Guidelines for the identification and management of substance use and substance use disorders in pregnancy

World Health Organization

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GLOSSARY OF TERMS USED IN THESE GUIDELINES

Abstinence

Refraining from alcohol or drug use. The term "abstinence" should not be confused with the term "abstinence syndrome", which refers to a withdrawal syndrome.

Alcohol

In chemical terminology, alcohols are a large group of organic compounds derived from hydrocarbons and containing one or more hydroxyl (-OH) groups. Ethanol (C_2H_5OH, ethyl alcohol) is one of this class of compounds, and is the main psychoactive ingredient in alcoholic beverages. By extension the term "alcohol" is also used to refer to alcoholic beverages. Alcohol is a sedative/hypnotic with effects similar to those of barbiturates.

Antagonist

A substance that counteracts the effects of another agent. Pharmacologically, an antagonist interacts with a receptor to inhibit the action of agents (agonists) that produce specific physiological or behavioural effects mediated by that receptor.

Amphetamines / amfetamines

One of a class of sympathomimetic amines with powerful stimulant actions on the central nervous system. The class includes amphetamine, dexamphetamine, and methamphetamine. Pharmacologically related drugs include methylphenidate, phenmetrazine and amphepramone (diethylpropion).

Barbiturate

One of a group of central nervous system depressants that chemically are substituted derivatives of barbituric acid; examples are amobarbital, pentobarbital, phenobarbital, and secobarbital. They are used as antiepileptics, anaesthetics, sedatives, hypnotics and, less commonly, as anxiolytics or anti-anxiety drugs (see sedative/hypnotic). Acute and chronic use induces effects similar to those of alcohol.

Benzodiazepine

One of a group of structurally related drugs used mainly as sedatives/hypnotics, muscle relaxants, and anti-epileptics, and once referred to by the now-deprecated term "minor tranquillisers". These agents are believed to produce therapeutic effects by potentiating the action of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter.

Bloodborne diseases

Diseases such as HIV and Hepatitis B and C, which are spread by blood-to-blood contact (e.g. needle-sharing).

Cannabis

A generic term used to denote the several psychoactive preparations of the marijuana (hemp) plant, *Cannabis sativa*. They include marijuana leaf (in street jargon: grass, pot, dope, weed or reefers), bhang, ganja or hashish (derived from the resin of the flowering heads of the plant), and hashish oil.

Cocaine

An alkaloid obtained from coca leaves or synthesized from ecgonine or its derivatives. Cocaine hydrochloride was commonly used as a local anaesthetic in dentistry, ophthalmology, and in ear, nose and throat surgery because its strong vasoconstrictor action helps to reduce local bleeding. Cocaine is a powerful central nervous system stimulant used non-medically to produce euphoria or wakefulness. Repeated use produces dependence.

Dependence

A cluster of physiological, behavioural and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol, or tobacco.

Detoxification

Also referred to as a managed withdrawal or supported withdrawal, detoxification refers to the process of an individual being withdrawn from the effects of a psychoactive substance. When referring to a clinical procedure, detoxification refers to a withdrawal process that is carried out in a safe and effective manner, minimizing the withdrawal symptoms, and supporting the person physically and mentally through the process.

Drug-related problem

Any of the range of adverse accompaniments of drug use, particularly illicit drug use. "Related" does not necessarily imply causality.

Fetal alcohol syndrome (FAS)

A pattern of retarded growth and development, both neuropsychological and physical, with typical facial dysmorphic features, found in some children exposed to alcohol during pregnancy. A spectrum of physical and neurodevelopmental abnormalities, which includes FAS, has been attributed to the effects of alcohol on the fetus. The level of maternal consumption that produces Fetal Alcohol Spectrum Disorders (FASD) has not been established and is influenced by genetic and other maternal and fetal characteristics.

Harmful substance use

A pattern of psychoactive substance use that causes damage to health (ICD-10 code F1x.1). The damage may be physical (e.g. in the cases of hepatitis from the self-administration of injected psychoactive substances) or mental.

Hazardous substance use

A pattern of substance use that increases the risk of harmful consequences for the user and fetus.

Intoxication

A condition that follows the administration or consumption of a psychoactive substance and results in disturbances in the level of consciousness, cognition, perception, judgement, affect, or behaviour, or other psychophysiological functions and responses.

Neonatal Abstinence Syndrome / Neonatal Withdrawal Syndrome

When a neonate shows signs of withdrawal from exposure to psychotropic substances in utero, this is referred to as neonatal abstinence or neonatal withdrawal.

Opioid maintenance treatment

Also referred to as opioid agonist maintenance treatment, or opioid substitution treatment. Examples of opioid maintenance therapies are methadone and buprenorphine maintenance treatment. Maintenance treatment can last from several months to more than 20 years, and is often accompanied by other treatment (e.g. psychosocial treatment).

Psychosocial intervention

Any non-pharmacological intervention carried out in a therapeutic context at an individual, family or group level. Psychosocial interventions range from structured, professionally administered psychological interventions (e.g. cognitive behaviour therapy or insight oriented psychotherapy) to non-professional psychological and social interventions (e.g. self-help groups and non-pharmacological interventions from traditional healers, as well as accommodation, financial support, legal support, information and outreach).

Substance use disorders

The concept of "substance use disorders" includes both the dependence syndrome and the harmful use of psychoactive substances such as alcohol, cannabis, amphetamine-type stimulants (ATS), cocaine, opioids and benzodiazepines.

Volatile substances

Substances that vaporize at ambient temperatures. Volatile substances that are inhaled for psychoactive effects (also called inhalants) include the organic solvents present in many domestic and industrial products (such as glue, aerosol, paints, industrial solvents, lacquer thinners, gasoline and cleaning fluids) and the aliphatic nitrites such as amyl nitrite.

Withdrawal syndrome (abstinence syndrome, withdrawal reaction, withdrawal state)

A group of symptoms of variable clustering and degree of severity that occur on cessation or reduction of use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period or in high doses (ICD-10 code F1x.3). The onset and course of withdrawal syndrome are time-limited and relate to the type of substance and dose being taken immediately before cessation or reduction of use. Typically, the features of withdrawal syndrome are the opposite of acute intoxication.

ACRONYMS & ABBREVIATIONS

AUDIT	alcohol use disorders identification test
ASSIST	alcohol, smoking and substance involvement screening test
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	amphetamine-type stimulants
CBT	cognitive behavioural therapy
CDT	carbohydrate-deficient transferrin
CI	confidence interval
CM	contingency management
CND	Commission on Narcotic Drugs
CNS	central nervous system
EUFASD	European Fetal Alcohol Spectrum Disorders Alliance
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorders
FIGO	International Federation of Gynecology and Obstetrics
GABA	gamma-aminobutyric acid
GDG	guidelines development group
GGT	gamma-glutamyl transpeptidase
DSM	Diagnostic and Statistical Manual of Mental Disorders
HCW	health-care workers
HIV	human immunodeficiency virus
ICD	International Classification of Diseases
IUGR	intrauterine growth retardation
ITT	intention-to-treat
IV	intravenous
MCV	mean corpuscular volume
M-H	Mantel-Haenszel
MD	mean differences
MI	motivational interviewing
N	number
NAS	neonatal abstinence syndrome
NICU	neonatal intensive care unit
OR	odds ratio
PAHO/AMRO	Pan American Health Organization/WHO Regional Office for the Americas
PCP	phencyclidine
PMNCH	Partnership for Maternal, Newborn and Child Health
PMTCT	prevention of mother-to-child transmission of HIV
RCT	randomized controlled trial

RevMAN	Review Manager
RR	risk ratio
SBIRT	screening, brief-intervention and referral to treatment
SD	standard deviation
SOF	summary of findings
STI	sexually transmitted infections
TLFB	timeline follow back
TAU	treatment as usual
THC	tetrahydrocannabinol
UN	United Nations
UNODC	United National Office on Drugs and Crime
WHO	World Health Organization
WIC	women, infants and children

EXECUTIVE SUMMARY

Use of alcohol, illicit drugs and other psychoactive substances during pregnancy can lead to multiple health and social problems for both mother and child. Use of alcohol during pregnancy can lead to fetal alcohol syndrome and other harms such as spontaneous abortion, stillbirth, low birthweight, prematurity and birth defects.

Dependence on alcohol and other drugs can also severely impair an individual's functioning as a parent, spouse or partner, and instigate and trigger gender-based and domestic violence, thus significantly affecting the physical, mental and emotional development of children.

Pregnancy may be an opportunity for women, their partners and other people living in their household to change their patterns of alcohol and other substance use. Health workers providing care for women with substance use disorders during pregnancy need to understand the complexity of the woman's social, mental and physical problems in order to provide appropriate advice and support throughout pregnancy and the postpartum period.

Why these guidelines were developed

These guidelines have been developed to enable professionals to assist women who are pregnant, or have recently had a child, and who use alcohol or drugs or who have a substance use disorder, to achieve healthy outcomes for themselves and their fetus or infant. They have been developed in response to requests from organizations, institutions and individuals for technical guidance on the identification and management of alcohol and other substance use and substance use disorders in pregnant women. They were developed in tandem with the WHO recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy. There are currently no global guidelines providing evidence-based recommendations for identifying and managing substance use and substance use disorders in pregnancy. While several high-income countries have developed national guidelines covering these issues, low- and middle-income countries currently lack such guidance.

Who should use these guidelines

These guidelines have been primarily written for health-care providers managing women from conception to birth, and during the postnatal period, and their infants.

Objectives and scope of these guidelines

These guidelines aim to provide evidence-based technical advice to health-care providers on identifying and managing substance use and substance use disorders in pregnant women, which enables health-care practitioners to apply the scientific principles of a public health approach in their own countries. An equally important objective is to enable pregnant women to make healthy decisions about alcohol and other substance use in the context of pregnancy and breastfeeding.

After a broad review of the needs of this population and challenges faced by health-care providers working with pregnant women with substance use disorders, it was decided that the guidelines should focus on six areas:

1. Screening and brief intervention
2. Psychosocial interventions
3. Detoxification
4. Dependence management
5. Infant feeding
6. Management of infant withdrawal

How these guidelines were developed

The development of these guidelines began in mid 2012 as a collaborative effort between the WHO departments of Mental Health and Substance Abuse and the Tobacco Free Initiative with production of the guidelines proposal, a virtual meeting of the Guidelines Development Group (GDG), and subsequent approval of the guidelines proposal by the WHO Guidelines Review Committee. The GDG has conferred through teleconferences and virtual meetings, as well as at two face-to-face meetings. At the first meeting, held in Washington DC, USA, (29 January to 1 February 2013), the evidence for the harms of different patterns of alcohol and drug use in pregnancy was reviewed, and the scope and areas of evidence retrieval were established. At the second and final meeting, held at the WHO Headquarters in Geneva (11–13 September 2013) the evidence retrieved was presented using evidence profiles and GRADE tables (see annex), and final recommendations were formulated. The GDG used the evaluation of the evidence of effect, plus further evidence on harms, benefits, values, preferences, resource use and feasibility, to set the strength of the recommendations (see decision tables and evidence profiles in annex).

The **strength of the recommendation** was set as either:

> **'strong'**: meaning that the Guideline Development Group was confident that the quality of the evidence of effect, combined with *certainty* about the values, preferences, benefits and feasibility, made this a recommendation that should be done in most circumstances and settings;
>
> or
>
> **'conditional'**: meaning there was less certainty about the quality of the evidence and values, preferences, benefits and feasibility of this recommendation. Thus, there may be circumstances or settings in which the recommendation should not apply.

Recommendations

Governing principles

It was noted by the GDG that certain principles apply to all the recommendations described below. These overarching principles are proposed to provide guidance in the process of planning, implementing and evaluating the most suitable and relevant recommendations according to the national contexts and available resources.

I. **Prioritizing prevention.** Preventing, reducing and ceasing the use of alcohol and drugs during pregnancy and in the postpartum period are essential components in optimizing the health and well-being of women and their children.

II. **Ensuring access to prevention and treatment services.** All pregnant women and their families affected by substance use disorders should have access to affordable prevention and treatment services and interventions delivered with a special attention to confidentiality, national legislation and international human rights standards; women should not be excluded from accessing health care because of their substance use.

III. **Respecting patient autonomy.** The autonomy of pregnant and breastfeeding women should always be respected, and women with substance use disorders need to be fully informed about the risks and benefits, for themselves and for their fetuses or infants, of available treatment options, when making decisions about her health care.

IV. **Providing comprehensive care.** Services for pregnant and breastfeeding women with substance use disorders should have a level of comprehensiveness that matches the complexity and multifaceted nature of substance use disorders and their antecedents.

V. **Safeguarding against discrimination and stigmatization.** Prevention and treatment interventions should be provided to pregnant and breastfeeding women in a way that will prevent stigmatization, discrimination and marginalization, and promote family, community and social support, as well as social inclusion by fostering strong links with available childcare, employment, education, housing and other relevant services.

IDENTIFICATION AND MANAGEMENT OF SUBSTANCE USE AND SUBSTANCE USE DISORDERS IN PREGNANCY

No.	Recommendation	Strength of recommendation	Quality of evidence
Screening and brief interventions for hazardous and harmful substance use during pregnancy			
1	Health-care providers should ask all pregnant women about their use of alcohol and other substances (past and present) as early as possible in the pregnancy and at every antenatal visit.	Strong	Low
2	Health-care providers should offer a brief intervention to all pregnant women using alcohol or drugs.	Strong	Low
Psychosocial interventions for substance use disorders[1] in pregnancy			
3	Health-care providers managing pregnant or postpartum women with alcohol or other substance use disorders should offer comprehensive assessment[2], and individualized care.[3]	Conditional	Very low
Detoxification or quitting programmes for substance dependence in pregnancy			
4	Health-care providers should at the earliest opportunity advise pregnant women dependent on alcohol or drugs to cease their alcohol or drug use and offer, or refer to, detoxification services under medical supervision where necessary and applicable.[4]	Strong	Very low
5	Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment[5] whenever available rather than to attempt opioid detoxification.	Strong	Very low
6	Pregnant women with benzodiazepine dependence should undergo a gradual[6] dose reduction, using long-acting benzodiazepines.	Strong	Very low
7	Pregnant women who develop withdrawal symptoms following the cessation of alcohol consumption should be managed with the short-term use of a long-acting benzodiazepine.[7]	Strong	Very low
8	In withdrawal management for pregnant women with stimulant dependence, psychopharmacological medications may be useful to assist with symptoms of psychiatric disorders but are not routinely required.	Strong	Very low
Pharmacological treatment (maintenance and relapse prevention) for substance dependence in pregnancy			
9	Pharmacotherapy is not recommended for routine treatment of dependence on amphetamine-type stimulants, cannabis, cocaine, or volatile agents in pregnant patients.	Conditional	Very low
10	Given that the safety and efficacy of medications for the treatment of alcohol dependence has not been established in pregnancy, an individual risk-benefit analysis should be conducted for each woman.	Conditional	Very low
11	Pregnant patients with opioid dependence should be advised to continue or commence opioid maintenance therapy with either methadone or buprenorphine.	Strong	Very low
Breastfeeding with maternal alcohol and/or substance dependence			
12	A. Mothers with substance use disorders should be encouraged to breastfeed unless the risks clearly outweigh the benefits. B. Breastfeeding women using alcohol or drugs should be advised and supported to cease alcohol or drug use; however, substance use is not necessarily a contraindication to breastfeeding.	Conditional	Low

No.	Recommendation	Strength of recommendation	Quality of evidence
13	Skin-to-skin contact is important regardless of feeding choice and needs to be actively encouraged for the mother with a substance use disorder who is able to respond to her baby's needs.	Strong	Low
14	Mothers who are stable on opioid maintenance treatment with either methadone or buprenorphine should be encouraged to breastfeed unless the risks clearly outweigh the benefits.	Strong	Low
Management of infants exposed to alcohol and other psychoactive substances			
15	Health-care facilities providing obstetric care should have a protocol in place for identifying, assessing, monitoring and intervening, using non-pharmacological and pharmacological methods, for neonates prenatally exposed to opioids.	Strong	Very low
16	An opioid should be used as initial treatment for an infant with neonatal opioid withdrawal syndrome if required.	Strong	Very low
17	If an infant has signs of a neonatal withdrawal syndrome due to withdrawal from sedatives or alcohol, or the substance the infant was exposed to is unknown, then phenobarbital may be a preferable initial treatment option.	Conditional	Very low
18	All infants born to women with alcohol use disorders should be assessed for signs of fetal alcohol syndrome.[8]	Conditional	Very low

[1] The concept of "substance use disorders" includes dependence syndrome and harmful use of psychoactive substances such as alcohol, cannabis, amphetamine-type stimulants (ATS), cocaine, benzodiazepines etc.
[2] A comprehensive assessment of women using alcohol or drugs in pregnancy and the postpartum period include assessment of patterns of substance use, medical or psychiatric co-morbidity, family context and social problems.
[3] Individual care planning involves selecting appropriate psychosocial and pharmacological interventions based on a comprehensive assessment.
[4] Pregnant women dependent on alcohol or drugs who agree to undergo detoxification should be offered the supported withdrawal from substance use in an inpatient or hospital facility, if medically indicated; equal attention should be paid to the health of mother and fetus and treatment adjusted accordingly.
[5] Methadone maintenance treatment or buprenorphine maintenance treatment.
[6] For as short a time as is medically feasible.
[7] Management of alcohol withdrawal usually includes administration of thiamine.
[8] Signs of Fetal Alcohol Syndrome (FAS) include growth impairment, dysmorphic facial features (short palpebral fissures, smooth or flattened philtrum, thin upper lip) and central nervous system abnormalities.

INTRODUCTION

Use of alcohol, illicit drugs and other psychoactive substances during pregnancy is common and can lead to multiple health and social problems for both mother and child.

Use of alcohol during pregnancy can lead to fetal alcohol syndrome and other harms such as spontaneous abortion, stillbirth, low birthweight, prematurity and birth defects. Use of alcohol and other drugs can also severely impair an individual's functioning as a parent, spouse or partner, and trigger gender-based and domestic violence, thus significantly affecting the physical, mental and emotional development of children. Injecting drug use is also associated with an increased risk of transmission of HIV and viral hepatitis to pregnant women and their infants.

Alcohol and other substance use by expectant mothers and other people living in their households is not only detrimental to maternal and child health – the topics of UN Millennium Development Goals 2, 4, 5 and 6 – but can also undermine the social and health gains achieved in many low- and middle-income countries.

Pregnancy may be an opportunity for women, their partners and other people living in their household to change their patterns of alcohol and other substance use. Health workers providing care for women with substance use disorders during pregnancy need to understand the complexity of the woman's social, mental and physical problems and to provide the right advice and support throughout pregnancy and the postpartum period.

WHY THESE GUIDELINES WERE DEVELOPED

These guidelines have been developed to enable professionals to assist pregnant women who use alcohol or drugs or with substance use disorders to achieve healthy outcomes. There are currently no global guidelines providing evidence-based recommendations for identifying and managing substance use and substance use disorders in pregnancy. While several high-income countries have developed national guidelines covering these issues, low- and middle-income countries currently lack such guidance.

