psychosocial interventions, for promoting the retention of pregnant women in treatment and reducing illicit substance use and for improving child health status and reducing neonatal mortality.

Methods

In order to select the studies for inclusion in this review, we set the following criteria. We decided to search and include all the experimental or quasi-experimental studies involving the treatment of opioid dependence for pregnant women. As the focus was pregnancy, we excluded any studies that were initiated postpartum. Participants in the studies included needed to have a diagnosis of opioid dependence (in agreement with the standards set by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; DSM-IV) but no criteria were set for gestational age or existing comorbidity.

In terms of treatment, we included studies comparing any type of pharmacological intervention alone or in combination with any type of psychosocial intervention. These treatments had to be compared with no intervention or psychosocial interventions only.

The primary outcomes were considered separately for the women and the newborn babies concerned.

Measures of treatment success for the woman were considered as the number of women who remained in treatment for the whole time planned; evidence of use of illicit substances during and/or after the conclusion of the treatment/birth of the child. On the obstetric outcomes, the measures considered were third trimester bleeding, foetal distress and meconium aspiration, caesarean section, non-normal presentation, medical complications at delivery, breastfeeding following obstetric delivery and puerperal morbidity.

Secondary outcomes considered relevant for the pregnant woman/mother were nicotine consumption, use of other substances (licit or illicit) and side effects for the pregnant woman/mother. The wellbeing of the child was measured as health status (birth weight, Apgar ([5]) score), NAS, prenatal and neonatal mortality and any other side effects for the child.

Search strategy

In order to identify all of the studies falling within our inclusion criteria, we performed structured web-based searches using a combination of relevant keywords. These search strategies were adapted to query the specialised databases available, namely the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, April 2013, and in particular the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register — an inventory of studies included in the systematic reviews of evidence; PubMed, the platform of the American National Library of Medicine, also called MEDLINE (1966 to October 2013); and EMBASE — a medical database containing information on drugs and diseases from pre-clinical studies to searches on critical toxicological information (Elsevier, EMBASE.com, 1974 to October 2013). Two other databases, namely the Cumulative Index to Nursing and Allied Health Literature (CINAHL including nursing and allied health journals, 1982 to October 2013) and the Web of Science, were also consulted. For details of the search strategies for all databases, see Annex 2.

Searching other resources

In addition to the web-based searches, we checked our results against the reference lists of all relevant papers to identify further studies; some of the main electronic sources of ongoing trials (National Research Register, meta-Register of Controlled Trials; Clinical Trials.gov, Agenzia Italiana del Farmaco); conference proceedings likely to contain trials relevant to the review (College on Problems of Drug Dependence); national focal points for drug research (e.g. National Institute of Drug Abuse, National Drug and Alcohol Research Centre); and authors of included studies and experts in the field in various countries were contacted to find out if they knew of any other published or unpublished controlled trials. There were no language restrictions at search strategy level. If an interesting paper was found in a language the screening authors did not read, the paper's author(s) was/were contacted for translation.

Data collection and analysis

Two authors independently screened the titles and abstracts of studies obtained by the search strategy. Each potentially

([5]) Activity, pulse, grimace, appearance and respiration.

relevant study located in the search was obtained as full text and assessed for inclusion independently by the two authors; where disagreements occurred, a third author was consulted. Data were extracted independently by the two authors. Any disagreements were discussed and resolved by consensus.

Assessment of the risk of bias

The quality of studies must be assessed in order to reduce the risk of distorted results due to bias. The risk of bias assessment for randomised controlled trials (RCTs) and controlled clinical trials (CCTs) in this review was performed using the criteria recommended by the Cochrane handbook (Higgins et al., 2011). The recommended approach for assessing risk of bias in studies included in the Cochrane handbook is a two-part tool, addressing seven specific domains, namely sequence generation and allocation concealment (selection bias); blinding of participants and providers (performance bias); blinding of outcome assessor (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other source of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry (low, high or unclear). To make these judgements, we used the criteria indicated by the handbook adapted to the addiction field (see Annex 3 for details).

The domains of sequence generation and allocation concealment (avoidance of selection bias) were addressed in the tool by a single entry for each study. Blinding of participants to treatment, blinding of personnel and outcome assessors to the allocation of patients (avoidance of performance bias and detection bias) were considered separately for objective outcomes (e.g. dropout, use of substance of abuse measured by urine analysis, subjects relapsed at the end of follow-up, subjects engaged in further treatments) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, patient self-reported use of substance and side effects). Data were extracted independently by two authors. Any disagreement was resolved by discussion.

What is bias?

The main objective of epidemiological research is to find explanations to the manifestation of diseases in the population. Bias is a false result influenced by uncontrolled factors. A typical example of bias is an unwanted selection of the population studied so that the sample does not adequately represent the target population. Bias has been defined as 'incorrect assessment of the association between an exposure and an effect in the target population' (Delgado-Rodríguez and Llorca, 2004). The quality of studies is highly linked to the reduction of possible bias. There are many known types of bias, including **selection bias,** the risk of selecting the sample for uncontrolled characteristics (Delgado-Rodríguez and Llorca, 2004); **attrition bias,** one type of selection bias which is related to the number of patients that leave a study before the final assessment; **indication bias,** which emerges in RCTs when patients, instead of being assigned to treatment randomly, are assigned on the basis of some characteristics, for example a higher susceptibility to some disease; and **assessment bias** or **detection bias,** when the professionals assessing the results of an intervention are influenced by their knowledge of the interventions provided. A typical example is a nurse who measures body temperature more often or more accurately in the patients given placebo than in those given the active substance.

Why are some studies defined as 'blinded'?

Blinding refers to all of the strategies put in place to prevent knowledge of the intervention influencing behaviour (of patients or clinicians, carers or outcome assessors), hence leading to biased results (performance bias). In an RCT, patients are often blinded to the intervention so that they cannot over-report or under-report some symptoms. The same strategy applies to assessors. The term 'double blind' describes a situation in which neither the patient nor the assessor of the outcome (for example, the professional asking questions) aware of the treatment provided to the specific patient.

Measures of treatment effect

Measures of effects were calculated separately for two main types of outcomes. Dichotomous outcomes include those that can have only two results (the typical one being mortality, as a person can be only dead or alive). These outcomes were analysed calculating the risk ratio (RR) for each trial. The RR is used to compare the risk in the two different groups of people, i.e. treated and control groups, in order to ascertain whether belonging to one group or another increases or decreases the risk of developing certain outcomes. As a general rule, a RR that is lower than 1 indicates a reduction in risk while a RR exceeding 1 indicates an increased risk.

Confidence intervals are a measure of the uncertainty of a result that indicates the minimum and the maximum the result can assume for the effect of chance. Confidence intervals include two measures: the lower and the upper. As a rule of thumb in interpretation, a confidence interval including 1 is considered not statistically significant because it includes the case in which the RRs in the two groups compared is equal and the intervention tested has no effect.

Continuous outcomes can assume many different measures (for example, blood pressure). These outcomes were analysed calculating the mean difference (MD) or the standardised mean difference with confidence intervals of 95 %.

Furthermore, when data on the number of participants using a substance (dichotomous outcome) were reported, we used these data instead of the data presented as the number of positive urine tests over the total number of tests (continuous measure) in the experimental and control group, as a 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, multiple tests on the same patients cannot be considered independent observations. Nevertheless, if only continuous measures were available, we used them.

Assessment of heterogeneity

Overviews such as the present one typically include several studies which, by definition, differ: they have been conducted in various places and times and include several populations (they are heterogeneous). The difference can be clinical (i.e. related to the interventions and the patients) or statistical. Statistical heterogeneity occurs when the variation is higher than expected for the mere effect of chance. While clinical heterogeneity brings important information (for example, it says that one intervention is more effective in patients with some characteristics than in others), statistical heterogeneity can be misleading. For this reason, techniques exist to minimise the effect of the heterogeneity. In order to consider this heterogeneity in the meta-analysis (the pooled estimate of study results), some specific statistical tests were used. The test that was used in this overview to measure and control the heterogeneity was the I^2 statistic and chi-squared test for heterogeneity (Higgins et al., 2003). A heterogeneity test higher than 50 % indicates that the results of the analysis must be interpreted with caution.

Grading of evidence

In order to classify the quality of the evidence, the Grading of Recommendation, Assessment, Development, and Evaluation Working Group (GRADE) developed a system (Guyatt et al., 2008; Schünemann et al., 2003) which takes into account issues related not only to internal validity — for example the risks of bias — but also to external validity, or generalisability of results, such as directness of results ([6]). The overall quality of the evidence for the primary outcome was assessed using the GRADE system.

Table 4 presents the main findings of the review and key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.

Data synthesis

The outcome measures from the individual trials were combined through meta-analysis where possible (comparability of intervention and outcomes between trials) using the fixed effects model ([7]), as the studies were expected to be similar in terms of types of participants, settings and treatments administered.