The project was initiated in response to requests from organizations, institutions and individuals for technical guidance on the identification and management of alcohol and other substance use disorders in pregnant women. These recommendations have been developed in tandem with the WHO recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy.

These guidelines are also a response to Resolution 63.13 of the World Health Assembly (outlining and endorsing a Global Strategy to Reduce the Harmful Use of Alcohol), and the Political Declaration and Plan of Action on International Cooperation Towards an Integrated and Balanced Strategy to Counter the World Drug Problem (agreed at the High Level Segment of the 52nd Session of the Commission of Narcotic Drugs; CND).

Development of these guidelines is part of a range of activities carried out by the WHO Department of Mental Health and Substance Abuse (MSD). These include the development and dissemination of the ASSIST tool for screening for substance use in health-care settings; the ASSIST-linked brief intervention manual; the WHO mhGAP intervention package for management of priority mental health and behavioural disorders; the WHO guidelines for the psychosocially assisted pharmacological treatment of opioid dependence; the UNODC/WHO discussion paper on the principles of drug dependence treatment; and the UNODC/WHO programme on drug dependence treatment and care.

EXISTING RELEVANT GUIDELINES ON RELATED PROBLEMS AND DISORDERS

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): Manual for use in primary care
http://whqlibdoc.who.int/publications/2010/9789241599382_eng.pdf

Brief Intervention. The ASSIST-linked brief intervention for hazardous or harmful substance use. Manual for use in primary care.
http://whqlibdoc.who.int/publications/2010/9789241599399_eng.pdf

AUDIT: Alcohol Use Disorders Identification Test: Guidelines for use in primary care*
http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6a.pdf

Brief Intervention for Hazardous and Harmful Drinking: Manual for use in primary care*
http://whqlibdoc.who.int/hq/2001/WHO_MSD_MSB_01.6b.pdf

Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence
http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf

mhGAP – Intervention Guide
http://www.who.int/mental_health/publications/mhGAP_intervention_guide/en/
Contains recommendations on the management of alcohol and drug use disorders in non-psychiatric settings which are applicable to antenatal services.

Working with Individuals, Families and Communities to Improve Maternal and Newborn Health
http://whqlibdoc.who.int/hq/2010/WHO_MPS_09.04_eng.pdf

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice
http://www.who.int/maternal_child_adolescent/documents/924159084x/en/index.html

PMTCT Strategic Vision 2010–2015
http://whqlibdoc.who.int/publications/2010/9789241599030_eng.pdf
Contains recommendations on the prevention of mother-to-child transmission of HIV in women who inject drugs.

Guidelines on HIV and Infant Feeding 2010
http://www.who.int/maternal_child_adolescent/documents/9789241599535/en/index.html
Contains recommendations on postnatal care in HIV-positive women relevant to intravenous drug users.

Acceptable Medical Reasons for Use of Breast-milk Substitutes
http://whqlibdoc.who.int/hq/2009/WHO_FCH_CAH_09.01_eng.pdf
Contains recommendations on circumstances when breastfeeding is not advised.

* Although these guidelines were published in 2001, prior to establishment of current WHO guideline methodology requiring systematic review of the evidence, the effectiveness of brief interventions for hazardous and harmful alcohol drinking has been confirmed in recent WHO guidelines approved by the WHO Guideline Review Committee, including the mhGAP Intervention Guide in the above table.

WHO SHOULD USE THESE GUIDELINES

These guidelines have been primarily written for health-care providers managing women from conception to birth and the postnatal period, and their infants.

OBJECTIVES AND SCOPE OF THE DOCUMENT

These guidelines aim to provide evidence-based technical advice to health-care providers on identifying and managing substance use in pregnant women, which enables users to apply the scientific principles of a public health approach in their own countries. An equally important objective is to enable pregnant women to make healthy decisions about alcohol and other substance use in the context of pregnancy, breastfeeding and the postnatal period.

After a broad search of the needs of this population and challenges faced by health-care providers working with pregnant women with substance use disorders, it was agreed by the Guideline Development Group (GDG) that these guidelines should focus on six areas:

1. screening and brief intervention
2. psychosocial interventions
3. detoxification
4. dependence management
5. infant feeding
6. management of neonatal withdrawal.

INDIVIDUALS AND PARTNERS INVOLVED IN DEVELOPMENT OF THE GUIDELINES

WHO steering group

An internal steering group was drawn from the WHO departments of Mental Health and Substance Abuse, Reproductive Health and Research, Gender Equity and Human Rights, and the Tobacco Free Initiative. The full list of names is provided in Annex 4.

Guideline Development Group

The Guideline Development Group was made up of people with content expertise, relevant experience in health care in low- and middle-income countries and expertise in evidence-based guideline methodology. The Guideline Development Group selection also ensured gender balance and regional diversity. Members have been drawn from all WHO regions.

Consultants with expertise in evidence search and GRADE methodology supported the Guideline Development Group. The full list of the Guideline Development Group members and consultants along with their expertise, affiliations and geographical base is provided in Annex 4.

External review group

External reviewers were drawn from end-users, agencies and partners working in the subject area of the guidelines. Their names, affiliations, areas of interest and geographical base are given in Annex 4.

External reviewers were asked to evaluate and comment at different stages of development of the guidelines. Some members of the external review group attended the initial scoping meeting and the final recommendation decision meeting as ‘special invitees’ where they acted as observers providing comments but had no

involvement in decision-making. They reviewed the scoping questions, outcomes of interest, evidence profiles, and the final guideline document. Reviewer response was compiled and comments used to refine the scope of the guidelines, the outcomes of interest, and the final recommendations.

Management of conflicts of interest

All Guideline Development Group members, external reviewers and consultants completed the WHO declaration of interest forms. Several Guideline Development Group members declared academic and financial interests. These were then reviewed by the secretariat for potential conflicts of interest (see summary in Annex 5). Hendree Jones had received funding from Reckitt Benckiser, a manufacturer of buprenorphine. She received small honoraria for presenting at conferences, and received free buprenorphine for use in her clinical trials. Gabriele Fischer received a small amount of consultancy funding from Reckitt Benckiser, a manufacturer of buprenorphine, Mundipharma, a manufacturer of morphine, and Lannacher, a manufacturer of psychiatric medication. Anju Dhawan had received funding for a clinical trial from Rusan Pharmaceuticals, a manufacturer of both methadone and buprenorphine. As these members are well-recognized researchers and clinicians in this field and, taking into consideration the level of funding, it was agreed that they should not be excluded from the GDG but that these potential competing interests should be managed by excluding them from active discussion and decision-making related to the pharmaceuticals produced by companies from which they had received funds. Both meetings began with an open declaration of interests. It was made clear that those Guideline Development Group members with pharmaceutical industry funding could not participate in discussions on questions related to the medications associated with such companies.

HOW THE GUIDELINES WERE DEVELOPED

The development of these guidelines began in mid 2012 as a collaborative effort between the WHO departments of Mental Health and Substance Abuse and the Tobacco Free Initiative with production of the guidelines proposal, a virtual meeting of the Guideline Development Group (GDG), and subsequent approval of the guidelines proposal by the WHO Guideline Review Committee. The GDG has conferred through teleconferences and virtual meetings, as well as at two face-to-face meetings. At the first meeting, held at the WHO offices in Washington DC, USA (29 January to 1 February 2013), the evidence for the harms of different patterns of alcohol and drug use in pregnancy was reviewed, and the scope and areas of evidence retrieval were established. At the second and final meeting, held at the WHO headquarters in Geneva, Switzerland (11–13 September 2013), the evidence retrieved was presented using evidence profiles and GRADE tables (see annex), and final recommendations were formulated. These were then reviewed by the external review group and finalized by the GDG using online discussions and a final teleconference.

EVIDENCE SEARCH AND RETRIEVAL

The six focus areas agreed upon by the GDG were used to generate appropriate evidence questions to govern systematic searches for evidence. In April 2013, the GDG were asked to select and rate outcomes on a scale from 1 to 9, where 9 is most important (critical) and 1 is least important. Means were calculated for each outcome and the top seven outcomes used for the evidence review, except where the GDG agreed that more than seven outcomes were necessary (see evidence profiles and GRADE tables in Annex 1).

Four investigators (two consultants, two WHO interns) managed the evidence retrieval. The database search was conducted by Tomas Allen, WHO information specialist, who searched multiple databases: PubMed, EmBase, CENTRAL, Psychinfo, CINAHL (see Annex 2 for details of MeSH terms, etc). Essentially, the search strategy was to identify all randomized controlled trials (RCTs) and systematic reviews conducted in pregnant women using alcohol or drugs, and then to allocate these to the different areas of evidence retrieval. The search identified approximately 6000 articles, which were screened on the basis of title and abstract, then on the full paper (see Figure 1, and Tables 1 & 2, below). Where a recent Cochrane review or other high-quality systematic review was identified, this was used as the evidence base and results presented in GRADE tables. Where a Cochrane review or equivalent was not available, RCTs were identified and a systematic review

TABLE 1. NUMBER OF RECORDS BY DATABASE SEARCHED

Database	Number of records
PubMed	1479
EmBase	3614
CENTRAL	84
PsychInfo	512
CINAHL	754
TOTAL	6443
Deduplicated	5632

FIGURE 1: SCREENING OF RECORDS FROM THE LITERATURE SEARCH TO ELIGIBLE ARTICLES

TABLE 2. NUMBER OF ARTICLES AND DISTINCT RCTs BY EVIDENCE RETRIEVAL AREA

Intervention	Articles	RCTs
Screening and brief intervention	17	10
Psychosocial interventions	30	15
Detoxification	0	0
Dependence management	36	4
Lactation	0	0
Management of the infant	5	4
Unclassified	5	n/a
Total	93	33

conducted using Cochrane methods, including meta-analysis, where appropriate, to generate results that were then evaluated using GRADE.

To supplement gaps in the RCT literature, the other studies identified in the systematic literature search were also allocated to each area of evidence retrieval used to provide supplementary information in the GRADE profiles. There were 598 such articles that were not RCTs but still considered relevant to the key issues covered by the guidelines.

A values and preferences survey was conducted over three weeks in August 2013. Respondents – many of them health-care workers or pregnant (or recently pregnant) women – were asked to rate their preference for each draft recommendation and to provide comments on how it might affect them. At the final face-to-face guideline development group meeting, held in September 2013, an analysis of the responses was presented during discussion of each recommendation. These results were used by the GDG to weigh values and preferences when setting the strength of each recommendation. The form can be accessed at: https://sryyz.enketo.formhub.org/webform

EVIDENCE TO RECOMMENDATIONS

The GRADE system for assessing quality of evidence and using evidence to inform decisions was applied by the GDG when drafting the final recommendations. For each of the six areas of scoping focus, an evidence profile was provided summarizing the evidence retrieved, including evidence on values, preferences, benefits, harms and feasibility. Wherever possible, the evidence retrieved was evaluated using GRADE and GRADE tables were provided. Evidence of effectiveness was rated as high, moderate, low or very low depending on the certainty of effect measured in the studies evaluated. For many of the EVIDENCE questions the evidence was either lacking or very limited, leading to a rating of very low quality evidence. The GDG recognized that extensive research needs to be done to provide a solid evidence base for management of pregnant women with substance use and substance use disorders. A decision table was used by the Guideline Development Group to assess and agree on the quality of evidence and certainty about harms and benefits, values and preferences, feasibility and resource implications (see annex for details of each decision, presented in Evidence Profiles 1–6).

The **strength of the recommendation** was set as either:

> **'strong'**: meaning that the Guideline Development Group was confident that the quality of the evidence of effect, combined with *certainty* about the values, preferences, benefits and feasibility, made this a recommendation that should be done in most circumstances and settings;
>
> or
>
> **'conditional'**: meaning there was less certainty about the quality of the evidence and values, preferences, benefits and feasibility of this recommendation. Thus, there may be circumstances or settings in which it should not apply.

Decisions were usually made by consensus but where there was disagreement, the GDG members voted and a two-thirds majority was required for a decision to be carried. Where a two-thirds majority was not achieved initially, it was agreed that the recommendation should be reworded and a vote taken again. This was necessary in only one instance – for recommendation 8, concerning management of stimulant withdrawal.

RECOMMENDATIONS

Following an extensive review of the evidence in each of the six scoping areas, the GDG agreed on the following recommendations for the identification and management of substance use and substance use disorders during pregnancy. Each recommendation is followed by remarks clarifying contextual issues and relevant aspects of management. During development of the recommendations, the GDG identified considerable research gaps and agreed on a list of research priorities and questions, which are listed after the recommendations.

Overarching principles

It was noted by the Guideline Development Group that certain principles apply to all the recommendations described below. These overarching principles are proposed to provide guidance in the process of planning, implementing and evaluating the most suitable and relevant recommendations according to the national contexts and available resources.

I. **Prioritizing prevention.** *Preventing, reducing and ceasing the use of alcohol and drugs during pregnancy and in the postpartum period are essential components in optimizing the health and well-being of women and their children.*

This effort requires a multifaceted approach with multidisciplinary actions, including the right to accurate information about the risks of alcohol and drug use in pregnancy, a health-care system that implements

prevention strategies and supports healthy choices about substance use among women of childbearing age, and health promotion efforts encouraging a healthy home and social environment, supporting pregnant women and their partners in making healthy choices about their substance use and protecting from pressures to drink alcohol or use drugs.

II. **Ensuring access to prevention and treatment services.** *All pregnant women and their families affected by substance use disorders should have access to affordable prevention and treatment services and interventions delivered with a special attention to confidentiality, national legislation and international human rights standards; women should not be excluded from accessing health care because of their substance use.*

Health-care services should be able to identify and manage substance use and substance use disorders in pregnancy. Substance use disorders should be identified by the health-care system at the earliest opportunity and quality, affordable and accessible treatment offered. Specialized services for women with substance use disorders should be recognized as an important component of the health system and need to be available proportional to the clinical need. Health-care services for women with substance use disorders should take into consideration the childcare needs of women when considering the accessibility of their services. Confidentiality, a fundamental right of every health-care user, is also affected by the organization of services.

III. **Respecting patient autonomy.** *The autonomy of pregnant and breastfeeding women should always be respected; women with substance use disorders need to be fully informed about the risks and benefits, for themselves and for their fetuses or infants, of available treatment options, when making decisions about their health care.*

Patient autonomy and patient-centred care are crucial components of health-care services for pregnant women. Treatment decisions should be based on accepted principles of medical-care ethics, respecting a women's autonomy in decisions related to her care and the health of her fetus, and her right to privacy and confidentiality when discussing treatment options. It is essential to provide clear, accurate and consistent information to pregnant and breastfeeding women about the risks of alcohol and drug use, and all women with substance use disorders should have access to information about effective contraception.

IV. **Providing comprehensive care.** *Services for pregnant and breastfeeding women with substance use disorders should have a level of comprehensiveness that matches the complexity and multifaceted nature of substance use disorders and their antecedents.*

Comprehensive services for pregnant and breastfeeding women include a range of gender-sensitive prevention and treatment interventions that can respond to multiple needs, including childcare needs, comorbid mental and concurrent medical conditions, bloodborne and other infectious diseases, poor diet and psychosocial problems such as relationships with a partner/other people living in the same household, homelessness, poverty and violence. Comprehensive services that offer a continuity of care are generally much easier for vulnerable groups to access.

V. **Safeguarding against discrimination and stigmatization.** *Prevention and treatment interventions should be provided to pregnant and breastfeeding women in ways that prevent stigmatization, discrimination, marginalization, and promote family, community and social support as well as social inclusion by fostering strong links with available childcare, employment, education, housing and other relevant services.*

Health-care providers should seek to establish a clinician-patient relationship without discrimination or stigmatization. All important information about the risks of substance use and the benefits of treatment should be communicated in a non-judgemental, respectful, non-stigmatizing and empathic manner, sensitive to age, culture and language differences. All important information has to be provided verbally, as well as in writing, at reading and comprehension levels that are congruent with the patient's level of literacy. Health-care providers should respond to disclosure of private and distressing information (e.g. gender-based violence or self-harm) with sensitivity.

Screening and brief interventions for hazardous and harmful substance use during pregnancy *(Evidence Profile 1: see Annex 1, page 22)*

Much of the evidence underlying the effectiveness of screening and brief interventions during pregnancy comes from a period when reporting standards and measures of bias were not in standard use, hence the evidence quality is graded as low or very low. However, the evidence retrieved indicated that being asked about alcohol and other substance use in a detailed and comprehensive manner may increase a woman's awareness of the risks associated with alcohol and drug use and may function to modify her behaviour.

A brief motivational intervention has been found to reduce the number of drinks and the number of heavy drinking days during the postpartum period. Pregnant women with higher levels of alcohol use may reduce their alcohol use following a brief intervention that includes their partner.

Pregnant adolescent girls with a substance use disorder have been shown to reduce their substance use after a single-session, standardized brief intervention. Full details of studies evaluated, harms and benefits, feasibility and resource use are provided in Annex 1, page 22.

RECOMMENDATION 1

Health-care providers should ask all pregnant women about their use of alcohol and other substances (past and present) as early as possible in the pregnancy and at every antenatal visit.

Strength of recommendation: Strong **Quality of evidence: Low**

Remarks:

- Asking at every visit is important as some women are more likely to report sensitive information only after a trusting relationship has been solidly established.
- Pregnant women should be advised of the potential health risks to themselves and to their babies posed by alcohol and drug use.
- Validated screening instruments for alcohol and other substance use and use disorders are available (see Annex 3).
- Health-care providers should be prepared to intervene or refer all pregnant women who are identified as using alcohol and/or drugs (past and present).
- It was decided that despite the low quality of evidence of effect, the benefit – potential reduction of alcohol and substance use – outweighed any potential harms of a brief psychosocial intervention, which were considered minimal. Therefore the balance of benefits versus harms was clearly positive despite uncertainty about the degree of benefit. In addition, the burden of implementation was minimal.

RECOMMENDATION 2

Health-care providers should offer a brief intervention to all pregnant women using alcohol or drugs.

Strength of recommendation: Strong **Quality of evidence: Low**

Remarks:

- Brief intervention is a structured therapy of short duration (typically 5–30 minutes) offered with the aim of assisting an individual to cease or reduce the use of a psychoactive substance. It is designed in particular for general practitioners and other primary health-care workers.
- Health-care providers should be given appropriate training and resource materials.
- The brief intervention should be individualized, and include feedback and advice on ceasing or reducing alcohol and other substance use during pregnancy. There may need to be follow-up with the patient, with the possibility of referral to treatment for those patients who are unable to reduce or eliminate such use.
- The approach/attitude of health-care providers is an important contributor to the effectiveness of brief interventions.
- As for recommendation 1, it was decided that, despite the low quality of evidence of effectiveness, this should be a strong recommendation because the potential benefit – reduction of alcohol and/other substance use – likely outweighs any potential harms of a brief psychosocial intervention which were considered minimal. Therefore the balance of benefits versus harms was clearly positive, although there was uncertainty about the degree of benefit. In addition the burden of implementation was minimal.