Sensitivity analysis for risk of bias

It is possible to assess the risk of bias in the included studies (see box 'What is bias? on page 6) before conducting the meta-analysis. The method used in this type of review helps visualise studies that are outliers in respect of several outcomes. In order to include an assessment of the risk of bias in the review process, we can start by plotting the intervention effect estimates against the assessment of risk of bias. If we find significant associations between the measures of effect and risk of bias, this would exclude from the analysis studies with a high risk of bias. The items considered in the sensitivity analysis would be random sequence generation, allocation

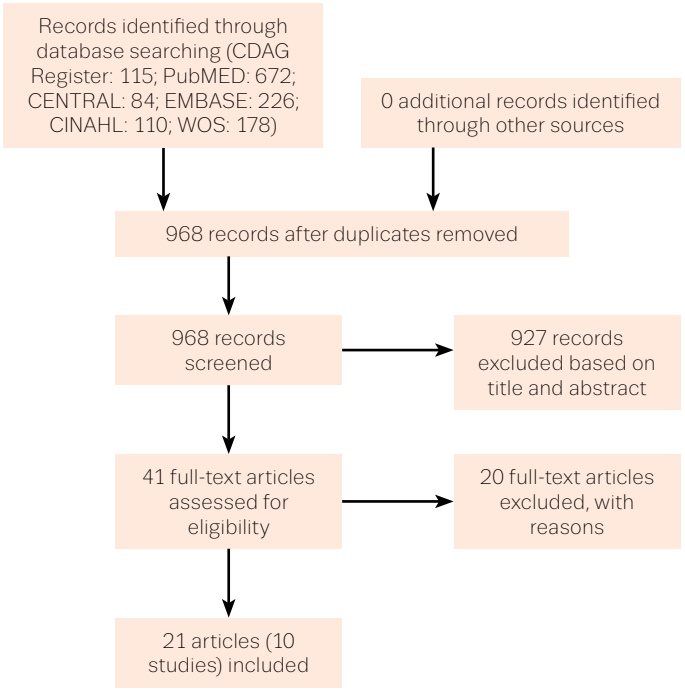
([6]) More details about the GRADE system can be found at gradeworkinggroup.org/

([7]) The fixed effects model is a statistical technique that is used when studies are expected to be sufficiently similar to be pooled together without the need to balance for heterogeneity.

concealment, blinding of personnel and outcome assessors. However, in the present overview it was not possible to perform such a sensitivity analysis because of the small number of studies included.

Results

FIGURE 1
Flow chart of the process



Results of the search

We identified a total of 968 records (Figure 1) but 927 were excluded because the title and abstract were not relevant and 41 articles were retrieved as full text in order to perform a more detailed evaluation. Following this evaluation, 20 were excluded, leaving 10 studies (21 references) that satisfied all the criteria for inclusion. We did not find any unpublished studies. We wrote to the first authors of published studies and one replied, who confirmed that, to his knowledge, there were no unpublished trials.

Included studies

Ten studies involving 728 participants satisfied the criteria for inclusion (Carroll et al., 1995; Fischer et al., 1999; Fischer et al., 2006; Haug et al., 2004; Jones et al., 2005; Jones et al., 2011; MOTHER Study; O'Neill et al., 1996; Silverman et al., 2001; Tuten et al., 2012).

Trials ranged from 2 to 36 weeks, with a mean duration of 18 weeks. The countries covered by the trials were the United States (six), Austria (two), Australia (one) and Austria, Canada and the United States (one). The last was the MOTHER Study — a multicentre international study. Four trials, with a total of 271 participants, assessed the effectiveness of agonist maintenance treatments. Three of them compared methadone (dose between 20 and 140 mg/day) with buprenorphine (dose between 2 and 32 mg /day) (Fischer et al., 2006; Jones et al., 2005; MOTHER Study) and one compared methadone (mean dose at delivery 53.48 mg) with slow-release oral morphine (SROM; mean dose at delivery 300.43 mg) (Fischer et al., 1999). Six studies involving 457 participants (Carroll et al., 1995; Haug et al., 2004; Jones et al., 2011; O'Neill et al., 1996; Silverman et al., 2001; Tuten et al., 2012) assessed the effectiveness of psychosocial interventions combined with agonist maintenance treatment.

Nine studies were conducted in outpatient settings and one in an inpatient setting. Four studies were conducted in both settings. The psychosocial interventions considered in the studies were CM — three studies (Carroll et al., 1995, Silverman et al., 2001, Tuten et al., 2012); MET — one study (Haug et al., 2004); Cognitive Behavioral Relapse Prevention Therapy — one study (O'Neill et al., 1996); and one therapeutic workplace study (Tuten et al., 2012). The six studies that assessed the effectiveness of psychosocial interventions combined with agonist maintenance treatment were very heterogeneous in terms of study objective, types of interventions compared, types of outcomes and ways of measuring outcomes. A pooled analysis of the results was possible only for retention in treatment within each subgroup; the other results have been described in a narrative way.

The total number of participants was 728 opiate-dependent pregnant women meeting DSM-IV criteria with a mean age of 28.9 years and a mean gestational age of 25 weeks.

For a detailed description of characteristics of included studies, see Annex 1.

TABLE 2
Methodological quality of included studies

Level of risk	Random sequence generation (selection bias)	Allocation concealment (indication bias)	Blinding of participants and outcome assessors (performance and assessment or detection bias)	Incomplete data outcomes (attrition bias)
Low risk of bias	Jones et al., 2005; Jones et al., 2011; Silverman et al., 2001	Fischer et al., 2006; Jones et al., 2005; MOTHER Study	Fischer et al., 2006; Jones et al., 2005; MOTHER Study	Carroll et al., 1995; Fischer et al., 1999; Jones et al., 2011; O'Neill et al., 1996
Description unclear	Carroll et al., 1995; Fischer et al., 1999; Fischer et al., 2006; Haug et al., 2004; MOTHER Study; O'Neill et al., 1996; Tuten et al., 2012	Carroll et al., 1995; Fischer et al., 1999; Haug et al., 2004; Jones et al., 2011; O'Neill et al., 1996; Silverman et al., 2001; Tuten et al., 2012		
Any risk of bias			Carroll et al., 1995; Fischer et al., 1999; Haug et al., 2004; Jones et al., 2011; O'Neill et al., 1996; Silverman et al., 2001; Tuten et al., 2012	Fischer et al., 2006; Haug et al., 2004; Jones et al., 2005; MOTHER Study; Silverman et al., 2001; Tuten et al., 2012

Note: All the studies were randomised controlled trails.

As shown in Table 2 above, random sequence generation (selection bias) exists in three studies (Jones et al., 2005; Jones et al., 2011; Silverman et al., 2001). These used a random sequence generation method at low risk of selection bias. All other studies were judged at unclear risk of bias. Allocation concealment (selection bias) was at low risk of bias in three studies (Fischer et al., 2006; Jones et al., 2005; MOTHER Study) and unclear risk in all the others. Concerning the blinding of participants and/or personnel (performance bias) and outcome assessor (assessment or detection bias): for subjective outcomes, three studies (Fischer et al., 2006; Jones et al., 2005; MOTHER Study) were double-blind judged at low risk; seven studies were judged at high risk of performance bias, one (Fischer et al., 1999) because it was an open study and the other six (Carroll et al., 1995; Haug et al., 2004; Jones et al., 2011; O'Neill et al., 1996; Silverman et al., 2001; Tuten et al., 2012) because blinding of participants and personnel was not possible for the types of intervention compared. For objective outcomes, all studies were judged at low risk of performance and detection bias. For incomplete outcome data (attrition bias), only one study had no attrition. Four studies were judged at low risk of bias (Carroll et al., 1995; Fischer et al., 1999; Jones et al., 2011; O'Neill et al., 1996). The other studies were judged at high risk of attrition bias because the attrition rate was high and not balanced between groups.

Effects of interventions

Mothers

1. Retention in treatment

The studies showed that both patients treated with methadone and those given SROM remained in treatment as planned. Adding cognitive behavioural interventions and CM to treatment was found to potentially improve retention in treatment.

2. Use of substances

Methadone and SROM helped patients to abstain from using illicit substances. The addition of CM or cognitive behavioural approaches did not change the results in two studies out of three (but some results were apparent at 9-month follow-up, when the control group increased use). Other illicit substances were found in the urine analysis and the only relevant result was the effect of CM on reducing cocaine use. No significant differences were observed among groups for the number of cigarettes smoked per day.

3. Obstetrical outcomes

3.1. Premature delivery

In two out of three studies there were more premature deliveries in the methadone group than in the buprenorphine group, and in the morphine group the mean week of delivery was lower. However, no statistically significant differences were reported in any of the studies. The addition of CM seemed to improve the completion of gestation.

3.2. Caesarean section

In one out of three studies, the percentage of caesareans was lower in the patients in the buprenorphine group. No differences were reported in the remaining patients.

3.3. Foetal presentation and puerperal morbidity

In one of the studies, there were more newborn babies with abnormal presentation (i.e. not head first) in methadone-

rather than in buprenorphine-treated mothers. Nevertheless, the difference was considered not statistically significant. None of the mothers participating in the studies had any illness in the 10 days after giving birth.

3.4. Side effects for the mothers

The side effects were not statistically significant and more frequent in methadone- than in buprenorphine-treated women.

Newborn babies

1. Birth weight

In one of the studies, the newborns of mothers treated with buprenorphine had higher weight at birth, and in another study, the babies of mothers provided with CM in addition to usual care had a higher birth weight.