Psychosocial interventions for substance use disorders in pregnancy *(Evidence Profile 2: see Annex 1, page 44)*

The concept of "substance use disorders" includes dependence syndrome and harmful use of psychoactive substances such as alcohol, cannabis, amphetamine-type stimulants (ATS), cocaine, opioids and benzodiazepines. The evidence review sought trials evaluating the effectiveness of psychosocial interventions, including trials of cognitive behavioural therapy (CBT), motivational interviewing (MI), contingency management (CM), and home visits. All the trials were conducted in services specializing in the management of substance use in pregnancy. "Treatment-as-usual" in this context is best considered a form of unstructured psychosocial intervention rather than the absence of psychosocial support.

- Findings suggest that CBT may be superior to treatment-as-usual in terms of treatment retention, reductions in risky sex and needle use, and occurrence of preterm birth.
- Findings support the superiority of contingency management (CM) to treatment-as-usual in terms of retention in treatment, percentage of negative urines, and weeks of continuous cocaine abstinence.
- Findings do not support the superiority of MI to treatment-as-usual or educational control, with similar results for maternal retention in treatment and maternal substance abuse.
- A review of randomized trials suggests that increased home visits following delivery are not effective in reducing maternal substance use, or alcohol use, nor in improving adherence to treatment of substance use disorders.

RECOMMENDATION 3

Health-care providers managing pregnant or postpartum women with alcohol or other substance use disorders should offer comprehensive assessment and individualized care.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- A comprehensive assessment of women using alcohol or drugs in pregnancy and the postpartum period includes an assessment of patterns of substance use, medical or psychiatric comorbidity, family context, as well as social problems.
- Individualized care involves selecting appropriate psychosocial interventions of different intensity based on the particular needs of the pregnant women and the resources available. Psychosocial interventions include a number of psychological treatments and social supports, ranging from lesser to higher intensity. The psychosocial treatment and support referred to in this section is a more intensive set of interventions typically delivered by people with specific training in the management of substance use disorders, and usually includes repeated contact with the patient. The kinds of specific psychological techniques considered in this category include cognitive behavioural therapy, contingency management and motivational interviewing/enhancement. The kinds of social support referred to in this section include assistance with accommodation, vocational training, parenting training, life-skills training, legal advice, home-visiting and outreach.
- Despite the benefits of psychosocial treatment outweighing the harms, this recommendation was considered to be conditional given the absence of strong evidence and the potential resource implications.

Detoxification or quitting programmes for alcohol and other substance dependence in pregnancy *(Evidence Profile 3: see Annex 1, page 93)*

A withdrawal syndrome requiring pharmacological treatment in pregnancy can be said to occur for three substances: benzodiazepines, alcohol, and opioids. The withdrawal syndrome associated with the cessation of other substances (such as psychostimulants) has not been considered to justify the use of psychotropic medication. For those pregnant women for whom medication-assisted withdrawal is successful, there does not appear to be any evidence of significant fetal distress during detoxification, no increased risk of fetal demise or premature delivery.

For opioid dependence, in addition to recommending cessation of opioid use, there is the option of prescribing long-acting opioids such as methadone and buprenorphine to maintain stable opioid levels (see also Evidence Profile 4 in Annex 1). Although this treatment approach includes a risk of neonatal opioid withdrawal symptoms, opioids are essentially non-toxic at stable levels. Cessation of opioids, on the other hand carries a higher risk of relapse to unstable patterns of short-acting opioid use (such as heroin). The decision, therefore, is between opioid maintenance treatment approach with a known risk of neonatal withdrawal but a low risk of relapse, and opioid detoxification, which, if successful, carries no risk of neonatal withdrawal, but, if unsuccessful, has a high risk of adverse neonatal outcomes, including neonatal opioid withdrawal and intrauterine growth retardation (IUGR) and also adverse maternal outcomes such as overdose.

For dependence on other substances, there was considered to be no feasible maintenance treatment option.

RECOMMENDATION 4

Health-care providers should, at the earliest opportunity, advise pregnant women dependent on alcohol or drugs to cease their alcohol or drug use and offer, or refer to, detoxification services under medical supervision where necessary and applicable.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Pregnant women dependent on alcohol or drugs who agree to undergo detoxification should be offered the supported withdrawal from substance use in an inpatient or hospital facility, if medically indicated.
- Detoxification can be undertaken at any stage in pregnancy, but at no stage should antagonists (such as naloxone, or naltrexone – in the case of opioid withdrawal) be used to accelerate the detoxification process.
- Equal attention should be paid to the health of mother and fetus during detoxification and treatment adjusted accordingly.
- The exceptions to this recommendation are opioid and benzodiazepine dependence, which are covered by recommendations 5 and 6 separately.
- It was decided that this recommendation should be strong, despite the very low quality of evidence of the effectiveness of the health-care intervention because there is clear evidence of harm to the fetus of ongoing maternal substance use, and the benefit to both mother and fetus of ceasing alcohol and/or substance use under medical supervision strongly outweighs any potential harms.

RECOMMENDATION 5

Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available rather than to attempt opioid detoxification.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Opioid maintenance treatment in this context refers to either methadone maintenance treatment or buprenorphine maintenance treatment.
- Pregnant patients with opioid dependence who wish to undergo detoxification should be advised that relapse to opioid use is more likely following medication-assisted withdrawal than while undertaking opioid maintenance treatment.
- Such medication-assisted withdrawal from opioids should be attempted only in an inpatient unit, using a gradual reduction in methadone or buprenorphine doses. Inpatient care should also be considered for the initiation and optimization of maintenance treatment.
- Psychosocial treatment should be an integral component of such treatment.
- Pregnant women who fail to complete medication-assisted withdrawal should be offered opioid agonist pharmacotherapy.
- It was decided that this recommendation should be strong despite the low quality of evidence of effectiveness from randomized controlled trials, as the rate of relapse to opioid use following detoxification has been shown to be high and the risks of harm to both mother and fetus from failed detoxification are catastrophic compared to the very low risks of harm from opioid maintenance treatment.

RECOMMENDATION 6

Pregnant women with benzodiazepine dependence should undergo a gradual dose reduction, using long-acting benzodiazepines.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Long-acting benzodiazepines should only be used for as short a time as is medically feasible in managing benzodiazepine withdrawal.
- Psychosocial interventions should be offered throughout the period of benzodiazepine withdrawal.
- Inpatient care should be considered in the withdrawal management of pregnant women with benzodiazepine dependence.
- It was decided that this recommendation should be strong despite the very low quality of evidence of effectiveness because ongoing benzodiazepine use in pregnancy is associated with significant risk of harm. At the same time, abrupt cessation of benzodiazepines can result in a severe withdrawal syndrome including seizures and psychosis. This leaves gradual reduction as the only practicable alternative. Significant clinical experience indicates that this approach is feasible and safe. Hence the GDG was in agreement that the benefits of gradual dose reduction outweigh the harms of both ongoing use and abrupt cessation.

RECOMMENDATION 7

Pregnant women who develop withdrawal symptoms following the cessation of alcohol consumption should be managed with the short-term use of a long-acting benzodiazepine.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Management of alcohol withdrawal usually also includes administration of thiamine.
- Alcohol withdrawal management may be facilitated by the use of an alcohol-withdrawal scale such as the CIWA-Ar.
- Inpatient care should be considered in the withdrawal management of pregnant women with alcohol dependence.
- Alcohol withdrawal can be a severe and even life-threatening condition, provoking seizures and delirium. Evidence from non-pregnant populations has demonstrated the effectiveness of long-acting benzodiazepines for preventing seizures and delirium in alcohol withdrawal. Given the severity of alcohol withdrawal, and the lack of significant harm from short-term benzodiazepine use, and the evidence supporting the use of benzodiazepines in the management of alcohol withdrawal in the general population, the GDG decided that this recommendation should be strong despite the low quality of evidence in pregnant women.

RECOMMENDATION 8

In withdrawal management for pregnant women with stimulant dependence, psychopharmacological medications may be useful to assist with symptoms of psychiatric disorders but are not routinely required.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Except for the management of acute intoxication, withdrawal management in amphetamine-type stimulants (ATS) dependence or cocaine dependence does not include psychopharmacological medications as a primary approach to treatment in pregnant patients. There is no evidence that medication-assisted withdrawal would benefit pregnant women with these respective disorders.
- Inpatient care should be considered in the withdrawal management of pregnant women with stimulant dependence.
- It was decided that this recommendation should be strong despite the very low quality of evidence because the harms to mother and fetus of ongoing use of psychostimulants have been shown to be high. The risks of providing short-term appropriate non-teratogenic medications for short-term management of psychologically distressing symptoms in pregnancy are very low. Therefore, the potential benefits of this approach strongly outweigh the harms of providing psychopharmacological treatment of symptoms, if required, during psychostimulant withdrawal.

Pharmacological treatment (maintenance and relapse prevention) for alcohol and other substance dependence in pregnancy *(Evidence Profile 4: see Annex 1, page 100)*

Systematic reviews of psychopharmacological treatments, methadone versus buprenorphine and methadone compared to slow-release morphine for pregnant women with substance use disorders were performed and the evidence of effect evaluated (see GRADE tables and summary of findings tables in Annex 1 for full details). Findings in brief:

- Pharmacotherapy has been shown to be successful in the treatment of opioid dependence and benzodiazepine dependence. Methadone and buprenorphine have similar efficacy in the management of opioid dependence. While methadone may result in better maternal retention in treatment, buprenorphine may result in milder NAS, less preterm delivery and higher birthweight.
- Combining psychosocial interventions with pharmacotherapy has been shown to be superior to pharmacotherapy alone.
- No evidence was found on the use of medications for relapse prevention for alcohol dependence in pregnancy (acamprosate, disulfiram, nalmefene, naltrexone).
- No RCT evidence was found on the use of naltrexone in relapse prevention from opioid dependence in pregnancy.
- No evidence was found on the use of benzodiazepine maintenance for benzodiazepine dependence in pregnancy.

RECOMMENDATION 9

Pharmacotherapy is not recommended for routine treatment of dependence on amphetamine-type stimulants, cannabis, cocaine or volatile agents in pregnant patients.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- For pregnant patients who use cannabis, amphetamine-type stimulants, cocaine, and volatile agents, the focus of treatment should be on psychosocial interventions.
- The recommendation was considered conditional given the complete lack of research on this issue.

RECOMMENDATION 10

Given that the safety and efficacy of medications for the treatment of alcohol dependence has not been established in pregnancy, an individual risk benefit analysis should be conducted for each woman.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- Pregnant patients with alcohol dependence should be offered psychosocial interventions.
- The recommendation was considered conditional given the complete lack of research on this issue.

RECOMMENDATION 11

Pregnant patients with opioid dependence should be advised to continue or commence opioid maintenance therapy with either methadone or buprenorphine.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Pregnant patients with opioid dependence should be encouraged to commence opioid agonist pharmacotherapy, which should be combined with psychosocial interventions.
- 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.
- Regardless of the choice of medication, psychosocial interventions should be an integral component of treatment.
- Opioid-dependent pregnant patients who wish to receive opioid antagonist pharmacotherapy should be discouraged from such a choice.
- It was decided that this recommendation should be strong despite the low quality of evidence as the rate of relapse to opioid use following detoxification is high and the risks of harm from failed detoxification are catastrophic compared to the small risks of harm from opioid maintenance treatment.

Breastfeeding and maternal substance use *(Evidence Profile 5: see Annex 1, page 122)*

Enhanced maternal-infant attachment through breastfeeding is especially important, particularly for women feeling guilty about their prenatal substance use and those who lack self-confidence in parenting skills. Breastfeeding and/or breast milk may reduce the incidence and/or severity of neonatal withdrawal syndrome in opioid-exposed infants.

Evidence of decreased stress response and increased vagal tone, indicating better autonomic regulation, in lactating compared to non-lactating women is salient for drug-dependent women. Stress can be a major factor in the development of psychiatric symptoms, and has been linked to relapse to substance use. Alcohol use, binge drinking, tobacco and cannabis use rates rebound substantially in the postpartum period compared with use during pregnancy. Depression correlates with substance use, and new mothers with postpartum depression may be at high risk for substance use or return to substance use. Maternal psychopathology is more common in substance-dependent women than in the general population, and is not infrequently related to poor judgment, enhancing the physical risk to the breastfed infant. Maternal somnolence, lack of adequate sleep-wake cycling, or decreased reaction times due to alcohol or drug use may increase the risk of infant injury injury, including smothering the child by falling asleep while breastfeeding.

RECOMMENDATION 12

A. Mothers with substance use disorders should be encouraged to breastfeed unless the risks clearly outweigh the benefits.

B. Breastfeeding women using alcohol or drugs should be advised and supported to cease alcohol or drug use; however, substance use is not necessarily a contraindication to breastfeeding.

Strength of recommendation: Conditional **Quality of evidence: Low**

Remarks:

- A risk assessment should take into account the risks of exposure to alcohol and drugs in breast milk, HIV status, the specific pattern of substance use in each case, the availability of safe and affordable breast milk substitutes, as well as access to clean water, sterilizing equipment, and the age of the infant/child. Heavy daily alcohol consumption, such as in alcohol dependence, would constitute high risk to the infant, for example, and in the presence of safe breast milk alternatives, it would be preferable not to breastfeed.
- The message to breastfeeding women who have used alcohol and drugs to cease using alcohol and drugs while breastfeeding should be given in such a way that it does not undermine the potential benefits of breastfeeding.
- It is possible to reduce the risk of exposure through breastfeeding by altering the timing of breastfeeding, or by the use of temporary alternatives, such as stored (frozen) breast milk or breast milk substitutes where they are available and can be safely used. Women who use alcohol intermittently should be discouraged from breastfeeding for 2 hours after consuming one standard drink (10 g of pure alcohol), and 4–8 hours after consuming more than one drink in a single occasion. Breastfeeding advice for women with HIV should also take into consideration the risk of HIV transmission (refer to the WHO guidelines on breastfeeding and HIV).
- Mothers of infants with a neonatal withdrawal syndrome should be offered appropriate breastfeeding information and support.
- This recommendation was considered conditional because the different values and preferences of women and the lack of strong evidence of harms of low levels of substance use in pregnancy.

RECOMMENDATION 13

Skin-to-skin contact is important regardless of feeding choice and needs to be actively encouraged for a mother with a substance use disorder who is able to respond to her baby's needs.

Strength of recommendation: Strong **Quality of evidence: Low**

Remarks:

- It was decided that the recommendation should be strong despite the very low quality evidence as the risk of harm is minimal, it consumes no resources, the values and preferences were in favour of the recommendation, and there was considered to be certainty about the balance between benefits and harms.

RECOMMENDATION 14

Mothers who are stable on opioid maintenance treatment with either methadone or buprenorphine should be encouraged to breastfeed unless the risks clearly outweigh the benefits.

Strength of recommendation: Strong **Quality of evidence: Low**

Remarks:

- Women prescribed opioids such as methadone and buprenorphine and wishing to stop breastfeeding may wean their children off breast milk gradually to reduce the risk of developing withdrawal symptoms.
- It was decided that the recommendation should be strong, as, despite the low quality of evidence of effect, it was considered highly likely that the benefit of avoiding withdrawal symptoms in the infant strongly outweighed any potential harms. The values and preferences expressed by end-users surveyed were strongly in favour of the recommendation and there was certainty about the balance between benefits and resources being consumed.

Management of infants exposed to alcohol and other psychoactive substances *(Evidence Profile 6: see Annex 1, page 135)*

Note: The term "neonatal withdrawal syndrome" is used here to remain consistent with WHO nomenclature, but the term "neonatal abstinence syndrome (NAS)" is commonly used with the same meaning.

The small study size and risk of bias in the studies evaluated mean that the evidence of treatment effectiveness is very uncertain. Protocols for the management of neonatal withdrawal syndrome have changed considerably over the last 40+ years. Initial treatment guidelines were weight-based, and tables for treatment with phenobarbital and paregoric were published. Current treatment involves use of an opioid such as morphine sulfate or tincture of opium, or a sedative, typically phenobarbital, with infrequent use of a benzodiazepine. Systems for scoring withdrawal are usually used to guide treatment initiation, maintenance and weaning. Because there is neither a uniform assessment method for measuring neonatal withdrawal nor an established treatment protocol, and health-care practices worldwide are variable, it is difficult to state with any precision how neonatal withdrawal is treated across the globe.

RECOMMENDATION 15

Health-care facilities providing obstetric care should have a protocol in place for identifying, assessing, monitoring and intervening, using non-pharmacological and pharmacological methods, for neonates prenatally exposed to opioids.

Strength of recommendation: Strong **Quality of evidence: Low**

Remarks:

- Evidence of a dose-response relationship between opioid maintenance treatment and neonatal withdrawal syndrome has been inconsistent, which implies that all infants should be assessed.
- Infants exposed to opioids during pregnancy should remain in the hospital at least 4–7 days following birth and be monitored for neonatal withdrawal symptoms using a validated assessment instrument, which should be first administered 2 hours after birth and then every 4 hours thereafter.
- Non-pharmacological interventions including low lights, quiet environments, swaddling and skin-to-skin contact should be used with all neonates prenatally exposed to alcohol and drugs.
- It was decided that the recommendation should be strong despite the low quality of evidence of effect, as the GDG agreed that the benefits of such an approach strongly outweighed any potential harms. The values and preferences of end-users were in favour of the recommendation, and there was certainty that while resources would be consumed, the benefits strongly outweighed costs. There was a high value placed on identifying preventable suffering in affected neonates.

RECOMMENDATION 16

An opioid should be used as initial treatment for an infant with neonatal opioid withdrawal syndrome if required.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Prolonged treatment of neonatal opioid withdrawal syndrome with opioids is generally not necessary and aiming for shorter treatment is preferable.
- Phenobarbital can be considered as an additional therapy if there has been concurrent use of other drugs in pregnancy, particularly benzodiazepines, and if symptoms of neonatal opioid withdrawal are not adequately suppressed by an opioid alone. If opioids are unavailable, phenobarbital can be used as an alternative therapy.
- Infants with signs of a neonatal withdrawal syndrome in the absence of known maternal opioid use should be fully assessed for possible benzodiazepine, sedative or alcohol exposure.
- The strong recommendation to use opioids rather than phenobarbital despite the very low quality of evidence of effectiveness was based on vast clinical experience with opioids in the management of both adult and neonatal opioid withdrawal. There has only been very limited clinical experience with phenobarbital use. In addition, the values and preferences of end-users were in favour of the recommendation, and the GDG agreed that there was certainty about the balance between benefits and resources being consumed.

RECOMMENDATION 17

If an infant has signs of a neonatal withdrawal syndrome due to withdrawal from sedatives or alcohol or the substance the infant was exposed to is unknown, then phenobarbital may be a preferable initial treatment option.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- Infants with signs of a neonatal withdrawal syndrome in the absence of known maternal opioid use should be fully assessed for possible benzodiazepine, sedative, or alcohol exposure.
- This recommendation was considered conditional because of the lack of high-quality evidence and the lack of certainty of the balance between benefits and harms.

RECOMMENDATION 18

All infants born to women with alcohol use disorders should be assessed for signs of fetal alcohol syndrome.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- Signs of fetal alcohol syndrome (FAS) include growth impairment, dysmorphic facial features (short palpebral fissures, smooth or flattened philtrum, thin upper lip) and central nervous system abnormalities, including microcephaly.
- When assessing such infants the following information should be recorded:
  - birthweight and length
  - head circumference
  - dysmorphic facial features
  - gestation
  - prenatal exposure to alcohol
  - follow-up of infants with signs of FAS should be provided
- This recommendation was considered conditional because of the lack of high-quality evidence, and questions about the feasibility of implementation in all settings.

RESEARCH PRIORITIES AND GAPS

The extensive search for evidence of effective interventions for managing alcohol and other substance disorders in pregnancy yielded useful baseline information but also highlighted considerable gaps in knowledge. The GDG identified priority areas and questions that need to be researched in order to increase certainty about what works most effectively when managing pregnant women with these disorders.

General Remarks

The GDG calls upon the research community to:

- improve descriptions of current clinical practices – including routine clinical outcome data;
- agree on standardized outcomes;
- perform observational studies on risks and benefits of pharmacotherapies in pregnancy;
- conduct a global cohort study with standardized patient-centred outcome measurements and data repository;
- conduct qualitative research on ethical issues;
- encourage more research in low-income countries;
- evaluate the benefits of comprehensive-care models (e.g. psychosocial, spiritual support, programmes for very young children affected by maternal substance use in utero);
- provide better prevalence data on prescription opioid use.

Exposure to different drugs and medications in utero

The GDG calls upon the research community to conduct further research on the impact of substance use upon:

- maternal outcomes
- fetal outcomes
- neonatal outcomes
- long-term outcomes for the exposed children.

A number of critical questions on the optimal use of specific interventions in pregnancy remain unanswered.

Screening

- what is the best way for health-care workers to screen pregnant women for alcohol and other substance use and substance use disorders without being judgemental?
- which instruments are most effective?
- what sort of training yields effective screening?
- what is the effectiveness and cost-effectiveness of screening in routine clinical practice?
- what are the optimal screening methods – for different substances/different settings, e.g. in low-income countries? A systematic review of screening instruments currently used is needed.
- what are the optimal ways of organizing screening and brief interventions in different settings?
- what factors modify the disclosure level?

Brief interventions

Brief interventions should be clinically trialled, using standardized outcomes and trial designs to determine:

- who should be targeted?
- does this vary according to levels of substance use and type of substance use?
- what elements of the brief intervention are effective?
- what level of brief intervention is most effective?
- what categories of health-care workers can provide brief interventions effectively?
- how late can a brief intervention be given effectively?

Psychosocial interventions

- better reporting and agreement on standardized designs and outcomes is needed.
- stronger RCT evidence of effect is needed, comparing interventions with different levels of intensity and models of care with different levels of comprehensiveness, and including cost-effectiveness analyses.

Detoxification

- what type of benzodiazepine reduction regimes work best for which types of patients?
- what medications are the safest and most effective for mother and fetus being withdrawn from alcohol?
- is fetal monitoring useful in determining the relative safety of detoxification during pregnancy?
- what are the best assessment tools to measure withdrawal in pregnant women?
- what are the best ways to manage withdrawal from cocaine, cannabis, ATS, alcohol or volatile solvents in pregnant women?
- how can fetal stress and potential intrauterine withdrawal be monitored when mothers are detoxified from opioids and other drugs?

Pharmacological treatment

- a confidential case registry of pregnancies exposed to different substances, including psychotropic medications used for the treatment of substance use disorders in pregnancy, could help explore the potential risks and benefits of pharmacotherapy in substance use disorders in pregnancy.
- further studies could explore the optimal method of treatment with methadone and buprenorphine in pregnancy (including further dose/response studies).
- data on the safety of pharmacotherapy for alcohol dependence in pregnancy is lacking.

Breastfeeding

- effects of breastfeeding and substance use on the neonate still need to be better understood.
- how best to promote the initiation and continuation of breastfeeding in appropriate situations, such as in mothers receiving opioid maintenance treatment?
- to what degree are different drugs and medications excreted in human milk?
- what is the safety of breastfeeding while the mother is using different drugs and psychoactive medications?
- what is the effect of breastfeeding on neonatal withdrawal for mothers receiving methadone or buprenorphine treatment.

Birth and labour

- what is the optimal treatment during labour, including pain management?

Management of infants exposed to alcohol or drugs in utero

- what is the sensitivity and specificity of screening for FAS in the neonatal period and what are the risks and benefits of early identification and intervention, including in low resource settings?

PLANS FOR DISSEMINATING, ADAPTING AND IMPLEMENTING THESE RECOMMENDATIONS

These recommendations will be used to provide guidance on the identification and management of substance use and substance use disorders in pregnancy through a range of derivative publications including training materials and a manual describing how best to put these recommendations into practice. This will be widely disseminated through the WHO regional and country offices, collaborating centres, professional organizations and partner agencies.

Local adaptation/implementation of these recommendations

These recommendations will be adapted for the field by developing suitable training materials in consultation with regional, national and local stakeholders. Adaptation will include translation into appropriate languages and ensuring that the interventions are acceptable in local sociocultural contexts suitable for local health systems.

EVALUATING THE IMPACT OF THESE RECOMMENDATIONS

The impact of these recommendations will be measured in the following ways:

- use of maternal and child health indicators to assess improvement in maternal and child health outcomes in this population;
- measurement of inclusion of alcohol and drugs into the routine screening protocols in different countries/ guidelines;
- WHO survey of resources for the prevention and treatment of substance use disorders;
- assessment of any increase in specialized services for pregnant women with substance use disorders; and
- assessment of number of references to the WHO guidelines in the medical literature.

REVIEW BY DATE

It is not expected that these recommendations will need to be reviewed until 2016. However, developments in the field will be continually monitored and should there be significant changes in practice and/or the evidence base that affect any of the recommendations, review may be undertaken earlier.

ANNEX 1: EVIDENCE PROFILES

Evidence Profile 1: Screening and brief interventions

Evidence question:

In pregnant or postpartum women using alcohol or drugs, does screening for alcohol or drug use, followed by a brief intervention (or referral to treatment for those with possible dependence), result in better maternal, fetal or neonatal outcomes (see separate outcome list) than treatment-as-usual (generally the absence of screening, or brief interventions and the occasional referral to treatment)?

Selection criteria for the systematic review:

Study design: RCTs

Population: Pregnant or postpartum women using alcohol or drugs (some studies included women who had alcohol or drug use only in the past; studies with up to one third of participants in this category were still eligible for inclusion).

Intervention: Systematic screening of all patients followed by a brief intervention. The Cochrane Review definition of brief intervention in the general population review was used (anything beyond simple advice or information up to 4 sessions), accepting any referral of more severe patients for treatment.

Control: Brief advice or information or no intervention.

Outcomes: The outcomes ranked as important were:

Outcome	Importance (0-9)
Maternal: Identification of substance use	8.89
Maternal: Provision of intervention for substance use	8.22
Maternal: Referral to relevant treatment of substance use	8.22
Maternal: Ongoing substance use during pregnancy	7.33
Infant: Birth defects	6.00
Infant: Gestational age at delivery	6.00
Infant: Birthweight	5.89
Infant: Spontaneous abortion	5.44
Infant: Head circumference at birth	5.44

EVIDENCE TO RECOMMENDATIONS TABLE

Screening and brief interventions for alcohol and other substance use in pregnancy in general health-care settings
Summary of the Evidence: For GRADING of evidence see summary of findings and GRADE tables below RCT evidence – 10 studies were included in the review. Most studies were underpowered and there were differences in study design and outcome measures used which limited the capacity for meta-analysis. As a result, the level of evidence for most outcomes was low or very low. Nonetheless, there was a small but consistent effect in favour of screening and brief interventions for both alcohol and, to a lesser extent, drugs. Other evidence: • Simply asking about alcohol and other substance use may result in a change in behaviour (Goler et al., 2008; Klesges et al., 2001; Nilsen, 2009). • Being asked about alcohol or other substance use in a detailed and comprehensive manner may increase a woman's awareness of actual levels of consumption and may function to modify her behavior (Delrahim-Howlett, 2011). • A brief motivational intervention has been shown to reduce the risk of an alcohol-exposed pregnancy (Floyd, 2007). • A brief alcohol intervention has been found to reduce the number of drinks and the number of heavy drinking days during the postpartum period (Fleming et al., 2008). Pregnant women with higher levels of alcohol use may reduce their alcohol use following a brief intervention that includes their partner (e.g., Chang, 2005). • Pregnant adolescent girls with a substance use disorder have been shown to reduce their substance use after a single-session, standardized brief intervention (Whicher et al., 2012).

Benefits and harms	
Benefits	• Discussion of alcohol and illicit substance use during pregnancy is a teachable moment (Chang et al., 2000) • Depending on the substance of use, brief interventions have been associated with these positive outcomes: – reduction in harmful consumption – reduction in risk to fetus – increase in birthweight – increase in the detection of harmful use and referral to treatment – improved general health of pregnant women – improved maternal psychological well-being – less risk of fetotoxicity – improved perinatal outcomes (e.g. reduction in preterm births, increased overall birthweights, reduction in number of low-birthweight infants) – reductions in congenital defects or anomalies
Harms	• Unpleasant symptoms associated with reduction or cessation of alcohol or substance use • Potential legal or social consequences for disclosing use • Social consequences – problematic interaction with partners/peers associated with reduction or cessation of alcohol or substance use • Cessation may interfere with activities of daily living • Referral for cessation intervention may induce time and economic burdens

EVIDENCE TO RECOMMENDATIONS TABLE

Values and preferences	
In favour: **Pregnant women**	• Value opportunity for greater personal contact and support • Value opportunity for development of coping strategies • Value positive responses from partners, family and, co-workers
Health-care workers (HCW)	• Value opportunity to identify problem early • Value opportunity to intervene • Value opportunity to improve fetal outcomes
Against: **Pregnant women**	• Resent stigmatization for drinking alcohol or using illicit substances during pregnancy • Resentment of questioning private life/behaviour • Resentment of consequences of referral – perceived time, logistical and financial burden imposed • Fear of possible negative responses from health-care providers, partners, family, friends and others in the woman's community
Health-care workers (HCW)	• HCW may resent extra time taken to screen. Estimates of screening time vary widely given the relatively large number of screening instruments that are available [Although a little bit dated, *CSAP Special Report 13: Maternal substance use assessment methods reference manual: a review of screening and clinical assessment instruments for examining maternal use of alcohol, tobacco, and other drugs Rockville, MD: US Department of Health and Human Services, Public Health Service, Substance Abuse and Mental Health Services Administration (Center for Substance Abuse Prevention, 1993*) contains an excellent review in regard to all such instruments], which vary in length from 4 questions to more than 100, and which can be administered by the clinician or require paper-and-pencil administration • HCW may resent difficulties of interaction when identifying a substance user • HCW may resent extra time and difficulty imposed by need to refer • HCW may be unwilling to provide intervention • HCW may believe they are not competent to screen: Gassman (2003) found that the biggest barrier to the implementation of screening and brief intervention among obstetricians was self-rated competence to deliver the intervention.
Costs and feasibility	
Costs and resource use	• Additional cost in terms of staff time should be minimal if integrated into routine care. However, there are no good estimates of cost for either the screening or the brief intervention, given the fact that a brief intervention may be no more than guidance provided in the office or a structured and standardized administration of a behavioural intervention by a counsellor • Appropriate staff training requires resource use • Appropriate intensive treatment needs to be made available for referral when substance use/alcohol use is identified and long-term, sustainable support is required. • Brief interventions have been assessed as highly cost-effective (Windsor, 1985; Ershoff, 1989; Dornelas, 2006: Parker, 2007)

EVIDENCE TO RECOMMENDATIONS TABLE

Feasibility (including economic consequences)	• Self-report screening has been shown to be accurate. Yonkers et al. (2011) found a high degree of agreement between urine toxicology and self-report results for cannabis and cocaine testing in 168 pregnant women. Moreover, self-report was found to lead to more positive reporting of use when a larger window was available for such reporting than was available for toxicology screening, leading to the conclusion that self-report may be a better indicator of use. • Some time is needed for the care provider to either complete and/or review the screening results. Diekman et al. (2000) have reported than only 23% of obstetricians in the USA used a standardized screening tool for the detection of substance use, yet research (e.g. Bailey & Sokol, 2008; Svikis & Reid-Quinones, 2003) has shown that such tools substantially increase the rate of detection of such use. Oser et al. (2011) found that less than 50% of USA obstetricians were using a standardized screening instrument, and of those using such an instrument, most were using the CAGE, which was not specifically developed for use with a pregnant population. • Effective interventions are labour intensive. Providing reading material is not as effective as a brief intervention. Face-to-face counselling about abstaining from alcohol (and other substances) is needed (Calabro, 1996). • Other research has shown that non-mental-health specialists can be trained to perform brief interventions in general health-care settings.

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Draft recommendations:

- Screening for use of alcohol and other substance use among all pregnant women is recommended in all health-care settings (e.g., primary care, obstetrical care).
- Pregnant women reporting hazardous or harmful alcohol or other substance use should receive a brief intervention.
- Pregnant women found to be dependent on alcohol or other substances should be referred to specialist services, where such services exist.

Final recommendations:

RECOMMENDATION 1

Health-care providers should ask all pregnant women about their use of alcohol and other substances (past and present) as early as possible in the pregnancy and at every antenatal visit.

Strength of recommendation: Strong **Quality of evidence: Low**

Remarks:

- Asking at every visit is important as some women are more likely to report sensitive information only after a trusting relationship has been solidly established.
- Pregnant women should be advised of the potential health risks to themselves and to their babies posed by alcohol and drug use.
- Validated screening instruments for alcohol and other substance use and use disorders are available (see Annex 3).
- Health-care providers should be prepared to intervene or refer all pregnant women who are identified as using alcohol and/or drugs (past and present).
- It was decided that despite the low quality of evidence of effect, the benefit – potential reduction of alcohol and substance use – outweighed any potential harms of a brief psychosocial intervention, which were considered minimal. Therefore the balance of benefits versus harms was clearly positive despite uncertainty about the degree of benefit. In addition, the burden of implementation was minimal.

RECOMMENDATION 2

Health-care providers should offer a brief intervention to all pregnant women using alcohol or drugs.

Strength of recommendation: Strong **Quality of evidence: Low**

Remarks:

- Brief intervention is a structured therapy of short duration (typically 5-30 minutes) offered with the aim of assisting an individual to cease or reduce the use of a psychoactive substance. It is designed in particular for general practitioners and other primary health-care workers.
- Health-care providers should be given appropriate training and resource materials.
- The brief intervention should be individualized, and include feedback and advice on ceasing or reducing alcohol and other substance use during pregnancy. There may need to be follow-up with the patient, with the possibility of referral to treatment for those patients who are unable to reduce or eliminate such use.
- The approach/attitude of health-care providers is an important contributor to the effectiveness of brief interventions.
- As for recommendation 1, it was decided that despite the low quality of evidence of effectiveness, this should be a strong recommendation because the potential benefit – reduction of alcohol and/other substance use – likely outweighs any potential harms of a brief psychosocial intervention which were considered minimal. Therefore the balance of benefits versus harms was clearly positive, although there was uncertainty about the degree of benefit. In addition the burden of implementation was minimal.

Factors in considering the strength of the recommendations (recommendations 1 & 2):

Factor	Decision
Is there high- or moderate-quality evidence? The higher the quality of evidence, the more likely is a strong recommendation.	**No**
Is there certainty about the balance of benefits versus harms and burdens? In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms? In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?	**Yes**
Are the expected values and preferences clearly in favour of the recommendation?	**Yes**
Is there certainty about the balance between benefits and resources being consumed? In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed? In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?	**Yes**

Research gaps

More evidence is needed from low-income countries. Topics in need of further research include training on sceening and brief interventions, how to screen (which instrument), cost-effectiveness, whether to screen for alcohol or drugs together, whether to ask about tobacco at the same time, and whether or not to combine with other issues (such as depression). There is a need for more real-world effectiveness studies, and a systematic review of screening instruments.