2. Neonatal abstinence syndrome

In three studies, the RR for the baby having NAS was not statistically significant and slightly higher in the buprenorphine- than in the methadone-treated group. The score for NAS peak over all observation days was lower in the buprenorphine group in one study and lower in the methadone group in another. The mean duration of treatment for NAS was not different across the groups and the total amount of morphine needed to treat NAS was lower in the buprenorphine group, the mean stay in hospital for the treatment of NAS was lower in the buprenorphine group.

When comparing methadone with SROM, there were no differences in the length of time the infants remained in hospital for detoxification. In one study, in the methadone group there were two fatalities. No prenatal or neonatal deaths occurred in the methadone versus SROM study.

3. Apgar score

The Apgar score is a clinical test for newborn babies at one and five minutes after birth. The one-minute score determines how well the baby tolerated the birthing process. The five-minute score tells the doctor how well the baby is doing outside the mother's womb (MedlinePlus, accessed July 2014).

Three studies reported the Apgar score at five minutes after birth as showing no differences among the groups.

4. Side effects for the baby

In one study there were more side effects in the babies born to mothers treated with methadone (statistically significant). Conversely, the non-serious side effects were higher in the buprenorphine-treated group (measure was non-statistically significant).

TABLE 3
Outcomes, interventions and effects of included studies

	Outcomes	Interventions	Effects	Quick guide	References	Additional information
	**Dropout from treatment**	Methadone versus buprenorphine	Results of the cumulative analysis show that patients on methadone tended to remain in treatment until the conclusion of the study. The risk ratio (RR) calculated on 223 patients was in favour of methadone 0.64 (95 % CI 0.41–1.01) but was not statistically significant	+ MMT	Fischer et al., 2006; Jones et al., 2005; MOTHER Study	
		Methadone versus SROM	No participants dropped out in either group	=	Fischer et al., 1999	
		CM approach plus usual care versus usual care	Comparison between the three groups of patients allocated to different interventions, RR 1.39 (95 % CI 0.71–2.69), the result is not statically significant	=	Jones et al., 2011; Tuten et al., 2012	
		Cognitive behavioural approach plus usual care versus usual care	More patients remained in the cognitive behavioural interventions, RR 1.12 (95 % CI 0.50–2.49); the result is not statistically significant	=	Haug et al., 2004; O'Neill et al., 1996	
		Therapeutic workplace with job skills training versus usual care	The therapeutic workplace intervention was not statistically significantly retaining more patients than the usual care, RR 0.75 (95 % CI 0.41– 1.37)	=	Silverman et al., 2001	
	Use of substance	Methadone versus buprenorphine	RR of 1.81 (95 % CI 0.70–4.69); the result is not statistically significant	=	Jones et al., 2005; MOTHER Study	
		Methadone versus SROM	SROM helped patients to reduce heroin use, particularly in the third trimester of pregnancy, RR: 2.40 (95 % CI 1.00–5.77); the result was in favour of SROM	+ SROM	Fischer et al., 1999	Result should be interpreted with caution because heroin use was investigated by physical examination to search for injection sites, which indicate intravenous heroin use, and patient self-reports, since slow-release morphine cannot be differentiated from heroin with standard urine analysis methods
		CM approach plus usual care versus usual care	Urine analysis for illicit opiates gave similar results between patients given CM and those in usual care in two studies: Carroll et al., 1995 (data commented in the article not reported) and Tuten et al., 2012. The number of opioid-negative urine tests in the groups of patients provided with the escalating or the fixed CM was not statistically significantly different from those reported in the group treated with usual care ($F(1,58.7)=0.01$, $P=0.93$), as well as the longest consecutive number of negative urines ($F(1,56.5)=1.06$, $P=0.51$). CM resulted effective in one study (Jones et al., 2011). There was a significant effect of the incentives on the rate of opiate-positive urine samples ($F(1,78)=5.76$, $P<0.05$) during the first week of the outpatient period (days 8–14). As soon as the vouchers given for the CM were no longer available, the rates of positive urine samples were no longer different between the two groups for weeks two (opiates $F(1,78)= 0.153$, $P>0.05$), three (opiates $F(1,78)=0.924$, $P>0.05$) and four (opiates $F(1,78)=0.183$, $P>0.05$)	= (one study, effects visible as long as vouchers were available)	Carroll et al., 1995; Jones et al., 2011; Tuten et al., 2012	

	Outcomes	Interventions	Effects	Quick guide	References	Additional information
		Cognitive behavioural approach plus usual care versus usual care	In two studies, the two interventions gave no differences in the number of positive urine tests among groups. One study (Haug et al., 2004) reported no significant difference for urine tests positive for opioids. Another study (O'Neill et al., 1996) showed no difference in self-reported drug use between groups. At 9-month follow-up the intervention group reduced the frequency of drug injection while the control group increased it (*F* (df 1,71)=6.083, *P*= 0.016)	=	Haug et al., 2004; O'Neill et al., 1996	
	Nicotine consumption	Methadone versus buprenorphine	Smoking data were available from 124 of the patients enrolled in the MOTHER Study (methadone, *n* = 67 and buprenorphine, *n* = 57). Of the sample, 95 % reported cigarette smoking at treatment entry. The fitted difference in change in adjusted cigarettes per day between the two conditions was small and non-significant (â = 0.08, SE = 0.05, *P* =0.132	=	MOTHER Study	
		Methadone versus SROM	At the start of the trial, the mean number of cigarettes smoked per day was 27.56 (SD 16.28) and 31.30 (SD 22.56) for the methadone and morphine groups, respectively. At delivery it was 15.89 (SD 12.24) and 15.20 (SD 8.24), respectively WMD -4.43 (95 % CI -1.47 to 10.33); the results were not statistically significant, but there is a trend in favour of morphine.	= (+ trend SROM)	Fischer et al., 1999	
		Cognitive behavioural approach plus usual care versus usual care	Haug et al. (2004) reported that results of one-way analysis of covariance did not show a significant difference between treatment conditions on self-reported cigarette use per day, CO or cotinine.	=	Haug et al., 2004	
	Use of other substance(s) of abuse	Methadone versus buprenorphine	Jones et al. (2005) reported the percentage of positive urine tests for each substance during the study period for the methadone and buprenorphine groups respectively as follows: cocaine: 15.6 % and 16.7 %; benzodiazepines: 0.4 % and 2.5 %; amphetamine: 0 % and 0 %; marijuana 7.5 % and 0 %. Fischer et al. (2006) reported the median number of urine samples positive for methadone and buprenorphine groups respectively as follows: cocaine: 0.00, 0.00; benzodiazepines: 7.82 and 5.36. No data are reported in the MOTHER Study	?	Jones et al., 2005; Fischer et al., 2006	
		Methadone versus SROM	The study reported the percentage of negative urine toxicology during each week of treatment for methadone and slow-release morphine only in a graph: the mean percentages for the whole study period were about 95 % and 90 % respectively for cocaine and 54 % and 89 % for benzodiazepines.	?	Fischer et al., 1999	

	Outcomes	Interventions	Effects	Quick guide	References	Additional information
		CM approach plus usual care versus usual care	Carroll et al. (1995) reported that there were no significant differences between the enhanced and standard treatment groups with respect to percentage of maternal urine toxicology screens that were positive for cocaine or any other drug, but data are not shown. In Jones et al. (2011) there was a significant effect of the incentives on the rate of cocaine use (F (1,78)= 7.05, P<0.05); as soon as the vouchers were no longer available, the rates of positive urine samples were no longer different between the two groups. In Tuten et al. (2012) the number of cocaine-negative urine tests was not statistically significantly different in the comparison combining escalating and fixed reinforcement condition vesus usual care (F (1, 54.3)= 0.01, P= 0.91), as well as the longest consecutive number of negative urine tests (F (1, 60.2)= 1.08, P=0.30).	=	Carroll et al., 1995; Jones et al., 2011; Tuten et al., 2012	
		Cognitive behavioural approach plus usual care versus usual care	Haug et al. (2004) reported that no significant differences were found between treatment conditions for positive urine tests for cocaine.	=	Haug et al., 2004	
	Obstetric outcomes preterm delivery	Methadone versus buprenorphine	In Fischer et al. (2006), three babies were delivered prematurely in the methadone group and two in the buprenorphine group. In the MOTHER Study 19 % of deliveries were preterm in the methadone group and 7 % in the buprenorphine group. The difference was not statistically significant.	=	Fischer et al., 2006; MOTHER Study	
		Methadone versus SROM	One female delivered at 31 weeks due to early amniotic rupture, but it is not reported which group she belonged to. Mean week of delivery for methadone: 38.92 (SD 1.74) and morphine: 37.79 (SD 2.55). The difference was not statistically significant.	=	Fischer et al., 1999	
		CM approach plus usual care versus usual care	Only Carroll et al. (1995) reported obstetric outcomes and the only outcome reported was the median term of delivery (CM: 40), usual care 38.	?	Carroll et al., 1995	
	Caesarean section	Methadone versus buprenorphine	In Jones et al. (2005), all but one birth in each group were vaginal. In Fischer et al. (2006), two women maintained on buprenorphine delivered by planned caesarean section at week 40. In the MOTHER Study there were 37 % caesarean sections in the methadone group and 29 % in the buprenorphine group. The difference was not statistically significant.	=	Jones et al., 2005; Fischer et al., 2006; MOTHER Study	
		Methadone versus SROM	25 % in both groups.	=	Fischer et al., 1999	
	Complications at delivery	Methadone versus buprenorphine	In Fischer et al. (2006) one woman in the methadone group required vacuum extraction due to a prolonged delivery. No medical complications occurred in Jones et al. (2005). In the MOTHER Study there were 51 % medical complications at delivery in the methadone group and 31 % in the buprenorphine group (P= 0.03).	= (one study + bupre-norphine)	Jones et al., 2005; Fischer et al., 2006; MOTHER Study	
		Methadone versus SROM	8.3 % in both groups.	=	Fischer et al., 1999	

	Outcomes	Interventions	Effects	Quick guide	References	Additional information
	Meconium aspiration	Methadone versus buprenorphine	In the MOTHER Study, there was one case of meconium aspiration in the buprenorphine group.	=	MOTHER Study	
	Foetal presentation	Methadone versus buprenorphine	In Jones et al. (2005) all births were normal presentations; in the MOTHER Study there were 14 % abnormal foetal presentations in the methadone group and 5 % in the buprenorphine group. Abnormal presentations are considered as all non-cephalic (head first) foetal positions at birth. The difference was not statistically significant.	=	Jones et al., 2005; MOTHER Study	
	Puerperal morbidity	Methadone versus buprenorphine	No cases of puerperal morbidity (any illness occurring in the 10 days postpartum) were observed in Jones et al. (2005) and in the MOTHER Study.	=	Jones et al., 2005; MOTHER Study	
	Side effects for the woman	Methadone versus buprenorphine	No side effects for the mother were reported in Jones et al. (2005) and Fischer et al. (2006). In the MOTHER Study there were 14/89 (16 %) serious adverse events in the methadone group and 8/86 (9 %) in the buprenorphine group; RR: 1.82 (95 % CI 0.72– 4.59). There were also 83/89 (93 %) non-serious adverse events in the methadone group and 66/86 (77 %) in the buprenorphine group; RR: 5.10 (95 % CI 0.60– 43.66); the result was not statistically significant.	=	MOTHER Study	The adverse events were, respectively: For the methadone group: abnormal foetal health (three cases), one case of cardiovascular symptoms, one of gastrointestinal symptoms, one of illicit drug use, six obstetric symptoms, one psychological problem and one psychosocial problem, one respiratory symptoms and one sexually transmitted disease. For the buprenorphine group: one case of gastrointestinal symptoms, one genitourinary symptoms, one case of illicit drug use, two obstetric symptoms, one skin condition, and one sleep disturbance.
		Methadone versus SROM	No side effects for women were reported.	=	Fischer et al., 1999	
	**Birth weight**	Methadone versus buprenorphine	In two studies (Jones et al. (2005); MOTHER Study) involving 150 participants, the baby weight MD was -224.91 (95 % CI -248.46 to -201.36). The results indicated that the babies of the woman treated with buprenorphine had higher birth weight. Fischer et al. (2006) did not report data but state that there were no statistically significant differences in the birth weight between groups (mean: 2820 g).	+ bupre-norphine	Jones et al., 2005; Fischer et al., 2006; MOTHER Study	
		Methadone versus SROM	WMD 124 (95 % CI -186 to 434); the result was not statistically significant.	=	Fischer et al., 1999	
		CM approach plus usual care versus usual care	In Carroll et al. (1995) women in the enhanced programme tended to have newborns with higher weight at birth (median: 3348 g vs. 2951 g) than women in standard treatment.	+ contingency	Carroll et al., 1995	

	Outcomes	Interventions	Effects	Quick guide	References	Additional information
	Neonatal abstinence syndrome	Methadone versus buprenorphine	**Number of newborns treated for NAS:** in three studies (Fischer et al., 2006; Jones et al., 2005; MOTHER Study) involving 166 participants, the RR for the baby having NAS was not statistically significant: RR 1.22 (95 % CI 0.89– 1.67). **NAS peak score over all observation days:** in Jones et al., 2005, involving 21 participants, the mean scores were 4.9 in the methadone group and 6.8 in the buprenorphine group but the standard deviation (needed to calculate the CIs) was not reported. Nevertheless, the results are reported as not statistically significant. In the MOTHER Study with 131 participants, the mean score in the methadone group was: 12.8 ±0.6 and in the buprenorphine group was 11.0 ±0.6; *P*= 0.04 in favour of buprenorphine. **Mean duration of treatment for NAS:** two studies (Fischer et al., 2006; MOTHER Study), 145 participants, MD 0.00 (95 % CI -0.03 to 0.03); the result is not statistically significant. **The total amount of morphine required to manage NAS:** two studies (Fischer et al., 2006; MOTHER Study), 145 participants: MD 8.49 (95 % CI 7.90– 9.08); the results are in favour of buprenorphine. **Length of hospital stay:** two studies (Jones et al., 2005, MOTHER Study), 152 participants, MD 5.07 (95 % CI 4.69– 5.46); the result is in favour of buprenorphine.	Number of newborns treated for NAS = NAS peak score = (one study + bupre-norphine) Mean duration treatment NAS = Total morphine required + bupre-norphine Length of hospital stay + bupre-norphine	Jones et al., 2005; Fischer et al., 2006; MOTHER Study	Concerning the total number of morphine drops administered: one study (Jones et al., 2005) covering 21 participants: methadone: 93.1, buprenorphine: 23.6; the result is not statistically significant.
		Methadone versus SROM	Mean duration of NAS treatment WMD -5.00 (95 % CI -10.97 to 0.97); the result was not statistically significant.	=	Fischer et al., 1999	
		CM approach plus usual care versus usual care	Carroll et al. (1995) reported that there were no differences in the length of time the infants remained in hospital for detoxification.	=	Carroll et al., 1995	
	Prenatal and neonatal mortality	Methadone versus buprenorphine	In one study (Fischer et al., 2006) there was one sudden intrauterine death at 38 weeks of pregnancy and one late abortion at 28 weeks of pregnancy, both in the methadone group.	=	Fischer et al., 2006	
		Methadone versus SROM	There was no prenatal or neonatal mortality in either group.	=	Fischer et al., 1999	
	Apgar score	Methadone versus buprenorphine	The Apgar score at five minutes after birth was reported in two studies (Jones et al., 2005; MOTHER Study) involving 163 participants and the MD in scoring in the two groups was zero (MD 0.00 (95 % CI -0.03 to 0.03)). The result is not statistically significant. Fischer et al. (2006) did not report data but state that there were no statistically significant differences in the Apgar score between groups.	=	Jones et al., 2005; Fischer et al., 2006; MOTHER Study	
	Side effect for the child	Methadone versus buprenorphine	No side effects for the child were reported in Jones et al. (2005) and Fischer et al. (2006). In the MOTHER Study there were 6/73 (8 %) serious adverse events in the methadone group and 1/58 (2 %) in the buprenorphine group. The RR was 4.19 (95 % CI 1.59–11.03), in favour of buprenorphine. There were also 34/73 (47 %) non-serious adverse events in the methadone group and 29/58 (50 %) in the buprenorphine group; RR: 1.15 (95 % CI 0.57–2.30); the results were not statistically significant.	+ bupre-norpine	Jones et al., 2005; Fischer et al., 2006; MOTHER Study	Serious adverse events: two cardiovascular symptoms, two obstetric symptoms, two respiratory symptoms and one 'other symptom' in the methadone group, and one baby reporting several symptoms.

Note: CI, confidence interval; CM, contingency management; MD, mean difference; MMT, methadone maintenance treatment; NAS, neonatal abstinence syndrome; RR, risk ratio; SE, standard error; SROM, slow-release oral morphine; WMD, weighted mean difference.

TABLE 4

Methadone compared to buprenorphine for opiate-dependent pregnant women

Outcomes	Illustrative comparative risks (*) (95 % CI)		Relative effect (95 % CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Buprenorphine	Methadone			
Dropout Objective Follow-up: 15 to 18 weeks	Study population		RR 0.64 (0.41 to 1.01)	223 (3 studies)	⊕⊕⊖⊖ Low (1) (2)
	318 per 1000	204 per 1000 (134 to 321)			
	Moderate				
	326 per 1000	209 per 1000 (134 to 329)			
Use of primary substance Objective Follow-up: 15 to 18 weeks	Study population		RR 1.81 (0.7 to 4.69)	151 (2 studies)	⊕⊕⊖⊖ Low (1) (2)
	75 per 1000	135 per 1000 (52 to 350)			
	Moderate				
	43 per 1000	78 per 1000 (30 to 202)			
Birth weight Objective Follow-up: mean 18 weeks	The mean birth weight difference ranged across control groups from 3.53 to 3.09 g	The mean birth weight in the intervention groups was 224.91 g lower (248.46 g to 201.36 g lower)		150 (2 studies)	⊕⊕⊖⊖ Low (1) (2) (3) (4)
Apgar score Objective: Scale from 0 to 10 Follow-up: mean 18 weeks	The mean Apgar score ranged across control groups from 8.9 to 9.0	The mean Apgar score in the intervention groups was 0 higher (0.03 lower to 0.03 higher)		163 (2 studies)	⊕⊕⊖⊖ Low (1) (2)
Number treated for NAS Objective Follow-up: 15 to 18 weeks	Study population		RR 1.22 (0.89 to 1.67)	166 (3 studies)	⊕⊖⊖⊖ Very low (1) (2) (5)
	447 per 1000	546 per 1000 (398 to 747)			
	Moderate				
	466 per 1000	569 per 1000 (415 to 778)			

Apgar, activity, pulse, grimace, appearance and respiration score; CI, confidence interval; NAS, neonatal abstinence syndrome; RR, risk ratio.
GRADE Working Group grades of evidence.
High quality: Futher research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
(1) For incompete outcome data, we judged the studies at high reisk of attrition bias because the attrition rate was high and unbalanced between groups.
(2) Small sample size.
(3) Statistically significant heterogeneity.
(4) No explanation was provided.
(5) Variability in results

Discussion

Summary of the main results

The effectiveness of OST in pregnancy was measured in three studies (Fischer et al., 2006; Jones et al., 2005; MOTHER Study) comparing methadone with buprenorphine (223 participants) and one (Fischer et al., 1999) compared methadone with SROM (48 participants).