Summary of findings and GRADE tables

SCREENING AND BRIEF INTERVENTION VERSUS USUAL CARE FOR HARMFUL SUBSTANCE USE IN PREGNANCY

Patient or population: Patients with harmful substance use in pregnancy
Settings: Ante-natal and post-natal general health-care settings
Intervention: Screening and brief intervention versus usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Screening and brief intervention versus usual care				
Abstinence from drug use in the last 4 weeks – ITT analysis Follow-up: mean 38.6 days	**Study population** **733 per 1000**	**602 per 1000** (248 to 875)	**OR 0.55** (0.12 to 2.55)	30 (1 study)	⊕⊕◯◯ LOW[1,2,3]	
Total number of drinks in the past 28 days Follow-up: mean 6 months	The mean total number of drinks in the past 28 days in the control groups was **27.1 standard drinks**	The mean total number of drinks in the past 28 days in the intervention groups was **7.3 lower** (12.61 to 1.99 lower)		235 (1 study)	⊕⊕◯◯ LOW[1,4]	
Number of heavy drinking days in the past 28 days Follow-up: mean 6 months	The mean number of heavy drinking days in the past 28 days in the control groups was **2.6 days**	The mean number of heavy drinking days in the past 28 days in the intervention groups was **0.9 lower** (1.59 to 0.21 lower)		235 (1 study)	⊕⊕◯◯ LOW[1,4]	
Number of standard drinks per week Follow-up: mean 33 days	The mean number of standard drinks per week in the control groups was **0.13 standard drinks**	The mean number of standard drinks per week in the intervention groups was **0.19 higher** (0.31 lower to 0.69 higher)		50 (1 study)	⊕⊕◯◯ LOW[1,3]	
Estimated peak BAC Follow-up: 1–2 months	The mean estimated peak BACin the control groups was **0.004 g/dl**	The mean estimated peak BACin the intervention groups was **0 higher** (0.01 lower to 0.01 higher)		50 (2 studies)	⊕⊕◯◯ LOW[1,3]	
AUDIT score Follow-up: mean 58 days	The mean AUDIT score in the control groups was **2.22 AUDIT score**	The mean audit score in the intervention groups was **1.69 lower** (2.88 to 0.5 lower)		179 (1 study)	⊕⊕◯◯ LOW[1,4,6]	
Motivation to change Follow-up: mean 38.6 days	The mean motivation to change in the control groups was **77.4 Visual analogue scale**	The mean motivation to change in the intervention groups was **11.4 higher** (0.08 to 22.72 higher)		30 (1 study)	⊕⊕◯◯ LOW[1,2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Screening and brief intervention versus usual care				
Spontaneous abortion	**Study population**		**OR 0.84** (0.34 to 2.06)	753 (3 studies)	⊕◯◯◯ VERY LOW[1,2,3,4]	
	28 per 1000	**24 per 1000** (10 to 57)				
Head circumference Follow-up: mean 33 days	The mean head circumference in the control groups was **34.1 cm**	The mean head circumference in the intervention groups was **0.27 lower** (1.1 lower to 0.56 higher)		50 (1 study)	⊕⊕◯◯ LOW[1,3]	
Depression postpartum Follow-up: mean 6 months	The mean depression postpartum in the control groups was **8.06 Edinburgh postpartum depression scale**	The mean depression postpartum in the intervention groups was **1.22 lower** (2.71 lower to 0.27 higher)		205 (1 study)	⊕◯◯◯ VERY LOW[1,4,6,7]	
Birthweight – all participants	The mean birthweight – all participants in the control groups was **3240 grams**	The mean birthweight – all participants in the intervention groups was **57.8 higher** (77.26 lower to 192.86 higher)		555 (3 studies)	⊕◯◯◯ VERY LOW[1,2,3,4,6,8,9]	
Attending substance abuse treatment Follow-up: mean 38.6 days	**Study population**		**OR 0.31** (0.01 to 8.28)	30 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	
	67 per 1000	**22 per 1000** (1 to 372)				
Birthweight – drinking more than 1 drink per occasion or per day (post-hoc analysis)	The mean birthweight – drinking more than 1 drink per occasion or per day (post-hoc analysis) in the control groups was **3134 grams**	The mean birthweight – drinking more than 1 drink per occasion or per day (post-hoc analysis) in the intervention groups was **199.63 higher** (57.06 to 342.19 higher)		168 (2 studies)	⊕⊕◯◯ LOW[1,4,6,10]	

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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 The control group received a screening session
2 Up to a third of the participants were not heavy drinkers
3 Wide confidence interval
4 Cluster randomized trial not analysed as such
5 High dropout rate
6 Outcome assessment was not blinded
7 Post-hoc analysis, selective outcome reporting
8 No explanation was provided
9 Suggestion on funnel plot of publication bias
10 Post-hoc analysis

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Settings: Ante-natal and post-natal general health-care settings
Bibliography: Clark NC, Gehring E, Onyeka IN, Siegfried N. Screening and Brief Interventions for Harmful Substance Use in Pregnancy.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening and brief Intervention versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
Abstinence from drug use in the last 4 weeks – ITT analysis (follow-up mean 38.6 days)												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1,2]	serious[3]	none	9/15 (60%)	11/15 (73.3%)	OR 0.55 (0.12 to 2.55)	131 fewer per 1000 (from 485 fewer to 142 more)	⊕⊕◯◯ LOW	CRITICAL
Total number of drinks in the past 28 days (follow-up mean 6 months; better indicated by lower values)												
1	randomized trials	serious[4]	no serious inconsistency	serious[1]	no serious imprecision	none	122	113	—	MD 7.3 lower (12.61 to 1.99 lower)	⊕⊕◯◯ LOW	CRITICAL
Number of heavy drinking days in the past 28 days (follow-up mean 6 months; better indicated by lower values)												
1	randomized trials	serious[4]	no serious inconsistency	serious[1]	no serious imprecision	none	122	113	—	MD 0.9 lower (1.59 to 0.21 lower)	⊕⊕◯◯ LOW	CRITICAL
Number of standard drinks per week (follow-up mean 33 days; better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	27	23	—	MD 0.19 higher (0.31 lower to 0.69 higher)	⊕⊕◯◯ LOW	CRITICAL
Estimated peak BAC (follow-up 1-2 months; better indicated by lower values)												
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	27	23	—	MD 0 higher (0.01 lower to 0.01 higher)	⊕⊕◯◯ LOW	CRITICAL
AUDIT score (follow-up mean 58 days; better indicated by lower values)												
1	randomized trials	serious[4,6]	no serious inconsistency	serious[1]	no serious imprecision	none	97	82	—	MD 1.69 lower (2.88 to 0.5 lower)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening and brief Intervention versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
Motivation to change (follow-up mean 38.6 days; better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency	very serious[1,2]	no serious imprecision	none	15	15	—	MD 11.4 higher (0.08 to 22.72 higher)	⊕⊕◯◯ LOW	CRITICAL
Spontaneous abortion												
3	randomized trials	serious[4]	no serious inconsistency	serious[1,2]	serious[3]	none	9/367 (2.5%)	11/386 (2.8%)	OR 0.84 (0.34 to 2.06)	4 fewer per 1000 (from 19 fewer to 28 more)	⊕◯◯◯ VERY LOW	
Head circumference (follow-up mean 33 days; better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[3]	none	27	23	—	MD 0.27 lower (1.1 lower to 0.56 higher)	⊕⊕◯◯ LOW	IMPORTANT
Depression postpartum (follow-up mean 6 months; better indicated by lower values)												
1	randomized trials	very serious[4,6,7]	no serious inconsistency	serious[1]	no serious imprecision	none	97	108	—	MD 1.22 lower (2.71 lower to 0.27 higher	⊕◯◯◯ VERY LOW	CRITICAL
Birthweight – all participants (better indicated by lower values)												
3	randomized trials	serious[4,6]	serious[8]	serious[1,2]	serious[3]	none[9]	267	288	—	MD 57.8 higher (77.26 lower to 192.86 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Attending substance abuse treatment (follow-up mean 38.6 days)												

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening and brief Intervention versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
1	randomized trials	no serious risk of bias	no serious inconsistency	very serious[1,2]	serious[3]	none	0/15 (0%)	1/15 (6.7%)	OR 0.31 (0.01 to 8.28)	45 fewer per 1000 (from 66 fewer to 305 more)	⊕◯◯◯ VERY LOW	CRITICAL
Birthweight – drinking more than 1 drink per occasion or per day (post-hoc analysis) (better indicated by lower values)												
2	randomized trials	serious[4,6,10]	no serious inconsistency	serious[1]	no serious imprecision	none	81	87	—	MD 199.63 higher (57.06 to 342.19 higher)	⊕⊕◯◯ LOW	IMPORTANT

1 The control group received a screening session
2 Up to a third of the participants were not heavy drinkers
3 Wide confidence interval
4 Cluster Randomized trial not analysed as such
5 High dropout rate
6 Outcome assessment was not blinded
7 Post-hoc analysis, selective outcome reporting
8 No explanation was provided
9 Suggestion on funnel plot of publication bias
10 Post-hoc analysis

SCREENING AND BRIEF INTERVENTIONS vs USUAL CARE for harmful substance use in pregnancy

TABLE OF CHARACTERISTICS OF INCLUDED RCTS: 9 IN TOTAL

Trial ID	Methods	Participants	Interventions	Outcomes	Notes
Chang 1999	STUDY TYPE: RCT COUNTRY: USA SETTING: Brigham and Women's Hospital – General Ante-natal clinic DURATION OF RECRUITMENT: One year DURATION OF TRIAL: 22 months FOLLOW-UP: Post partum follow up interview	INCLUSION CRITERIA: pregnant women presenting for ante-natal care screen positive on an alcohol survey for hazardous or harmful use. EXCLUSION CRITERIA: (1) gestational age greater than 28 weeks (44%), (2) no alcohol consumption in the immediate 6 months before study participation (19%), (3) miscarriage in the time between survey completion and telephone interview (14%), (4) intention to receive prenatal care elsewhere (7%), (5) non-English-speaking (3%), (6) intended abortion or false pregnancy (3%), (7) current substance abuse treatment (1%) and (8) other (9%). Screened: 1165 Agreed to participate: 886 Screen positive: 532 Met inclusion/exclusion criteria: 250 N. of participants randomized: 250 (123 to intervention group, and 127 to control group) N. followed up: 247 N. included in the analysis: 250	INTERVENTION: Screening and comprehensive Assessment and Brief Intervention The BI was structured as follows: (1) review the subject's general health and course of pregnancy to date, (2) review the subject's life-style changes made since pregnancy, including work schedule, exercise, diet, cigarette smoking and alcohol consumption, (3) request that the subject articulate her drinking goals while pregnant and their reason, (4) have the subject identify circumstances when she might be tempted to drink, (5) identify alternatives to drinking when she is tempted to drink, and (6) summarize the session by emphasizing four key points (drinking goal, motivation, risk situations for drinking and alternatives to alcohol) and noting them in the take-home manual, "How to prevent alcohol-related problems", given to the subject. This manual was based on materials provided by the WHO Amethyst Project (Babor et al., 1987; Babor & Grant, 1992; WHO Brief Intervention Study Group, 1996). All subjects receiving the BI were informed of the recommendation of the US Surgeon General, with prenatal abstinence being the most prudent drinking goal. Time: 45 minutes CONTROL: Screening and comprehensive assessment The comprehensive assessment was administered by a research assistant over the course of 2 hours and consisted of: (1) the alcohol and drug abuse modules from the Structured Clinical In-terview for DSM-III-R to generate standard diagnoses (SCID, Spitzer et al., 1990); (2) the Addiction Severity Index (ASI, McLellan et al., 1980); (3) the Alcohol Use Disorders Identification Test (AUDIT, Bohn, Babor & Kranzler, 1995); (4) the Short Michigan Alco- holism Screening Test (SMAST, Selzer, Vinokur & van Rooijen, 1975); (5) the Timeline Follow- back interview for the quantity and frequency of alcohol consumption for the 90 days immediately before study assessment (Sobell & Sobell, 1992); (6) the Alcohol Craving Scale, a visual analog scale to measure the desire to drink at the moment and in the past week (Wewers, Rachfal & Ahijevych, 1990); (7) the Global Assessment of Functioning (GAF, Endicott et al., 1976); and (8) the Situational Confidence Questionnaire, a measure of the subject's confidence in managing drinking situations (Annis, 1981). Subjects were asked to report any alcohol consumed, even a sip, when completing the Timeline Follow-back interview (Allen & Columbus, 1995). In this study, alcohol consumption was quantified by drinks per drinking day, since few pregnant women drink daily (Jacobson et al., 1991). Drinking episodes, defined with each episode beginning with a drinking day and ending with 7 consecutive days of abstinence, were also calculated. Additional details about the alcohol assessment are available elsewhere (Chang et al., 1998).	MATERNAL OUTCOMES: Alcohol consumption Drinks per drinking day INFANT OUTCOMES: Birthweight APGAR score	ETHICS: Approved by the human subjects committee of the Brigham and Women's Hospital INFORMED CONSENT: Obtained FUNDING: This study was supported by ROI AA 9670 from the National Institute on Alcohol Abuse and Alcoholism (Dr Chang)

Chang 2005	STUDY TYPE: RCT COUNTRY: United States SETTING: 1 of 3 obstetric practices (clinic, faculty, or private group affiliate) of the Brigham and Women's Hospital in Boston, MA DURATION OF RECRUITMENT: February 2000 to September 2002 FOLLOW-UP: Post-partum follow-up interview	INCLUSION CRITERIA: 1) positive T-ACE, with a total score of 2 or more, 2) being at risk for prenatal alcohol use, which was defined as any alcohol consumption in the 3 months before study enrolment (while pregnant), or consumption of at least one drink per day in the 6 months before study enrolment, or drinking during a previous pregnancy, 3)gestation less than 28 weeks and intention to carry pregnancy to term. EXCLUSION CRITERIA: 1) current treatment for alcohol or drug abuse, or substance abuse–related medical illness, 2) current physical dependence on alcohol requiring medically supervised detoxification, 3) current use of opiates, cocaine, or other illicit substances. N. of participants screened: 2927 N. of screened positive: 802 N. of participants successfully contacted: 399 N. randomized: 304 (Brief intervention group: 152, loss to follow-up in brief intervention group: 10. Control group: 152, loss to follow-up in control group: 6) N. included in the analysis: 152 for both groups	IINTERVENTION: Single session brief intervention given to the woman and her partner CONTROL: Screening and diagnostic interview only	MATERNAL OUTCOMES: Alcohol consumption	

Fleming 2008	STUDY TYPE: Cluster randomized controlled trial COUNTRY: USA SETTING: 34 obstetrical practices from 15 counties in Wisconsin. DURATION OF RECRUITMENT: Obstetricians were recruited in 2001. Actual duration was not stated. Postpartum women were recruited between 2002 and 2004. DURATION OF TRIAL: 2002 to 2005 FOLLOW-UP: Mothers attended two 15-minute face-to-face visits were scheduled 1 month apart for a brief intervention and a reinforcement session, followed by a phone-call 2 weeks after each face-to-face meeting. There were a total of 4 contacts to the participants spread over an 8 week period. Follow-up procedures included a telephone interview at 6 months by one of the researchers not assigned to participant's clinic.	INCLUSION CRITERIA: Physicians: Trained in obstetrics and gynecology, practice medicine at least 50% time, amenable to having a research team identify and work with their patients, willingness to have their office staff complete research protocols. Postpartum women: 18 years or older, seeing their obstetrician or advanced practice nurse for a postpartum visit, 20 or more standard drinks in the previous 28 days or 4 or more drinks on 4 or more occasions in the last 28 days or 20 or more drinking days in the last 28 days. All postpartum patients 18 years or older were asked to complete a health screening survey (HSS). Computer-generated allocation method was used to assign participants to the experimental and control groups in each physician's office. Number of participants randomized: 235 (the unit of randomization was the individual patient). 122 postpartum women randomized to intervention group and 113 to control group. There were no significant statistical differences in baseline data between the two groups.	INTERVENTION: brief intervention GROUP Participants in the experimental group received health booklet (on general health issues) plus face-to-face 30-minute session and were followed up at 6 months. CONTROL: usual care GROUP Those assigned to the control group received a health booklet (on general health issues) and were followed up at 6 months. COMPLIANCE: Participants took the workbook home between visits and filled out a number of homework assignments, and were asked to fill out drinking diary cards between visits, and follow-up phone calls were made to reinforced the drinking limits set at each visit, challenges they faced in cutting down on drinking and offering continued support. CO-INTERVENTIONS: Participants were paid a total of $150 if they completed the required procedures.	MATERNAL OUTCOMES: Primary: Alcohol use as measured by total number of drinks, number of drinking days, and number of heavy drinking days (4 or more drinks in a day), in the previous 28 days. Secondary : Other outcomes of interest such as depression, accidents, injuries, driving while intoxicated, and health care utilization.	ETHICS: Research protocol approved by the University of Wisconsin Health Sciences Human Subjects Committee and 11 additional human subject committees specific to the different health care systems. INFORMED CONSENT: All participants gave written informed consent. FUNDING: NIH NIAAA grant number R01 AA12522.

Handmaker 1999	STUDY TYPE: Randomized controlled trial COUNTRY: USA SETTING: University of New Mexico (UNM) Medical Center obstetric clinics DURATION OF RECRUITMENT: Not stated. DURATION OF TRIAL: Not stated. FOLLOW-UP: Pregnant women were interviewed two months later using the Follow-up Drinker Profile (FDP)	INCLUSION CRITERIA: Not stated EXCLUSION CRITERIA: Not stated Number of participants randomized: 42 (20 randomized to intervention group and 22 to control group). It was not stated if there were any significant statistical differences in baseline data between the two groups.	All participants were initially assessed using the Brief Drinker Profile (BDP), supplemented by calendar for timeline reconstruction of drinking during the previous 2 months. Subsequently, the interviewer privately opened a prepared envelope to determine the randomized group assignment. INTERVENTION: Pregnant women in the treatment group completed SOCRATES, a measure of motivation for change. The motivational interview lasted for 1 hour, starting with ascertaining participant's knowledge of the effects of alcohol on pregnancy, feedback on severity of participant's drinking, and showing chart of fetal development by gestational week. They were followed-up 2 months later. CONTROL: Those assigned to the control group were sent letters informing them about the potential risks of drinking during pregnancy and referring them to their healthcare provide and were followed up at 2 months. COMPLIANCE: Not stated CO-INTERVENTIONS: To corroborate self-report, participants' significant others were interviewed (with the participant's permission) at intake and follow-up, using a Collateral Information Form. All participants were paid $20.00 for completing baseline assessment, were entered into a lottery drawing for a $50 cash prize upon completing follow-up sessions, and those in the intervention group were paid $ 10 upon completing SOCRATES again after the interview.	MATERNAL OUTCOMES: Alcohol consumption as measured by total standard ethanol content (SEC), estimated peak blood alcohol concentration (BACs) and total days abstinent during the most recent 2 months of pregnancy. INFANT OUTCOMES: Not stated.	ETHICS: Not stated INFORMED CONSENT: All participants gave informed consent – it was not stated if it was verbal or written. FUNDING: Partly supported by a grant from the New Mexico Developmental Disabilities Planning Council and by grants T32-AA07460 and K05-AA00133 from the National Institute on Alcohol Abuse and Alcoholism.