For the women, the dropout rate was lower in the methadone group, whereas there was no difference in use of primary substance between methadone and buprenorphine. SROM seemed superior to methadone in helping women to abstain from the use of heroin during pregnancy.

For the newborns, in the comparison between methadone and buprenorphine, birth weight was higher in the buprenorphine group in the two trials that could be pooled. The third study (MOTHER Study) reported that there was no statistically significant difference. For the Apgar score, all studies which compared methadone with buprenorphine did not find significant differences. The studies used a variety of measures to assess NAS. For some of them, there were no statistically significant differences between groups (number of newborns treated for NAS, mean duration of treatment for NAS, total number of morphine drops administered), while others were in favour of buprenorphine (the NAS peak score over all observation days (MOTHER Study), the total amount of morphine required to manage NAS and the length of hospital stay). The comparison of methadone with SROM did not result in any statistically significant difference for birth weight and mean duration of NAS. The Apgar score was not considered in the study (Fischer et al., 1999).

Only one study (MOTHER Study), which compared methadone with buprenorphine, reported side effects: for the woman, no statistically significant differences were observed; for the newborns, the buprenorphine group showed significantly fewer serious side effects.

In the comparison between methadone and SROM, no side effects were reported for the woman, whereas one child in the methadone group had central apnea and one child in the morphine group had obstructive apnea.

Nevertheless, it should be considered that cigarette smoking has an effect on newborn babies' outcomes. Only one study (Fischer et al., 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 most of the included studies. The level of nicotine exposure during pregnancy does affect birth weight and might also affect NAS.

For the effectiveness of any psychosocial intervention combined with agonist maintenance treatment, six studies with 457 participants satisfied the criteria for the assessment of adding psychosocial interventions to standard agonist maintenance treatment (MTT plus counselling) in order to be included in the review. The studies were very heterogeneous in terms of study objective, types of interventions compared, types of outcome and outcome measurements. They have been grouped into three categories: studies on the CM approach (three studies), studies on the cognitive behavioural approach (two studies) and studies on therapeutic workplace approach (one study). All studies assessed the efficacy of the addition of a further psychosocial approach to standard care (methadone maintenance treatment and counselling).

The dropout rate was not significantly different in all three comparisons. For drug use, the CM approach seemed to be efficacious in reducing drug use in one study only. Drug use was not significantly different between groups in studies assessing the efficacy of a cognitive behavioural approach. The study assessing the efficacy of the therapeutic workplace did not assess this outcome.

Obstetric outcomes were not assessed in the included studies. One study on the efficacy of CM assessed these outcomes for the infants. Women in the enhanced programme tended to have heavier infants than women in standard treatment. However, there were no differences in length of time the infants remained in hospital for detoxification.

Quality of the evidence

Regarding the effectiveness of agonist maintenance treatment, three out of four studies had an adequate allocation concealment and were double blinded. The major uncertainty with the results of the studies is for attrition bias: three out of four studies had a high dropout rate of between 30 % and 40 %, unbalanced between groups. Of course this is because of the distinctive condition of this target population.

On the effectiveness of any psychosocial intervention combined with agonist maintenance treatment, only two studies were able to perform an adequate method of random sequence generation. Four studies were judged at low risk of attrition bias and two at unclear risk. None of the studies was 'double blinded' (see box 'What is a bias?' on page 6). Furthermore, information on whether the outcome assessor was blinded was not specified in any of the studies and overall

the methodological information available in the articles did not enter into details, but this can be owing to the lack of space allowed by the editors. We searched for unpublished studies but we did not find any.

Conclusions

The pharmacological interventions studied in this overview were methadone, buprenorphine and SROM. The observed differences between the three approaches did not show a homogeneous and comprehensive pattern that would allow us to conclude that one treatment is superior to the others for all relevant outcomes. While methadone seems superior in retaining patients in treatment, buprenorphine seems to yield to less severe NAS and higher birth weight. In addition, the recently published multicentre international trial on 175 pregnant women is still too small to draw firm conclusions about the equivalence of the treatments compared. 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.

Although conducted before the publication of the World Health Organization's guidelines on pregnant women (WHO, 2014), our results are consistent with the recommendations included therein. In fact, these guidelines affirm that methadone and buprenorphine are equally effective in the treatment of opioid-dependent pregnant women. The two pharmacological approaches differ, with methadone resulting in better maternal retention in treatment and buprenorphine may result in milder NAS, fewer preterm deliveries and higher birth weight.

The guidelines, based on the consensus of the experts involved, recommend that:

> 'opioid-dependent pregnant women who are already taking opioid maintenance therapy with methadone should not be advised to switch to buprenorphine due to the risk of opioid withdrawal. Pregnant opioid-dependent women taking buprenorphine should not be advised to switch to methadone unless they are not responding well to their current treatment. In opioid-dependent pregnant women, the buprenorphine mono formulation should be used in preference to the buprenorphine/naloxone formulation.'
>
> (WHO, 2014)

Psychosocial interventions, when taken together, are not associated with greater retention in treatment or illicit drug abstinence. There are no data on the impact of psychosocial interventions on neonatal and obstetric outcomes. Nevertheless, the guidelines consider psychosocial interventions as an integral component of treatment (regardless of the type of medication selected for the OST).

We still need large RCTs comparing different pharmacological maintenance treatments with longer follow-up periods (ideally up to 1 year) which consider also the level of nicotine exposure, the concomitant use during pregnancy of other prescribed medications (such as selective serotonin reuptake inhibitors, benzodiazepines) and non-prescribed drugs, including cocaine, alcohol and marijuana. Moreover, studies should be carried out to assess the effectiveness of psychosocial treatments in adjunct with pharmacological treatments versus pharmacological treatments alone. We need large RCTs with obstetric and neonatal end points, as well as with longer follow-up periods, in order to examine whether or not psychosocial interventions help pregnant women with illicit drug dependence. Ideally these studies would have multiple sites in order to capture a greater diversity of study patients, which would increase the generalisability of the findings.

Nevertheless, as it is considered important to offer more options to patients entering or remaining in treatment, it is worthwhile to point out that after many years of methadone being the only indication for the treatment of opioid-dependent pregnant women, buprenorphine has now been shown to be acceptable and to create less severe NAS for newborns. This characteristic in particular may help overcome possible resistance by patients and carers, in order to encourage opioid-dependent pregnant women in treatment. Studies of pregnant women are complex for several reasons, including ethical and practical difficulties. It is therefore crucial that we exhaustively analyse all elements of existing studies in order to add to the discussion.

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Annex 1

Characteristics of included studies

Author, year	Study design	Participants	Country	Intervention	Outcome measures
Carroll et al., 1995	Randomised controlled trial. Blindness not possible.	*N*=20 pregnant women enrolled and 14 assigned to methadone maintenance. (1)7 (2)7. Mean age 27.6 years; 78.6 % non-minority (11/14); 78.6 % single; 100 % unemployed; 8 (±6) weeks gestational age upon entry into MMT; mean 2.7 days cocaine use in past 30 days. Exclusion: > 28 weeks pregnant.	USA	For all daily MMT, weekly group counselling, three times/week urine toxicology screening. (1) weekly prenatal classes, weekly relapse prevention groups, childcare during treatment visits, and CM awards – $15/week for three consecutive negative urine screens. (2) MMT and weekly group counselling. No difference between groups in terms of MMT dose (mean 50 mg). Duration: average 23 weeks (range 13–31 weeks). Outpatients.	Attendance was measured in terms of % number of groups attended. Infant outcomes measured as mean gestational age at delivery, mean weight and mean number of days in hospital. Urine toxicology was measure as % positive for cocaine, opiates or other drugs.
Fischer et al., 1999	Randomised controlled trial. Open.	*N*=48 pregnant adults; mean age 26 years; 39.6 % unmarried; duration of opioid dependence: mean 57.2 months. Mean gestational age at entry: 22 weeks. Inclusion criteria: opioid-dependent and polysubstance abuse pregnant females meeting DSM-IV criteria.	Austria	(1) oral methadone (24 participants) versus (2) oral slow-release 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.	Neonatal outcomes: foetal distress; birth weight; NAS (Finnegan scale). Maternal outcomes: retention; cocaine and benzodiazepine consumption (urine analysis); opioid use (identification of injection sites for morphine-maintained group and urine analysis for methadone-maintained group).
Fischer et al., 2006	Randomised controlled trial. Double-blind.	*N*=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.	Austria	(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.	Neonatal outcomes: birth weight; NAS (Finnegan scale); child health status; Apgar score. Maternal outcomes: retention; maternal withdrawal symptoms (Wang Withdrawal Questionnaire); illicit drug use: opioid, cocaine, benzodiazepine (urine analysis).
Haug et al., 2004	Randomised controlled trial. Blindness not possible.	*N*=77 pregnant opioid-dependent women enrolled and 66 assigned to interventions, ≤ 26 weeks' gestational age, receiving MMT and ≥5 cigarettes/day. (1) 30 (2) 36. Mean age 29.7 years; 84 % African American; 79 % single or never married; 97 % unemployed; 94 % less than high school education. DSM-III-R: all heroin dependent (100 %), 41 (35 %) cocaine dependent, 10 (16 %) marijuana dependent, 17 (27 %) alcohol dependent, all (100 %) nicotine dependent. Exclusion: not stated.	USA	For all MMT. All received $10 voucher after initial battery and $20 when 10-week interview was completed. Mean MMT dose 65.2 mg. (1) four MET sessions using a modification of the Project MATCH MET manual (Miller et al., 1995) with the primary goal to assist participants in quitting tobacco smoking. Visit 1: rapport building; visit 2 (1 week later): personalised feedback on positive behaviours, negative consequences of smoking and stage of change; visit 3 (week 4): commitment and plan for change developed; visit 4 (week 6): barriers to long-term change addressed. (2) Information leaflet about the risk of smoking for the woman and the child. Duration 10 weeks. Inpatients in the first phase, then outpatients.	Retention in treatment as % attrition. Cigarette consumption. Urine toxicology done at the 10-week follow-up.

Author, year	Study design	Participants	Country	Intervention	Outcome measures
Jones et al., 2005	Randomised controlled trial. Double-blind.	*N*=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; cocaine use: past 30 days 75 %; opioid use: >4 x 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 preterm labour; evidence of foetal malformation; positive HIV test.	USA	(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.	Neonatal outcomes: Number of neonates treated for NAS; peaks of NAS score; length of neonatal hospitalisation; birth weight, child health status; Apgar score. Maternal outcomes: retention; illicit drug use (urine analysis).
Jones et al., 2011	Randomised controlled trial. Blindness not possible.	*N*=85 pregnant women on MMT, greater than age 18, meeting DSM-II-R criteria for opiate dependence with cocaine abuse, admitted for first time for substance abuse treatment. (1) 47 (2) 38. Mean age 28 years; mean gestational age 23.4 weeks; 96 % unemployed; 85 % single/never married; 76 % African American; 20 % chronic medical conditions; DSM-III-R: 100 % opiate dependent, 69 % cocaine, 5 % marijuana, 10 % alcohol.	USA	Treatment consisted of group counselling and at least once-a-week individual psychotherapy and MMT; mean dose 42 mg for all. (1) Money vouchers could be earned for specific target behaviour: attend at least 4 hours' counselling and (days 8-14) provide a cocaine-negative urine sample. (2) No voucher incentives. Duration 2 weeks. First week inpatients, then outpatients (7 days/week, 6.5 hours/day).	Attendance was measured as mean full-day attendance as well as 'perfect treatment attendance' defined as attendance on at least 13 or 14 full days of treatment. Retention was measured as the % dropout. Urine samples were collected daily from days 8 to 14 and reported as % positive.
MOTHER Study	Multicentre randomised controlled trial. Double-blind, double dummy.	*N*=175 pregnant adults, 131 assigned to interventions; Mean age 27.3 years; 83.2 % white; employed 13.3 %; mean estimated gestational age of foetus 18.6 weeks, mean years of education 11.3; substance use: heroin previous 30 days 10.2 %, cocaine previous 30 days 4.8 %, any alcohol previous 30 days 0.4, % benzodiazepines previous 30 days 0.8 %. Inclusion criteria: opioid-dependent women between the ages of 18 and 41 years with a singleton pregnancy between 6 and 30 weeks of gestation. Exclusion criteria: no medical or other conditions contraindicating participation; pending legal action; disorders related to the use of benzodiazepines or alcohol; planning to give birth outside the hospital at the study site.	United States, Austria, Canada	(1) Sublingual tablets of buprenorphine (58 participants) vs. (2) oral methadone (73 participants). Flexible dose range of 2 to 32 mg of buprenorphine; dose range of 20–140 mg of methadone. Setting: outpatients. Follow-up: up to 10 days after delivery.	Neonatal outcome measures: neonates requiring treatment for NAS, peak NAS score, total amount of morphine needed for treatment of NAS, length of hospital stay, head circumference, number of days during which medication was given for NAS, weight and length at birth, preterm birth, gestational age at delivery and 1-minute and 5-minute, Apgar scores. Maternal outcomes: caesarean section, weight gain, abnormal foetal presentation during delivery, anaesthesia during delivery, the results of drug screening at delivery, medical complications at delivery, study discontinuation, amount of voucher money earned for drug-negative tests, and number of prenatal obstetric visits. Adverse events for child and mothers.

Author, year	Study design	Participants	Country	Intervention	Outcome measures
O'Neill et al., 1996	Randomised controlled trial. Blindness not possible.	*N*=92 pregnant women enrolled in MMT who injected drugs. (1) 47 (2) 45. Mean age 26.2 years; mean years education 10.2; 53 % ever sex worker; mean gestational age 22 weeks; DSM-III-R: 85 % opiate dependent, 15 % cocaine, 59 % marijuana, 32 % alcohol, 98 % nicotine.	Australia	All participants received MMT (mean methadone dose 49 mg) and counselling about HIV risk. (1) Six sessions of manual-based cognitive behavioural relapse prevention therapy aimed at avoiding behaviours at risk for HIV infection (needle sharing and unsafe sex) lasting 60–90 minutes. (2) No intervention. Duration 36 weeks. Outpatients.	Retention was measured as a proportion. Attendance was measured as the average number of missed appointments.
Silverman et al., 2001	Randomised controlled trial. Blindness not possible.	*N*=40 pregnant, unemployed, women 18–50 years old on MMT, and with positive urine toxicology for opiates within 6 weeks prior to enrolment. (1) 20 (2) 20. Mean age 32 years; 83 % African America; 65 % high school or greater education; 7.5 % married; 100 % unemployed; 100 % used cocaine; Exclusion: at risk for suicide, psychiatric disorder.	USA	For all participants, substance abuse counselling and MMT provided. Details of counselling not given. No mention of MMT doses or schedule. (1) Therapeutic workplace 3 hours/day for 6 months. Job skills training provided. Base-pay voucher given out at the end of shift. Entrance to workplace contingent upon negative urine sample. Job skills focused on data entry. Vouchers used to promote abstinence and maintain workplace attendance. (2) 'Routine' drug treatment services provided by the centre. Details not given. Duration 24 weeks. First week inpatients, then outpatients.	Retention in treatment defined as remaining in the study through 24 weeks and reported as *N* and %. Urine toxicology reported as % negative over total study period for each group, and reported as overall positive and drug-specific positive. Attendance in therapeutic workplace was calculated and presented in a bar graph for each individual.
Tuten et al., 2012	Randomised controlled trial. Blindness not possible.	*N*=143 pregnant women with an estimated gestational age of less than 28 weeks who were opioid dependent and methadone stabilised. Average of 30.0 years old (SD=5.2) , 71.4 % African American, 69.9 % never married, mean 11.6 (SD=1.5) years of education, 6.0 % currently employed. 72 % used cocaine in the last 30 days, 21 % used alcohol in the last 30 days. Exclusion: not receiving methadone maintenance, non-compliant with study or Centre for Addiction Pregnancy procedures, had a miscarriage or terminated the pregnancy, transferred programmes or had a negative pregnancy test.	USA	All patients received group and individual counselling, obstetric care, mental health treatment and transportation assistance. (1) Escalating reinforcement condition, earned a $7.50 voucher for the first opioid-negative and cocaine-negative urine sample submitted. Value of voucher increased by $1/day on the specimen collection days until delivery or until the participant reached $42.50 in earnings, after which earnings were capped and remained constant at this amount. If relapse occurred, there was no reward for positive urine sample and the value of the voucher was reset to $7.50. Participants earned vouchers until delivery. (2) Fixed reinforcement condition, participants received a $25 voucher each time they provided a drug-negative urine sample. Participants who remained drug abstinent through the incentive period had total potential earnings of $950. Earnings continued if it occurred after week 13. A drug-positive sample or missed urine sample precluded voucher earnings, but earnings resumed upon submission of next drug-free sample. (3) Attendance control condition, fixed and escalating participants were linked to an attendance control participant. Each time the fixed or escalating reinforcement participant received a voucher, the yoked participant received the same amount, regardless of urine test results for that individual. Control participants were not aware they were linked, but were told there was a chance that they might or might not be paid for delivering urine samples. Study duration was 13 weeks or until delivery with 1 week of inpatient treatment (when participants could earn two vouchers and 12 outpatient weeks during which participants could earn three vouchers weekly).	Drug abstinence (number of urine screening tests negative for both opiates and cocaine, number of negative urine tests prior to the first positive test and longest consecutive number of negative urine tests), opioid use (with similar parameters as drug abstinence), cocaine use (with similar parameters).