Magnusson 2005	STUDY TYPE: Randomized controlled trial COUNTRY: Sweden SETTING: Two antenatal care clinics of central Stockholm DURATION OF RECRUITMENT: September 1, 2001, and May 30, 2002 FOLLOW-UP: Screening interview after standard admission in the clinics. Following evaluation, blood was obtained for analysis of biomarkers for the intervention group.	INCLUSION CRITERIA: 1106 admissions between September 1, 2001, and May 30, 2002. Among these, 303 were randomly selected by offering participation to all admissions to the respective clinic on randomly alternating weekdays to avoid bias caused by the possibility that subjects with hazardous alcohol use avoid scheduling visits immediately after weekends. N. of participants randomised: 303 Intervention group: 147 participants Control group: 156 participants	INTERVENTION: The women in the intervention group were evaluated by the research midwife in addition to and independently of regular antenatal care. Following evaluation, blood was obtained for analysis of biomarkers. Screening methods used: 1) TLFB: the period assessed by TLFB varied depending on the week of pregnancy at the time of the clinic visit (median [range] = 12 [8-24] weeks). An interviewer administered the TLFB with the standard elements of this technique. 2) AUDIT: applied to behavior during the 12-month period preceding pregnancy. 3) Biomarkers: Following the interview, together with ordinary routine laboratory tests, a venous blood sample was drawn and analyzed for the following biomarkers (with upper reference interval limit indicated for each): MCV (76-96 f/L), GGT (< 0.80 pkat/L), AST (< 0.60. pkat/L), ALT (< 0.60 pkat/L) and CDT (< 1.5%). CONTROL: The women in the control group returned to continued regular care only.	MATERNAL OUTCOMES: TLFB and AUDIT scores, biomarker levels INFANT OUTCOMES: none	ETHICS: The project followed the Declaration of Helsinki and was approved by Stockholm South Human Subjects Ethics committee (199/00). INFORMED CONSENT: Subjects gave their informed consent FUNDING: Funding for this study was obtained from the County of Stockholm Research and Development Fund, from the Swedish Government Social Ministry and from the Swedish Alcohol Monopoly Research Foundation.
Marais 2011	STUDY TYPE: Cluster randomized trial COUNTRY: South Africa SETTING: 8 clinics in a chosen sub-district DURATION OF RECRUITMENT: March to September 2007 DURATION OF TRIAL: The recruitment plus follow-up interviews stretched over a period of 9 months FOLLOW-UP: Initial assessment interview lasted one hour. 2 follow-up interviews (a month and a half apart), and a last follow-up interview before the birth.	INCLUSION CRITERIA: 1) All pregnant women attending any one of the eight clinics in the area, 2) less than 20 weeks pregnant, 3) more than 15 years of age. Women who reported no drinking were not excluded. Number of eligible participants: 711 Excluded: 517 Sample size: 194 All clinics in the area, 8, were cluster randomized Intervention group: 98 women from 4 randomized clinics Control group: 96 women from 4 randomized clinics randomized to intervention group, and to control group. Number included in the analysis in the intervention group: 97 Number included in the analysis in the control group: 82	INTERVENTION: 1) Initial assessment interview – lasting an hour – included the consent form, the personal questionnaire, the Alcohol Use Disorders Identification Test (AUDIT), explaining the meaning of AUDIT results, Brief Intervention (BI) with setting drinking goals, and making notes in a take-home alcohol booklet. 2) In two follow-up interviews (a month and a half apart), the BI consisted of feedback on drinking behaviour, negotiations, goal setting, and reinforcement. A questionnaire on changes in drinking behaviour and bonding was completed. These interviews lasted 20 minutes on average. 3) The last follow-up interview before the birth comprised a BI and feedback on drinking behaviour, completing a questionnaire on changes in drinking behaviour, and completing a second AUDIT. Interviews were conducted by two trained fieldworkers. Incentives in the form of a food parcel were given to all participants in the trial. CONTROL: Involvement with respondents was kept to the minimum that was allowed ethically: 1) The initial assessment interview included the consent form, the personal questionnaire, the AUDIT, written material, i.e. the take-home alcohol booklet, and appointment for the follow-up interview, 2) the last follow-up interview just before the birth consisted of a second AUDIT and a questionnaire on changes in drinking behaviour.	MATERNAL OUTCOMES: AUDIT score at post-intervention was used to measure the intervention effect INFANT OUTCOMES: none	ETHICS: The protocol for the study was ethically approved by a university ethics committee INFORMED CONSENT: All participants were given the consent form at the first interview FUNDING The study was funded by the Western Cape Department of Social Development

O'Connor 2007	STUDY TYPE: Cluster randomized controlled trial COUNTRY: United States SETTING: community-based setting; 12 centers of the Public Health Foundation Enterprises Management Solutions Special Supplemental Nutrition Program for Women, Infants, and Children; PHFE-WIC DURATION OF RECRUITMENT: June 2001 to March 2004 FOLLOW-UP: Women were screened at every monthly prenatal visit and, if they were still drinking, were provided brief intervention or assessment only. Women were followed to the third trimester	Screened: 4980 Agree to participate: 4084 Use of alcohol post conception: 972 Currently drinking alcohol: 369 Number of participants randomized: 345 Intervention group: 162 Control group: 183 Number included in the analysis: Intervention group: 117 Control group at follow-up:138 Of 369 currently drinking, 24 were referred to an alcohol treatment programme (prior to randomization).	INTERVENTION: Within the 6 centers in the brief intervention condition, participants received the same comprehensive assessment of alcohol use plus a standardized workbook-driven brief intervention, designed specifically to help women reduce alcohol consumption during pregnancy. Women were screened at every monthly prenatal visit and, if they were still drinking, were provided brief intervention or assessment only. The brief intervention represented a logical extension of the individual nutrition education that women enrolled in WIC already receive. A brief intervention workbook was designed by study investigators to help nutritionists standardize and administer the intervention. The workbook consisted of traditional brief intervention techniques, including education and feedback, cognitive behavioral procedures, goal setting, and contracting. CONTROL: Within the 6 centers in the assessment- only condition, current drinkers received a comprehensive assessment of alcohol use and were advised to stop drinking during pregnancy	MATERNAL OUTCOMES: 1) Maximum drink per drinking occasion 2) TWEAK mean 3) Cannabis use 4) Cocaine use INFANT OUTCOMES: 1) Gestational age at delivery 2) Birth weight 3) Birth length	ETHICS: Protocols and consent forms were approved by the University of California, Los Angeles, institutional review board, and a Certificate of Confidentiality was obtained from the National Institute on Alcohol Abuse and Alcoholism INFORMED CONSENT: Women participating in this study were provided with a clear description of the study protocol and signed an informed consent form
Ondersma 2005	STUDY TYPE: Randomized controlled trial COUNTRY: USA SETTING: Large urban obstetric hospital in Detroit DURATION OF RECRUITMENT: between September 9, 2003, and February 26, 2004 DURATION OF TRIAL: Not stated FOLLOW-UP: A research assistant, blind to experimental condition, contacted the participants again by telephone at an average follow-up duration of 38.6 days (range 25–77).	INCLUSION CRITERIA: All participants were postpartum women who had given birth at a large urban obstetric hospital and who endorsed any illicit drug use in the month before becoming pregnant. Participation was further limited to those who had slept since giving birth, those who could understand spoken English, were between 18 and 45 years, and had not been administered narcotic pain medication in the past 3 hours. EXCLUSION CRITERIA: Not stated Number of participants randomized: 30 (15 randomized to intervention group, and 15 to control group). Participants had high rates of cannabis and cocaine use. There were no significant differences between intervention and control groups on any baseline substance-use variables.	INTERVENTION: assessment plus intervention conditions GROUP Participants viewed personalized feedback, the pros and cons of drug use, and optional goal-setting in counterbalanced order. Three visual analogue-scale items from the motivation to change measure were presented after each counterbalanced component. CONTROL: Assessment only GROUP Participants were only assessed for drug use.	MATERNAL OUTCOMES: Drug use Service involvement Motivation at follow-up INFANT OUTCOMES: None	ETHICS: Wayne State University Institutional Review Board. INFORMED CONSENT: All participants provided verbal informed consent for the screening and written informed consent for the full study. FUNDING: Grants DA00516 and DA14621 from the National Institute on Drug Abuse.

Tzilos 2011	STUDY TYPE: Randomized controlled trial COUNTRY: USA SETTING: Inner city prenatal care clinic at Michigan (exact city not stated). DURATION OF RECRUITMENT: Not stated. DURATION OF TRIAL: Not stated. FOLLOW-UP: Women were followed-up one month after the intervention, with average follow-up time of 33 days (SD: 7.9, range: 25 – 72 days). Follow-up was conducted over the telephone for approximately 10 – 15 minutes, and included TLFB assessment of drinking in the past month.	INCLUSION CRITERIA: Being pregnant, between ages 18 and 45 (with at least 1 month expected gestation remaining), able to understand spoken English, and either (1) meeting T-ACE criteria for problem alcohol use, (2) exceeding the National Institute on Alcohol Abuse and Alcoholism (NIAAA) ''normal'' sensible drinking limits before pregnancy (more than seven standard drinks a week or more than two drinks at a time), or (3) reporting drinking at least one time per month during pregnancy. EXCLUSION CRITERIA: Inability to provide informed consent (e.g., due to psychosis, intoxication, or other clear cognitive impairment), inability to communicate in English, and not having access to a phone (for follow-up). Number of participants randomized: 50 (27 randomized to intervention group, and 23 to control group).	INTERVENTION: Computer-delivered single-session brief intervention Participants self-administered and solely computer-delivered, with assistance available from the investigator as needed and it lasted for 15 – 20 minutes. The software tailored content based on the current drinking status of each participant. For women who reported they already quit, the narrator presented a section that focused on relapse prevention (''My plan to remain abstinent'') while asking the participant to provide the reasons/benefits to them of having made this change. The remaining women were asked about their current interest in quitting. Those reporting a goal of immediate abstinence moved more quickly to a section consistent with phase 2 of MI (primarily goal setting), whereas those who did not wish to quit received elements consistent with phase 1 of MI (e.g. pros and cons, feedback). CONTROL: Participants were administered series of questions about TV shows, videos of popular entertainers/shows, followed by requests for ratings of subjective preference. Duration was equivalent to that of intervention group. CO-INTERVENTIONS: All eligible participants received gift cards (equivalent to $30) for their participation at the baseline visit. .Women who completed the follow-up session received an additional gift card (equivalent to $5) by mail.	MATERNAL OUTCOMES: Feasibility of the computer-delivered approach as measured by rate of identification of at-risk drinking and the proportion of women completing the session. Acceptability of the computer-delivered SBIRT as measured by reported ease of use, helpfulness and overall satisfaction. Alcohol consumption as measured by frequency, quantity, and binge use post-intervention. INFANT OUTCOMES: Gestational age, birth weight, and head circumference as measured by information in from the medical records.	ETHICS: Wayne State University Institutional Review Board as well as the Detroit Medical Center Research Review Committee. INFORMED CONSENT: Participants provided signed informed consent. FUNDING: The research was supported by NIAAA training grant AA16256 (to G. K.T; mentor, S.J.O.).

Whaley 2003	STUDY TYPE: Cluster randomized trial COUNTRY: USA SETTING: Public Health Foundation Enterprises WIC center sites DURATION OF TRIAL: 25 months: from May 2000 to May 2002	Of the 53 PHFE-WIC sites in Los Angeles and Orange counties, 12 were randomly selected to administer a self-report alcohol screening tool to all pregnant women. The remaining 41 WIC sites continued to administer the WIC standard care. From these 41 sites, 12 control sites (matched to the intervention group on caseload size, size of the Hispanic population, maternal age, and maternal education) were selected for this analysis. INCLUSION CRITERIA: Pregnant women visiting the 24 WIC sites over the course of the study were included in the sample for each month of their pregnancy.	INTERVENTION: The alcohol screening tool incorporates 2 methods found in previous research to most accurately assess alcohol intake because of their ease of use and sensitivity. Quantity-frequency measures inquire about typical consumption patterns and include the amount of drinking on an average day (quantity) and the average number of days on which alcohol was consumed (frequency). The Time-line Followback method was also used on the alcohol screening tool, because it provides a more detailed picture of a person's drinking over designated time periods and has been evaluated extensively with clinical and nonclinical population. CONTROL: The 12 control clinics continued to administer the WIC standard of care.	MATERNAL OUTCOMES: ongoing substance use during pregnancy INFANT OUTCOMES: none	

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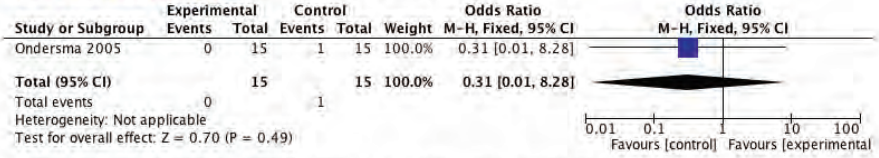
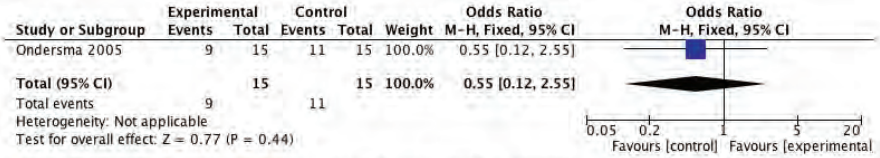
FIGURES

Figure 1 (Analysis 1.1)



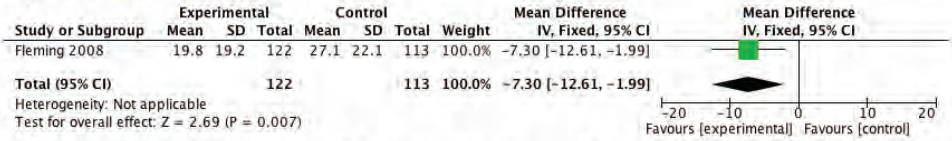
Forest plot of comparison: 1 Screening and Brief Intervention vs Screening Alone, outcome: 1.1 Attending substance abuse treatment.

Figure 2 (Analysis 1.3)



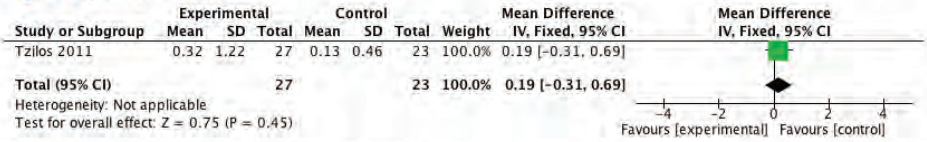
Forest plot of comparison: 1 Screening and Brief Intervention vs Screening Alone, outcome: 1.3 Abstinence from drug use in the last 4 weeks - ITT analysis.

Figure 3 (Analysis 1.4)



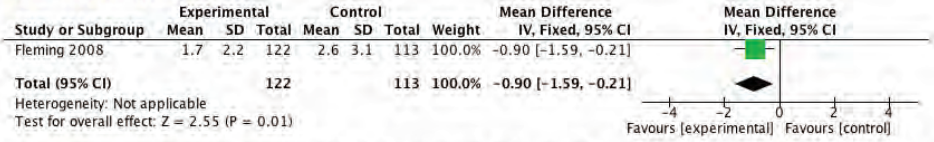
Forest plot of comparison: 1 Screening and Brief Intervention vs Screening Alone, outcome: 1.4 Total number of drinks in the past 28 days.

Figure 4 (Analysis 1.8)



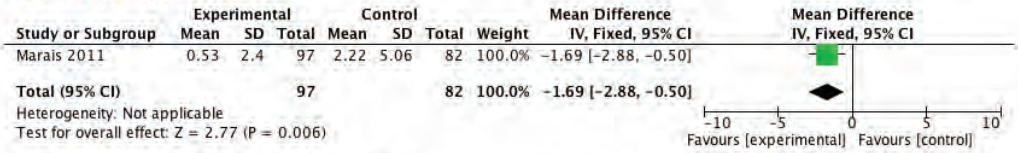
Forest plot of comparison: 1 Screening and Brief Intervention versus usual care, outcome: 1.8 Number of standard drinks per week.

Figure 5 (Analysis 1.6)



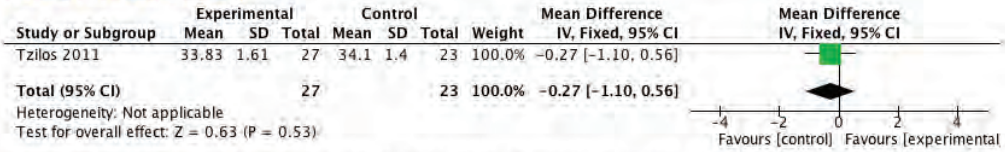
Forest plot of comparison: 1 Screening and Brief Intervention vs Screening Alone, outcome: 1.6 Number of heavy drinking days in the past 28 days.

Figure 6 (Analysis 1.15)



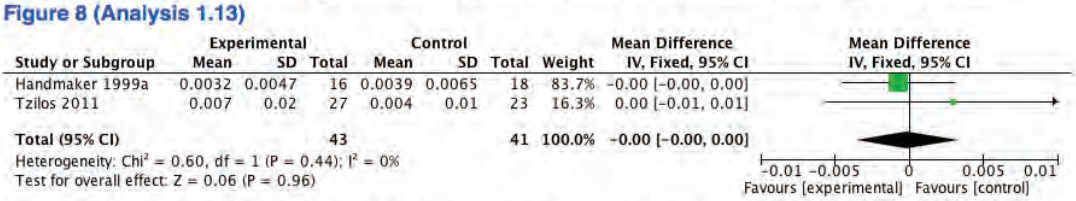
Forest plot of comparison: 1 Screening and Brief Intervention versus usual care, outcome: 1.15 Audit score.

Figure 7 (Analysis 1.24)



Forest plot of comparison: 1 Screening and Brief Intervention versus usual care, outcome: 1.24 Head Circumference.

Figure 8 (Analysis 1.13)

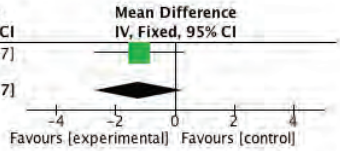


Forest plot of comparison: 1 Screening and Brief Intervention vs Screening Alone, outcome: 1.13 Estimated peak BAC.

Figure 9 (Analysis 1.26)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fleming 2008	6.84	5.2	97	8.06	5.7	108	100.0%	−1.22 [−2.71, 0.27]
Total (95% CI)			**97**			**108**	**100.0%**	**−1.22 [−2.71, 0.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.60 (P = 0.11)

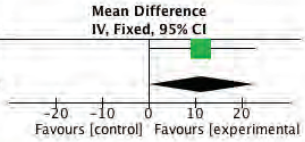


Forest plot of comparison: 1 Screening and Brief Intervention versus usual care, outcome: 1.26 Depression post partum.

Figure 12 (Analysis 1.19)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ondersma 2005	88.8	10	15	77.4	20	15	100.0%	11.40 [0.08, 22.72]
Total (95% CI)			**15**			**15**	**100.0%**	**11.40 [0.08, 22.72]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)

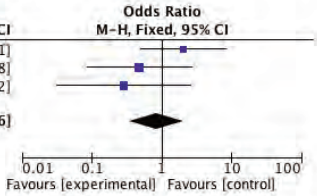


Forest plot of comparison: 1 Screening and Brief Intervention vs Screening Alone, outcome: 1.19 Motivation to change.

Figure 13 (Analysis 1.20)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chang 2005	6	152	3	152	27.5%	2.04 [0.50, 8.31]
Marais 2011	2	98	4	96	37.8%	0.48 [0.09, 2.68]
O'Connor 2007	1	117	4	138	34.7%	0.29 [0.03, 2.62]
Total (95% CI)		**367**		**386**	**100.0%**	**0.84 [0.34, 2.06]**
Total events	9		11			

Heterogeneity: $Chi^2 = 2.84$, df = 2 (P = 0.24); $I^2 = 30\%$
Test for overall effect: Z = 0.37 (P = 0.71)



Forest plot of comparison: 1 Screening and Brief Intervention vs Screening Alone, outcome: 1.20 Spontaneous abortion.