DSM, *Diagnostic and Statistical Manual of Mental Disorders*; HIV, human immunodeficiency virus; MET, motivational enhancement therapy; MMT, methadone maintenance treatment; NAS, neonatal abstinence syndrome; SD, standard deviation.

Annex 2

Search strategies

Cochrane Drugs and Alcohol Group Register of Trials search strategy

diagnosis=opioid* OR opiate* AND Pregnan* [TI, AB]

CENTRAL search strategy

1. MeSH descriptor: [Opioid-Related Disorders] explode all trees
2. ((drug or substance) near (abuse* or addict* or dependen* or disorder*)):ti,ab,kw (Word variations have been searched)
3. ((opioid* or opiate*) near (abuse* or addict* or dependen*)):ti,ab,kw (Word variations have been searched)
4. #1 or #2 or #3
5. MeSH descriptor: [Heroin] explode all trees
6. (opioid* or opiate* or opium or heroin):ti,ab,kw (Word variations have been searched)
7. MeSH descriptor: [Methadone] explode all trees
8. "methadone":ti,ab,kw (Word variations have been searched)
9. MeSH descriptor: [Buprenorphine] explode all trees
10. "buprenorphine":ti,ab,kw (Word variations have been searched)
11. "codeine":ti,ab,kw (Word variations have been searched)
12. "morphine":ti,ab,kw (Word variations have been searched
13. "LAAM":ti,ab,kw (Word variations have been searched)
14. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15. MeSH descriptor: [Pregnancy] explode all trees
16. pregnant:ti,ab,kw (Word variations have been searched)
17. "mother":ti,ab,kw (Word variations have been searched)
18. #15 or #16 or #17
19. #4 and #14 and #18

PubMed search strategy

1. "Opioid-Related Disorders"[MeSh]
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. Heroin[MeSH]
6. heroin[tiab]
7. (opioid* OR opiate* OR opium)
8. methadone[MeSH] OR methadone[tiab]
9. #5 OR #6 OR #7 OR #8
10. pregnan*[tiab]
11. "Pregnancy"[Mesh]
12. "Pregnancy Complications"[Mesh]
13. mother*[tiab]
14. #10 OR #11 OR #12 OR #13
15. randomized controlled trial [pt]
16. controlled clinical trial [pt]
17. randomized [tiab]
18. placebo [tiab]
19. drug therapy [sh]

20. randomly [tiab]
21. trial [tiab]
22. groups [tiab]
23. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24. animals [mh] NOT humans [mh]
25. #23 NOT #24
26. #4 AND #9 AND #14 AND #25

CINAHL search strategy

S1 (MH "Substance Use Disorders+")
S2 TX(drug N3 addict*) or TX(drug N3 dependen*) or TX(drug N3 abuse*) or TX(drug N3 misus*) or TX(drug N3 use*)
S3 TX(substance N3 addict*) or TX(substance N3 dependen*) or TX(substance N3 abuse*) or TX(substance N3 misus*)
S4 TX(opioid* N3 addict*) or TX(opioid* N3 dependen*) or TX(opioid* N3 abuse*) orTX(opiate* N3 addict*) or TX(opiate* N3 dependen*) or TX(opiate* N3 abuse*)
S5 S1 or S2 or S3 or S4
S6 MH "Heroin"
S7 TX heroin
S8 TX (opioid* or opiate*)
S9 opium
S10 (MH "Methadone")
S11 TX methadone
S12 S6 or S7 or S8 or S9 or S10
S13 (MH "Pregnancy+")
S14 TI pregnan* or AB pregnan* or TI mother* or AB mother*
S15 (MH "Pregnancy Complications+")
S16 S13 or S14 or S15
S17 MH "Clinical Trials+"
S18 PT Clinical trial
S19 TI clinic* N1 trial* or AB clinic* N1 trial*
S20 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S21 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S22 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S23 MH "Random Assignment"
S24 TI random* allocat* or AB random* allocat*
S25 MH "Placebos"
S26 TI placebo* or AB placebo*
S27 MH "Quantitative Studies"
S28 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27
S29 S5 AND S12 AND S16 AND S28

EMBASE search strategy

1. 'addiction'/exp
2. 'drug abuse'/exp
3. ((drug OR substance OR opioid* OR opiat*) NEXT/5 (abuse* OR addict* OR depend* OR disorder*)):ab,ti
4. #1 OR #2 OR #3
5. opioid*:ab,ti OR opiat*:ab,ti OR opium:ab,ti OR heroin*:ab,ti OR narcot*:ab,ti
6. 'methadone'/exp OR methadone:ab,ti OR 'buprenorphine'/exp OR buprenorphine:ab,ti OR 'codeine'/exp OR codeine:ab,ti OR 'diamorphine'/exp OR morphine:ab,ti OR laam:ab,ti
7. #5 OR #6
8. 'pregnancy'/exp OR 'pregnancy complication'/exp OR pregnan*:ab,ti
9. mother*:ab,ti

10. #8 OR #9
11. 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'single blind procedure'/exp OR 'controlled clinical trial'/exp OR 'clinical trial'/exp OR placebo:ab,ti OR 'double-blind':ab,ti OR 'single blind':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR random*:ab,ti OR factorial*:ab,ti ORcrossover:ab,ti OR (cross:ab,ti AND over:ab,ti) OR 'randomized controlled trial'/exp
12. #4 AND #7 AND #10 AND #11

Web of Science search strategy

Timespan=2007-06-01 - 2013-03-18. Databases=SCI-EXPANDED, SSCI, A&HCI.

Topic=(((opioid* OR opiate* OR opium OR heroin OR methadone) same (abuse* or addict* or dependen* or disorder*))) AND Topic=((pregnan* OR mother*)) AND Topic=((randomi* OR randomly OR placebo* OR trial*))

Annex 3

Criteria for risk of bias assessment

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process, such as random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation.
	High risk	The investigators describe a non-random component in the sequence generation process, such as odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk.
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement.
3. Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding. Blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but it is likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
4. Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Blinding of participants and providers and it is unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
5. Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
6. Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk.
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or drop out	Low risk	No missing outcome data. Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on observed effect size. Missing data have been imputed using appropriate methods. All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat).
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce clinically relevant bias in observed effect size. 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group).

Annex 4

Forest plot of comparisons

FIGURE A1

Methadone vs. buprenorphine, outcome: dropout.

Study or subgroup	Methadone		Buprenorphine		Weight	Risk ratio M-H, fixed, 95 % CI
	Events	Total	Events	Total		
Fischer et al., 2006	3	9	1	9	2.8%	3.00 (0.38–23.58)
Jones et al., 2005	4	15	6	15	16.9%	0.67 (0.23–1.89)
MOTHER Study	16	89	28	86	80.3%	0.55 (0.32–0.95)
Total (95% CI)		**113**		**110**	**100.0%**	**0.64 (0.41–1.01)**
Total events	23		35			
Heterogenety Chi² = 2.44, df = 2 (*P* = 0.29), I² = 18%						
Test for overall effect *Z* = 1.91 (*P* = 0.06)						

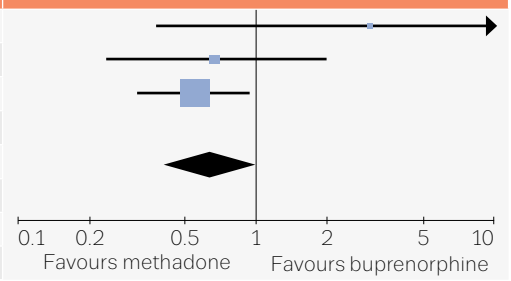


FIGURE A2

Methadone vs. buprenorphine, outcome: use of primary substance

Study or subgroup	Methadone		Buprenorphine		Weight	Risk ratio M-H, fixed, 95 % CI
	Events	Total	Events	Total		
Jones et al., 2005	1	11	0	9	8.9%	2.50 (0.11–54.87)
MOTHER Study	11	73	5	58	91.1%	1.75 (0.64–4.75)
Total (95% CI)		**84**		**67**	**100.0%**	**1.81 (0.70–4.69)**
Total events	12		5			
Heterogenety Chi² = 0.05, df = 1 (*P* = 0.83), I² = 0%						
Test for overall effect *Z* = 1.23 (*P* = 0.22)						

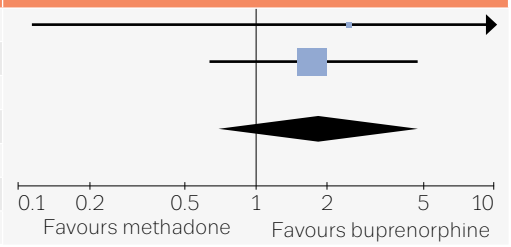


FIGURE A3

Methadone vs. buprenorphine, outcome: birth weight

Study or subgroup	Methadone			Buprenorphine			Weight	Mean difference IV, fixed, 95 % CI
	Mean	SD	Total	Mean	SD	Total		
Jones et al., 2005	3,000	120	11	3,530	162	8	3.1%	-530.00 (-662.78 to -397.22)
MOTHER Study	2,878	66	73	3,093	72	58	96.9%	-215,00 (-238.93 to -191,07)
Total (95% CI)			**84**			**68**	**100.0%**	**-224.91 (-248.46 to -201.36)**
Heterogenety Chi² = 20.94, df = 1 (*P* < 0.00001), I² = 95%								
Test for overall effect *Z* = 18.72 (*P* < 0.00001)								