Figure 14 (Analysis 1.25)

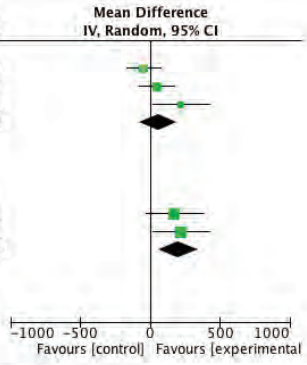
Study or Subgroup	Brief Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.25.1 All participants								
Chang 1999	3,360	500	123	3,406	500	127	37.8%	-46.00 [-169.97, 77.97]
O'Connor 2007	3,419.43	508.5	117	3,367.5	522.5	138	37.3%	51.93 [-74.91, 178.77]
Tzilos 2011	3,189.6	328	27	2,965.3	387.7	23	24.9%	224.30 [23.27, 425.33]
Subtotal (95% CI)			**267**			**288**	**100.0%**	**57.80 [-77.26, 192.86]**

Heterogeneity: $Tau^2 = 8550.75$; $Chi^2 = 5.11$, df = 2 (P = 0.08); $I^2 = 61\%$
Test for overall effect: Z = 0.84 (P = 0.40)

1.25.2 Drinking more than 1 drink per occasion or per day (post-hoc analysis)								
O'Connor 2007	3,486	538	54	3,312	581	64	49.8%	174.00 [-28.12, 376.12]
Tzilos 2011	3,190	328	27	2,965	388	23	50.2%	225.00 [23.88, 426.12]
Subtotal (95% CI)			**81**			**87**	**100.0%**	**199.63 [57.06, 342.19]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$
Test for overall effect: Z = 2.74 (P = 0.006)

Test for subgroup differences: $Chi^2 = 2.00$, df = 1 (P = 0.16), $I^2 = 50.1\%$



Forest plot of comparison: 1 Screening and Brief Intervention vs Screening Alone, outcome: 1.25 Birthweight.

Evidence Profile 2: Psychosocial interventions for harmful use and dependence on alcohol and other substances in pregnancy

Evidence question:

For pregnant and postpartum women with harmful alcohol or drug use, do some psychosocial interventions result in better maternal, fetal and infant outcomes than other psychosocial interventions or usual care?

Selection criteria for the systematic review:

Study design: RCTs

Population: Pregnant or postpartum women with harmful use of alcohol or drugs.

Interventions: Psychological or social interventions longer in duration and intensity than brief interventions.

Control: Other psychosocial interventions or usual care (usual obstetric care or usual specialist care).

Outcomes: The key outcomes selected were:

Outcome	Importance (0-9)
Maternal: Substance use	8.22
Maternal: Retention in substance use treatment	7.89
Infant: Birthweight	6.78
Custody of infant	6.56
Infant: Gestational age at delivery	6.44
Infant: Birth defects	6.00
Infant: Neonatal death	5.89

EVIDENCE TO RECOMMENDATIONS TABLE

Psychosocial interventions for harmful use and dependence on alcohol and other substances in pregnancy

Summary of evidence: see also summary of findings and GRADE tables below

Summary of RCT evidence:

With the exception of home visits, all RCTs compared a specific form of psychosocial intervention to treatment-as-usual in the specialist drug and alcohol treatment service, not usual obstetric care. As such, they are comparing one form of psychosocial intervention with another, since all specialist treatment is considered to include a component of psychosocial care.

Motivational Interviewing (MI)

Two randomized clinical trials have compared motivational interviewing (MI) to treatment-as-usual or educational control. Findings do not support the superiority of MI to treatment-as-usual or educational control, with similar results for maternal retention in treatment and maternal substance abuse. Data are absent regarding neonatal outcomes. Both samples were identified as needing substance-abuse treatment.

Cognitive Behavioural Therapy (CBT)

Two randomized clinical trials compared cognitive behavioural therapy (CBT) to treatment-as-usual. Findings suggest that CBT may be superior to treatment-as-usual in terms of treatment retention, reductions in sex and needle risk, and occurrence of preterm birth. One sample was in methadone treatment and the other sample was using alcohol or another illicit substance exclusive of opiates.

Contingency Management (CM)

Five randomized clinical trials compared contingency management (CM) to treatment-as-usual. Findings support the superiority of CM to treatment-as-usual in terms of retention in treatment, percentage of negative urines, and weeks of continuous cocaine abstinence. Three of the samples met requirements for methadone maintenance, one sample met requirements for opioid or cocaine dependence, and one met criteria for cocaine dependence.

Other

Standard management home visits have been shown not to be effective. A review of randomized trials (Turnbull & Osborn, 2012) suggests that home visits following delivery are not effective in reducing maternal retention in treatment, substance use or alcohol use. Findings from 4 other studies (Butz et al., 1998; Grant et al., 1996; Quinlivan et al., 2000; Schuler et al., 2000) omitted by Turnbull and Osborn (2013) are consistent with their conclusion.

Educational and counselling interventions may encourage women to cease alcohol use or reduce the amount of alcohol consumed during pregnancy (Stade, 2009).

Benefits and harms

Benefits

- Pregnancy presents a unique opportunity to help support women to reduce and ideally cease alcohol and/or illicit substance use (Chang et al., 2000)
- Depending on the substance of use, psychosocial interventions are considered to be superior to usual care in terms of:
  - reduction in harmful consumption
  - reduction in risk to fetus
  - increase in birthweight
  - improved general health of pregnant women
  - improved maternal psychological well-being
  - less risk of fetotoxicity
  - improved perinatal outcomes (e.g. reduction in preterm births, increased overall birthweights, reduction in number of low-birthweight infants)
  - reductions in congenital defects or anomalies (Lui, Terplan, & Smith, 2008; Terplan & Lui, 2007)
- There is a high incidence of mental health disorders in opioid-dependent pregnant women and psychosocial interventions may be appropriate in many instances (Martin et al., 2009)
- Considerable research supports a variety of psychosocial interventions for substance use and co-occurring mental disorders in non-pregnant populations (Drake, O'Neal, & Wallach, 2008)
- Retention in substance abuse treatment is an important factor in reducing illicit substance use (Laken, 1997)

EVIDENCE TO RECOMMENDATIONS TABLE

Harms	• Physical and mental symptoms associated with reduction or cessation of alcohol or substance use • Possible development of depression or anxiety as a result of cessation or reduction of alcohol or illicit substance use • Possible verbal and/or physical abuse by the partner as a result of the pregnant woman's behaviour change • Possible risk of switching from one substance to another substance • Between 7% and 15% of individuals participating in psychosocial interventions to treat substance use disorders may be worse off after treatment than before treatment. This decline in functioning may be due to a lack of bonding with the provider, lack of goal direction and monitoring, confrontation, criticism, and high emotional arousal and stigma (Moos, 2012) • Stigmatization-risk of incarceration/loss of infant in punitive systems • Economic and time burdens imposed by need to attend interventions • Conflict with partner/family/employer over time/ commitment to intervention
Values and preferences	
In favour: **Pregnant woman**	• Personal contact and support • Development of coping strategies • Commitment to behaviour change
Health-care worker	• Opportunity to intervene • Positive means of intervening • Effective means of intervening
Community	• Possible reduction of crime in the community • Possible reduction of sexually transmitted infection (STI) risk in the community • Possible positive responses from partners, family and, co-workers
Against: **Pregnant woman**	• Stigmatization of pregnant women who drink alcohol or use illicit substances during pregnancy • Stigmatization of women who are in need of counselling • Negative responses from partners, family and co-workers
Health-care workers	• Time and inconvenience involved in referral for intervention • Concern about effectiveness of intervention • Resentment of diversion of resources to intervention
Community	• Resentment of resources used for intervention • Disbelief in effectiveness • Partners/family may see changes in woman undergoing intervention as harmful
Costs and feasibility	
Costs	• Additional costs beyond routine care • Trained staff and a sustainable programme are required. Training for management of substance use disorders on the part of obstetricians and their staff can increase their self-efficacy regarding the treatment of patients who use substances (Schumacher, 2000).

EVIDENCE TO RECOMMENDATIONS TABLE

Feasibility (including economic consequences)	• Inconvenient for women • Requires patient monitoring to ensure patient remains enrolled in and engaged in the psychosocial intervention • A comprehensive care model in which obstetrical care is part of a women-centered, trauma-informed program would be the best model of care – and also potentially the costliest • A therapeutic workplace has been shown to be superior to usual care in reducing opioid and cocaine use in pregnant women with substance use disorders (Silverman et al., 2001) • Well-child care visits may not be sufficient to prevent deterioration in competence and social isolation in postpartum women who use substances (Taylor, 1998)

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Terplan M, Lui S. Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions. *Cochrane Database Syst Rev* 2007:CD006037.

Turnbull C, Osborn DA. Home visits during pregnancy and after birth for women with an alcohol or drug problem. *Cochrane Database Syst Rev* 2012;1:CD004456.

Draft recommendations:

- Pregnant women with dependent alcohol or other substance use (or harmful alcohol or other substance use not responding to brief interventions) should be offered intensive psychosocial support and treatment.
- Postpartum women with substance dependence should be offered intensive psychosocial support and treatment including home visits, parenting support, psychotherapy and social assistance.

Final recommendations:

RECOMMENDATION 3

Health-care providers managing pregnant or postpartum women with alcohol or other substance use disorders should offer comprehensive assessment and individualized care.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- A comprehensive assessment of women using alcohol or drugs in pregnancy and the postpartum period includes an assessment of patterns of substance use, medical or psychiatric comorbidity, family context, as well as social problems.
- Individualized care involves selecting appropriate psychosocial interventions of different intensity based on the particular needs of the pregnant women and the resources available. Psychosocial interventions include a number of psychological treatments and social supports, ranging from lesser to higher intensity. The psychosocial treatment and support referred to in this section is a more intensive set of interventions typically delivered by people with specific training in the management of substance use disorders, and usually includes repeated contact with the patient. The kinds of specific psychological techniques considered in this category include cognitive behavioural therapy, contingency management and motivational enhancement. The kinds of social support referred to in this section include assistance with accommodation, vocational training, parenting training, life-skills training, legal advice, home visiting and outreach.
- Despite the benefits of psychosocial treatment outweighing the harms, this recommendation was considered to be conditional given the absence of strong evidence and the potential resource implications.

Factors in considering the strength of the recommendation (recommendation 3):

Factor	Decision
Is there high or moderate quality evidence? The higher the quality of evidence, the more likely is a strong recommendation.	**No**
Is there certainty about the balance of benefits versus harms and burdens? In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms? In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?	**Yes**
Are the expected values and preferences clearly in favour of the recommendation?	**Yes**
Is there certainty about the balance between benefits and resources being consumed? In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed? In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?	**No**

Research recommendations

- Better reporting and agreement on standardized designs and outcomes is needed.
- Stronger RCT evidence of effect is needed, in particular comparing interventions with different levels of intensity and models of care with different levels of comprehensiveness, and including cost-effectiveness analyses.

Summary of findings and GRADE tables

CASE MANAGEMENT during pregnancy and after birth for women with an alcohol or drug problem

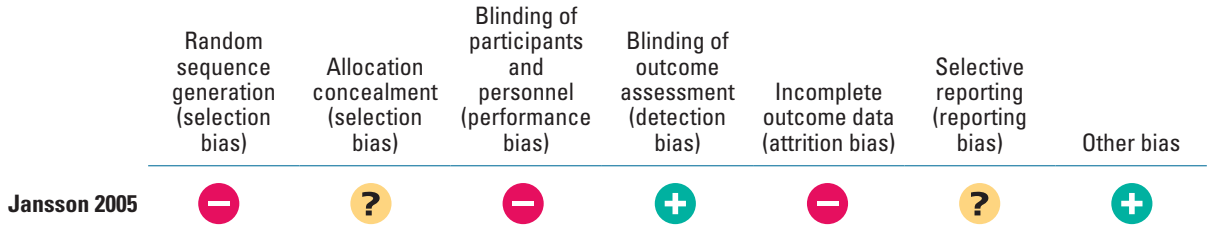
TABLE OF CHARACTERISTICS OF INCLUDED RCTs: 2 IN TOTAL (DATA AVAILABLE FOR 1)

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
INTERVENTION DURING PREGNANCY ONLY								
No trials were identified from these settings.								
INTERVENTION DURING AND AFTER PREGNANCY								
No trials were identified from these settings.								
INTERVENTION AFTER PREGNANCY ONLY								
Generalised treatment settings								
No trials were identified from these settings.								
Specialist treatment settings								
Jansson 2005	USA	56 R 40 A	Term, all women delivering infants at a community hospital in East Baltimore	Opioid or cocaine dependent women	All women received prenatal and drug abuse treatment services at a comprehensive treatment program which included access to methadone maintenance for qualifying opioid-dependent patients, case management, group and individual counseling, obstetrical care, psychiatric evaluation and treatment, general medical management, and on-site child care and paediatric care.	4 months	**Intensified Case Management:** As for Routine Case Management, but women also received bi-weekly case management services by telephone or in person (on-site at the treatment facility or through home visits). Intensive case management services focused on assessment, planning for necessary services and interventions, establishment of linkages with relevant agencies, monitoring of patient follow through with scheduled appointments and advocacy for the patient when needed to successfully navigate the health-care system. **Routine Case Management:** Offered at scheduled paediatric visit at clinic of treatment service: 2 wks, 1, 2 and 4 months postpartum. Women were asked about their status in substance abuse treatment, needs for themselves and their infants, and compliance with treatment, paediatric care, maternal health, and postpartum care and family planning. **Co-interventions:** US$50 gift voucher to compensate them for their time and effort at follow-up.	Not clearly reported as primary or secondary. MATERNAL • Treatment retention • Self-reported perception of utility of case management • Self-reported substance use • Urine drug toxicology INFANT • None

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
Walton-Moss 2006	USA	115 R 0 A	< 28 wks	Cocaine or Heroin abuse or dependence (DSM IIIR)	Specialist hospital setting	4 months	This RCT was conducted as part of the Maryland Better Chance Project which was initiated as a demonstration project to recruit pregnant substance users into active treatment. It was not completed as recruitment was too slow. **Case management:** Usual care including support groups plus case management. Details not provided. **Usual care:** Included support groups.	Nil, no outcome analysis reported, only baseline data

RCT – Randomized controlled trial
R – Number randomized
A – Number analysed

RISK OF BIAS IN EACH TRIAL INCLUDED IN THE CASE MANAGEMENT COMPARISON



Walton-Moss 2006 was an incompletely reported trial and as a result a risk of bias assessment was not conducted.

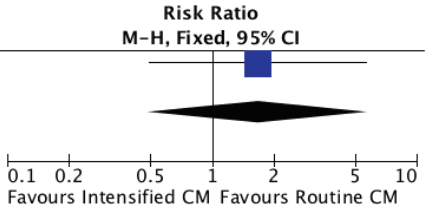
FOREST PLOTS OF CASE MANAGEMENT COMPARISON

1 Intensified Case Management vs Contingency Managment versus Routine Case Management

1.1 Maternal urine positive for opiates other than methadone

Study or Subgroup	Intensified CM Events	Total	Routine CM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jansson 2005	4	15	4	25	100.0%	1.67 [0.49, 5.70]
Total (95% CI)		**15**		**25**	**100.0%**	**1.67 [0.49, 5.70]**
Total events	4		4			

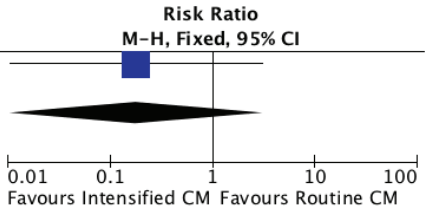
Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)



1.2 Maternal urine positive for cocaine

Study or Subgroup	Intensified CM Events	Total	Routine CM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jansson 2005	0	15	4	25	100.0%	0.18 [0.01, 3.14]
Total (95% CI)		**15**		**25**	**100.0%**	**0.18 [0.01, 3.14]**
Total events	0		4			

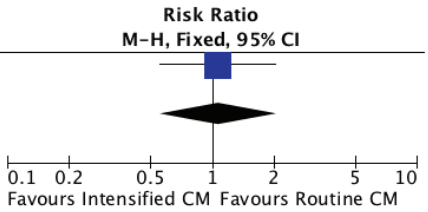
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)



1.3 Maternal Retention in treatment (Intention to treat analysis)

Study or Subgroup	Intensified CM Events	Total	Routine CM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jansson 2005	9	22	13	34	100.0%	1.07 [0.55, 2.07]
Total (95% CI)		**22**		**34**	**100.0%**	**1.07 [0.55, 2.07]**
Total events	9		13			

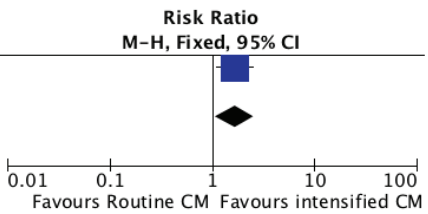
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)



1.4 Positive perception of utility of Case Management

Study or Subgroup	Intensified CM Events	Total	Routine CM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jansson 2005	13	15	13	25	100.0%	1.67 [1.09, 2.55]
Total (95% CI)		**15**		**25**	**100.0%**	**1.67 [1.09, 2.55]**
Total events	13		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)



INTENSIFIED CASE MANAGEMENT COMPARED TO ROUTINE CASE MANAGEMENT FOR PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE

Patient or population: Pregnant or postpartum women with problematic substance use

Settings: Specialist treatment outpatient

Intervention: Intensified case management

Comparison: Routine case management

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Routine case management	**Intensified case management**				
Maternal treatment retention (intention to treat analysis) Follow-up: 0–4 months	**382 per 1000**	**409 per 1000** (210 to 791)	**RR 1.07** (0.55 to 2.07)	56 (1 study)	⊕◯◯◯ VERY LOW[1,2]	
Maternal urine positive for opiates other than methadone Follow-up: 0–4 months	**160 per 1000**	**267 per 1000** (78 to 912)	**RR 1.67** (0.49 to 5.7)	40 (1 study)	⊕◯◯◯ VERY LOW[1,2]	
Maternal urine positive for cocaine Follow-up: 0–4 months	**160 per 1000**	**29 per 1000** (2 to 502)	**RR 0.18** (0.01 to 3.14)	40 (1 study)	⊕◯◯◯ VERY LOW[1,2]	
Infant birthweight	See comment	See comment	Not estimable	50 (1 study)	See comment	Not measured
Infant gestational age	See comment	See comment	Not estimable	50 (2 studies)	See comment	Not measured
Infant custody	See comment	See comment	Not estimable	179 (1 study)	See comment	Not measured
Infant head circumference	See comment	See comment	Not estimable	30 (1 study)	See comment	Not measured
Infant birth defects	See comment	See comment	Not estimable		See comment	Not measured

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High quality: Further 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 very 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] Risk of bias: rated as very serious. Randomization did not result in similar numbers in each group indicating a possible effect of chance or selection bias. Random generation and allocation concealment methods were not reported. Blinding was not possible for participants or providers and attrition was high.

[2] Imprecision: The sample size is small and the confidence interval wide.

Author(s): Nandi Siegrfried and Nicolas Clark

Date: 2013-09-03

Question: SHOULD INTENSIFIED CASE MANAGEMENT VS ROUTINE CASE MANAGEMENT BE USED IN PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE?