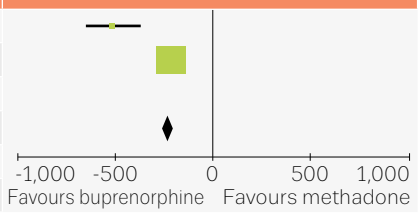


FIGURE A4

Methadone vs. buprenorphine, outcome: Apgar score

Study or subgroup	Methadone			Buprenorphine			Weight	Mean difference IV, fixed, 95 % CI
	Mean	SD	Total	Mean	SD	Total		
Jones et al., 2005	8.9	0.09	11	8.9	0.15	10	8,6%	0.00 (-0.11 to 0.11)
MOTHER Study	9	0.1	73	9	0.1	69	91,4%	0.00 (-0.03 to 0.03)
Total (95% CI)			**84**			**79**	**100.0%**	**0.00 (-0,03 to 0.03)**
Heterogenety Chi² = 0.00, df = 1 (*P* = 1.00), I² = 0%								
Test for overall effect *Z* = 0.00 (*P* = 1.00)								

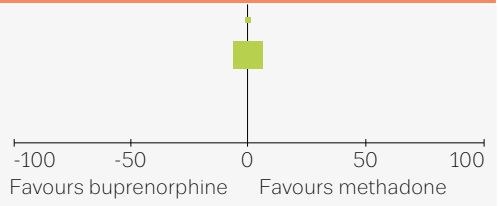


FIGURE A5

Methadone vs. buprenorphine, outcome: number treated for NAS

Study or subgroup	Methadone		Buprenorphine		Weight	Risk ratio M-H, fixed, 95 % CI
	Events	Total	Events	Total		
Fischer et al., 2006	3	6	5	8	11.8 %	0.80 (0.31–2.10)
Jones et al., 2005	5	11	2	10	5.7 %	2.27 (0.56–9.20)
MOTHER Study	41	73	27	58	82.5 %	1.21 (0.86–1.70)
Total (95 % CI)		**90**		**76**	**100.0 %**	**1.22 (0.89–1.67)**
Total events	49		34			
Heterogenety Chi² = 1.50, df = 2 (*P* = 0.47), I² = 0 %						
Test for overall effect *Z* = 1.24 (*P*=0.22)						

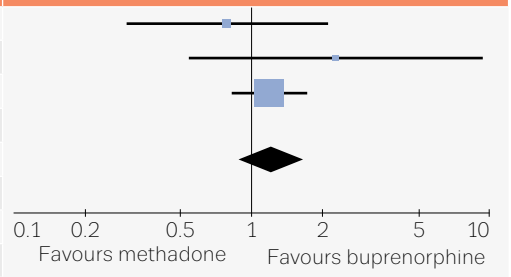


FIGURE A6

Methadone vs. buprenorphine, outcome: mean duration of NAS treatment

Study or subgroup	Methadone			Buprenorphine			Weight	Mean difference IV, fixed, 95 % CI
	Mean	SD	Total	Mean	SD	Total		
Fischer et al., 2006	5.3	1.5	6	4.8	2.9	8	0.0 %	0.50 (-1.84 to 2.84)
MOTHER Study	9	0.1	73	9	0.1	58	100.0 %	0.00 (-0,03 to 0.03)
Total (95 % CI)			**79**			**66**	**100.0 %**	**0.00 (-0.03 to 0.03)**
Heterogenety Chi² = 0.18, df = 1 (*P* = 0.68), I² = 0 %								
Test for overall effect *Z* = 0.01 (*P* = 1.00)								

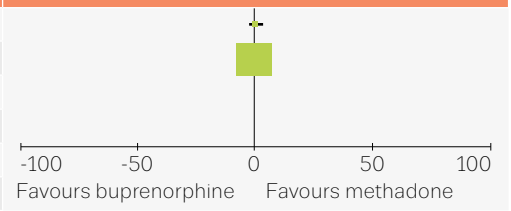


FIGURE A7

Methadone vs. buprenorphine, outcome: total amount of morphine for NAS

Study or subgroup	Methadone			Buprenorphine			Weight	Mean difference IV, fixed, 95 % CI
	Mean	SD	Total	Mean	SD	Total		
Fischer et al., 2006	2.71	1.68	6	2	2	8	9.4 %	0.71 (-1.22 to 2.64)
MOTHER Study	10.4	2.6	73	1.1	0.7	58	90.6 %	9.30 (8.68–9.92)
Total (95 % CI)			**79**			**66**	**100.0 %**	**8.49 (7.90–9.08)**
Heterogenety Chi² = 68.87, df = 1 (*P* < 0.00001), I² = 99 %								
Test for overall effect *Z* = 28.06 (*P* < 0.00001)								

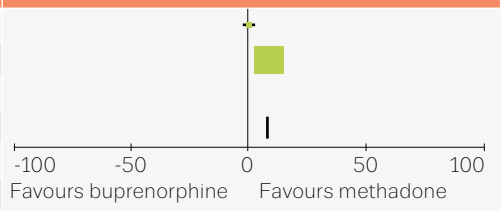


FIGURE A8

Methadone vs. buprenorphine, outcome: length of hospital stay

Study or subgroup	Methadone			Buprenorphine			Weight	Mean difference IV, fixed, 95 % CI
	Mean	SD	Total	Mean	SD	Total		
Jones et al., 2005	8.1	0.78	11	6.8	0.86	10	30.1 %	1.30 (0.60–2.00)
MOTHER Study	17.5	1.5	73	10.8	1.2	58	69.9 %	6.70 (6.24–7.16)
Total (95 % CI)			**84**			**68**	**100.0 %**	**5.07 (4.69–5.46)**
Heterogenety Chi² = 157.69, df = 1 (*P* < 0.00001), I² = 99 %								
Test for overall effect *Z* = 25.73 (*P* < 0.00001)								

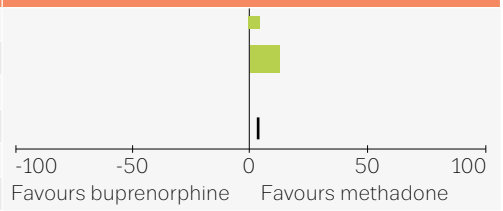


FIGURE A9

Contingency management versus control, outcome: drop out

Study or subgroup	Methadone		Buprenorphine		Weight	Risk ratio M-H, fixed, 95 % CI
	Events	Total	Events	Total		
Jones et al., 2011	3	47	2	38	17.1 %	1.21 (0.21–6.89)
Tuten et al., 2012	12	52	4	22	43.6 %	1.27 (0.46–3.51)
Tuten et al., 2012	11	38	4	22	39.3 %	1.59 (0.58–4.40)
Total (95 % CI)		**137**		**82**	**100.0 %**	**1.39 (0.71–2.69)**
Total events	26		10			
Heterogeneity Chi² = 0.12, df = 2 (*P* = 0.94), I² = 0 %						
Test for overall effect *Z* = 0.97 (*P* =0.33)						

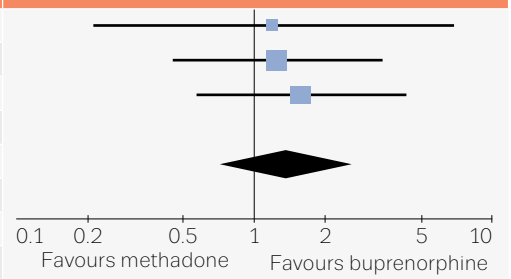
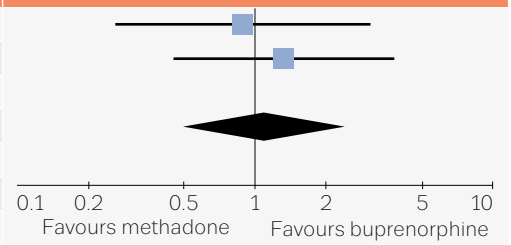


FIGURE A10

Manual-based interventions versus control, outcome: drop out

Study or subgroup	Methadone		Buprenorphine		Weight	Risk ratio M-H, fixed, 95 % CI
	Events	Total	Events	Total		
Haug et al., 2004	4	30	5	33	48.2 %	0.88 (0.26–2.98)
O'Neill et al., 1996	7	47	5	45	51.8 %	1.34 (0.46–3.92)
Total (95 % CI)		**77**		**78**	**100.0 %**	**1.12 (0.50–2.49)**
Total events	11		10			
Heterogeneity Chi² = 0.26, df = 1 (*P* = 0.61), I² = 0 %						
Test for overall effect *Z* = 0.27 (*P* =0.78)						



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About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction is the hub of drug-related information in Europe. Its mission is to provide the European Union and its Member States with 'factual, objective, reliable and comparable information' on drugs and drug addiction and their consequences. Established in 1993, it opened its doors in Lisbon in 1995, and is one of the European Union's decentralised agencies. The Centre offers policymakers the evidence base they need for drawing up drug laws and strategies. It also helps professionals and researchers pinpoint best practice and new areas for analysis.

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