Settings: Specialist treatment outpatient

Bibliography: Psychosocial interventions for pregnant or postpartum women with problematic substance use.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening and brief Intervention versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
Maternal treatment retention (intention to treat analysis) (follow-up 0–4 months)												
1	randomized trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/22 (40.9%)	13/34 (38.2%)	RR 1.07 (0.55 to 2.07)	27 more per 1000 (from 172 fewer to 409 more)	⊕◯◯◯ VERY LOW	CRITICAL
Maternal urine positive for opiates other than methadone (follow-up 0–4 months)												
1	randomized trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/15 (26.7%)	4/25 (16%)	RR 1.67 (0.49 to 5.7)	107 more per 1000 (from 82 fewer to 752 more)	⊕◯◯◯ VERY LOW	CRITICAL
Maternal urine positive for cocaine (follow-up 0–4 months)												
1	randomized trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/15 (0%)	4/25 (16%)	RR 0.18 (0.01 to 3.14)	131 fewer per 1000 (from 158 fewer to 342 more)	⊕◯◯◯ VERY LOW	CRITICAL
Infant birthweight – not measured												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Infant gestational age – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant custody – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening and brief Intervention versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
Infant head circumference – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant birth defects – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

[1] Risk of bias: rated as very serious. Randomization did not result in similar numbers in each group indicating a possible effect of chance or selection bias. Random generation and allocation concealment methods were not reported. Blinding was not possible for participants or providers and attrition was high.
[2] Imprecision: The sample size is small and the confidence interval wide.

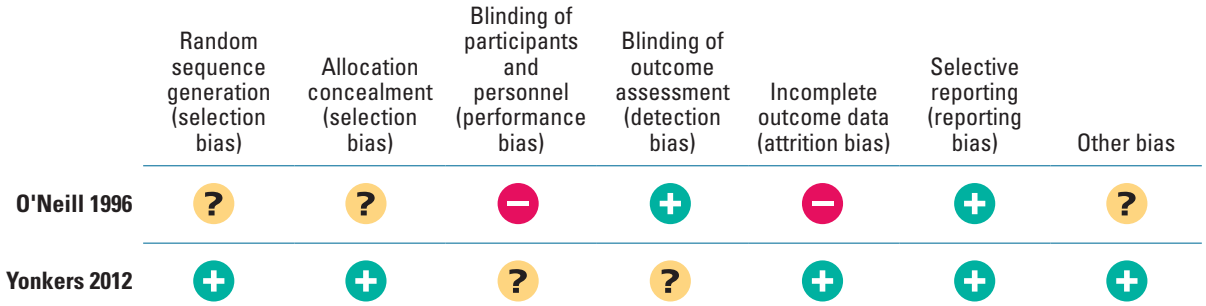
TABLE OF CHARACTERISTICS OF INCLUDED RCTs: 2 IN TOTAL

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
INTERVENTION DURING PREGNANCY ONLY								
Generalised treatment settings								
No trials were identified from these settings.								
Specialist treatment settings								
O'Neill 1996	Australia	92 R 80 A	Pregnancy and gestational age not stated for inclusion criteria; baseline EGA mean 22 (SD: 9.6) wks	On Methadone programme & the self-reported injection of any drug within the previous 6 months	Outpatient. Sites for recruitment included methadone unit and antenatal clinics involved in the study	6 week active treatment; study follow-up at 9 months	**Cognitive Behavioural Relapse Prevention:** Six sessions over six weeks: 1. Motivational interview 2. Identifying high-risk situations for sharing needles and unsafe sex 3. Coping with craving 4. Mini-decisions and life-style balance 5. Coping with lapses and the rule violation effect 6. Progress review and continued use of coping skills Sessions were delivered by three psychologists and lasted 60–90 min. **Usual care:** Participants received the counselling and advice about HIV risk-taking behaviour available as part of the methadone maintenance programme.	MATERNAL 1. HIV Risk-taking Behaviour Scale: a. Injecting risk-taking b. Sex risk-taking 2. Needle risk 3. Highest use needle risk INFANT None

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
INTERVENTION DURING AND AFTER PREGNANCY								
Generalised treatment settings								
Yonkers 2012	USA	183 R 168 A	< 28 wks	Using alcohol or an illicit drug (excluding opiates) during 28 days prior to screening OR scored at least '3' on TWEAK scale	Outpatient. Two hospital-based reproductive health clinics with appointments coordinated with regular prenatal visits. (Participants may have been inpatients at some point in study)	Intervention from intake until 3 months postpartum	**Cognitive Behavioural (CBT) & Motivational Enhancement Therapy (MET):** Individual behavioral therapy that combined MET and CBT formatted into 6 sessions delivered in conjunction with prenatal and immediate postnatal care visits. Content included motivational enhancement, functional analysis, safe sexual behavior, communication skills, relapse prevention and problem-solving skills. Delivered by a nurse therapist who had flexibility to offer additional treatment sessions according to time and need. Each session lasted approximately 30 min **Brief advice:** Brief advice covered risks of substance use, the importance of abstinence, and the benefit of seeking drug and alcohol treatment outside of the prenatal setting. Brief advice was administered by the participant's obstetrical provider and typically lasted around 1 min. Unclear whether the sessions took place at same frequency as for CBT-MET	MATERNAL 1. Substance use a. % of days of any alcohol or drug use in prior 28 days b. Self-reported abstinence c. Urine toxicology 2. Needle risk 3. Highest use needle risk INFANT 1. Birthweight 2. Preterm birth (< 37 wks) 3. Low birthweight (< 2500g)
Specialist treatment settings								
No trials were identified from these settings.								
INTERVENTION AFTER PREGNANCY ONLY								
Generalised treatment settings								
No trials were identified from these settings.								
Specialist treatment settings								
No trials were identified from these settings.								

RCT – Randomized controlled trial
R – Number randomized
A – Number analysed

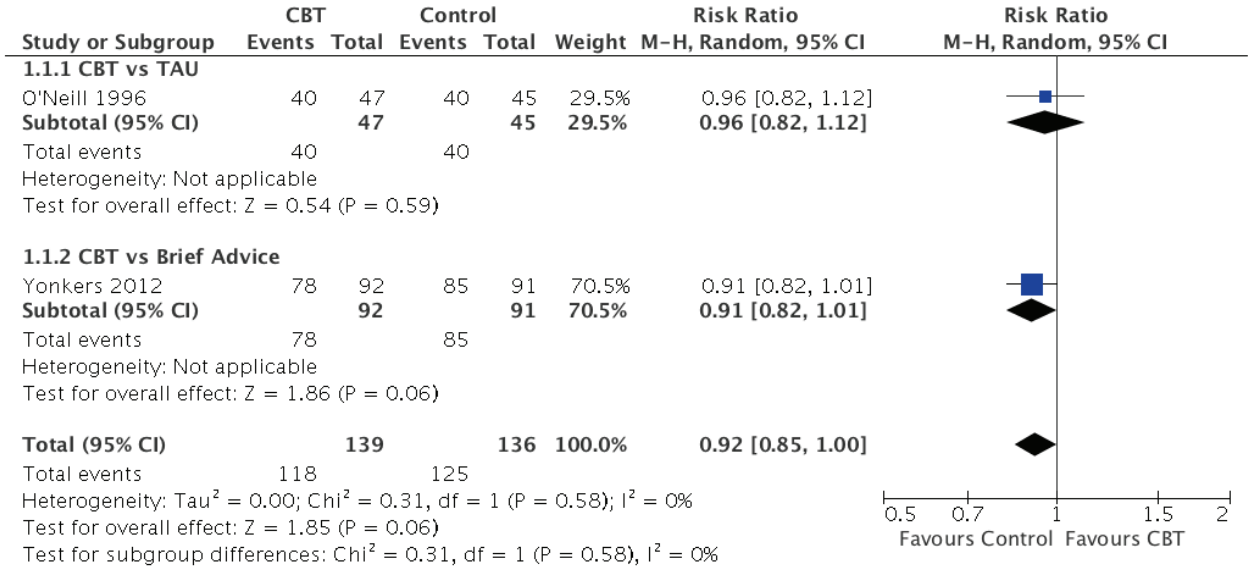
RISK OF BIAS IN EACH TRIAL INCLUDED IN THE COGNITIVE BEHAVIOURAL THERAPY COMPARISON



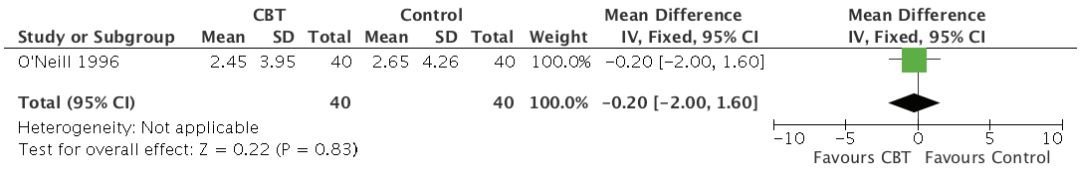
FOREST PLOTS OF COGNITIVE BEHAVIOURAL THERAPY COMPARISON

1 Cognitive Behavioural Therapy versus Control

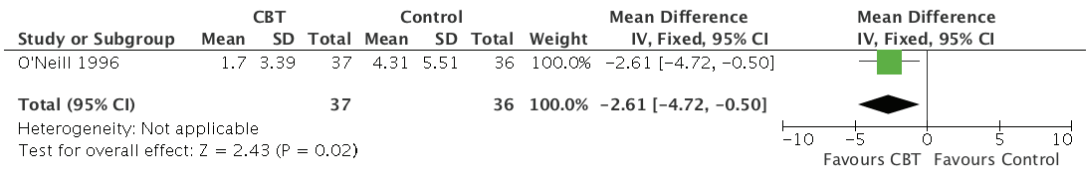
1.1 Treatment Retention



1.2 Needle risk (measured on HIV Risk-taking Behaviour Scale) at 6 weeks



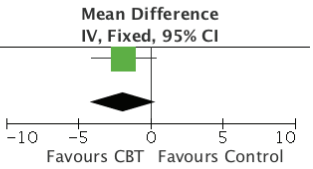
1.3 Needle risk (measured on HIV Risk-taking Behaviour Scale) at 9 months



1.4 HIghest Use Needle risk (measured on HIV Risk-taking Behaviour Scale for month in last 6 month with greatest injecting frequency) at 9 months

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Neill 1996	2.92	4.33	37	4.78	5.48	36	100.0%	-1.86 [-4.13, 0.41]
Total (95% CI)			**37**			**36**	**100.0%**	**-1.86 [-4.13, 0.41]**

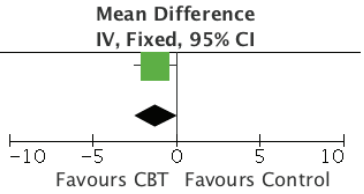
Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)



1.5 Sexual risk (measured on HIV Risk-taking Behaviour Scale) at 6 weeks

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Neill 1996	3.7	3.17	40	4.92	2.69	40	100.0%	-1.22 [-2.51, 0.07]
Total (95% CI)			**40**			**40**	**100.0%**	**-1.22 [-2.51, 0.07]**

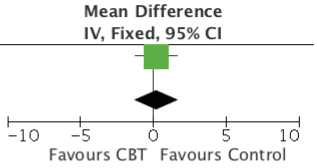
Heterogeneity: Not applicable
Test for overall effect: Z = 1.86 (P = 0.06)



1.6 Sexual risk (measured on HIV Risk-taking Behaviour Scale) at 9 months

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Neill 1996	4.32	3.47	37	4.08	2.94	36	100.0%	0.24 [-1.23, 1.71]
Total (95% CI)			**37**			**36**	**100.0%**	**0.24 [-1.23, 1.71]**

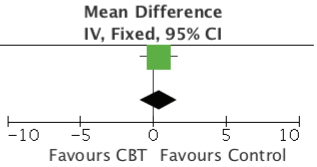
Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)



1.7 HIghest Use Sexual risk (measured on HIV Risk-taking Behaviour Scale for month in last 6 month with greatest injecting frequency) at 9 months

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
O'Neill 1996	5.46	2.76	37	5.06	2.86	37	100.0%	0.40 [-0.88, 1.68]
Total (95% CI)			**37**			**37**	**100.0%**	**0.40 [-0.88, 1.68]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)



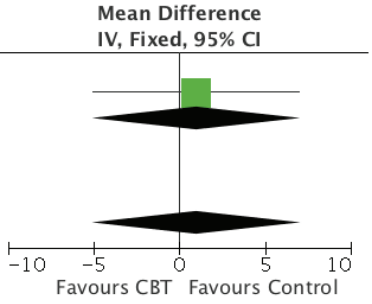
1.8 % days used drugs or alcohol in past month measured at delivery

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 CBT vs BA								
Yonkers 2012	7	22	80	6	17	83	100.0%	1.00 [-5.05, 7.05]
Subtotal (95% CI)			**80**			**83**	**100.0%**	**1.00 [-5.05, 7.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)

Total (95% CI)			**80**			**83**	**100.0%**	**1.00 [-5.05, 7.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable



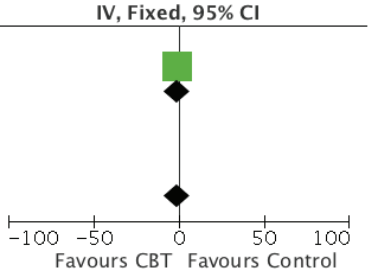
1.9 % days used drugs or alcohol in past month measured 3 months post-partum

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 CBT vs BA								
Yonkers 2012	13	24	71	14	25	72	100.0%	-1.00 [-9.03, 7.03]
Subtotal (95% CI)			**71**			**72**	**100.0%**	**-1.00 [-9.03, 7.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)

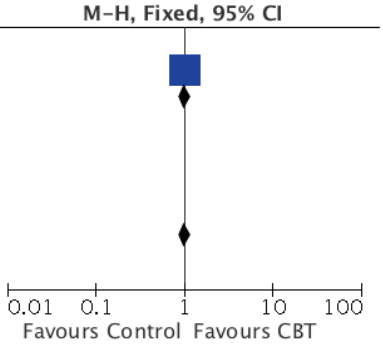
Total (95% CI)			**71**			**72**	**100.0%**	**-1.00 [-9.03, 7.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



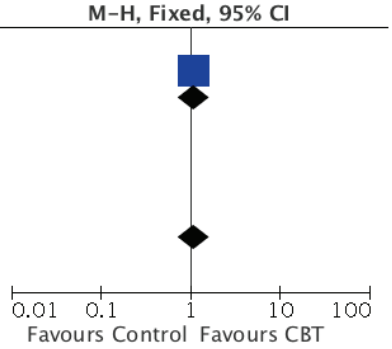
1.10 % abstinent from drugs and alcohol in past month by self-report (at delivery)

Study or Subgroup	CBT Events	CBT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 CBT vs Brief Advice						
Yonkers 2012	61	80	62	83	100.0%	1.02 [0.86, 1.22]
Subtotal (95% CI)		**80**		**83**	**100.0%**	**1.02 [0.86, 1.22]**
Total events	61		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**80**		**83**	**100.0%**	**1.02 [0.86, 1.22]**
Total events	61		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Not applicable						



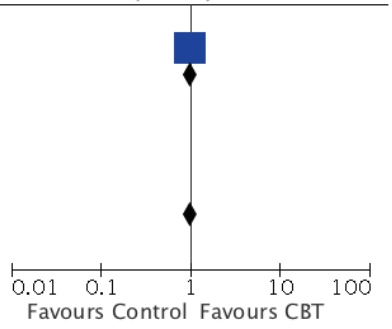
1.11 % abstinent from drugs and alcohol in past month by self-report (at 3 months post partum

Study or Subgroup	CBT Events	CBT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 CBT vs Brief Advice						
Yonkers 2012	29	71	27	72	100.0%	1.09 [0.72, 1.64]
Subtotal (95% CI)		**71**		**72**	**100.0%**	**1.09 [0.72, 1.64]**
Total events	29		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**71**		**72**	**100.0%**	**1.09 [0.72, 1.64]**
Total events	29		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Test for subgroup differences: Not applicable						



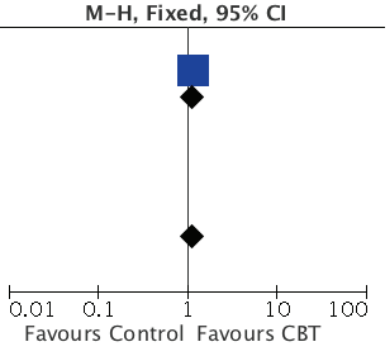
1.12 % abstinent from drugs and alcohol in past month by urine screen (at delivery)

Study or Subgroup	CBT Events	CBT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 CBT vs Brief Advice						
Yonkers 2012	46	55	43	51	100.0%	0.99 [0.84, 1.17]
Subtotal (95% CI)		**55**		**51**	**100.0%**	**0.99 [0.84, 1.17]**
Total events	46		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**55**		**51**	**100.0%**	**0.99 [0.84, 1.17]**
Total events	46		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Not applicable						



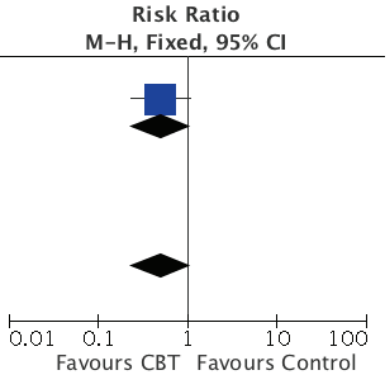
1.13 % abstinent from drugs and alcohol in past month by urine (at 3 months post partum

Study or Subgroup	CBT Events	CBT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 CBT vs Brief Advice						
Yonkers 2012	38	64	33	64	100.0%	1.15 [0.84, 1.57]
Subtotal (95% CI)		**64**		**64**	**100.0%**	**1.15 [0.84, 1.57]**
Total events	38		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.38)						
Total (95% CI)		**64**		**64**	**100.0%**	**1.15 [0.84, 1.57]**
Total events	38		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.38)						
Test for subgroup differences: Not applicable						



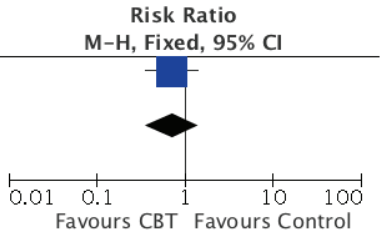
1.14 Preterm birth < 37 weeks

Study or Subgroup	CBT Events	CBT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 CBT vs BA						
Yonkers 2012	8	79	17	84	100.0%	0.50 [0.23, 1.09]
Subtotal (95% CI)		**79**		**84**	**100.0%**	**0.50 [0.23, 1.09]**
Total events	8		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
Total (95% CI)		**79**		**84**	**100.0%**	**0.50 [0.23, 1.09]**
Total events	8		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
Test for subgroup differences: Not applicable						



1.15 Low birth weight < 2500g

Study or Subgroup	CBT Events	CBT Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yonkers 2012	11	76	17	84	100.0%	0.72 [0.36, 1.43]
Total (95% CI)		**76**		**84**	**100.0%**	**0.72 [0.36, 1.43]**
Total events	11		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						



COGNITIVE BEHAVIOURAL THERAPY COMPARED TO CONTROL FOR PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE

Patient or population: Pregnant or postpartum women with problematic substance use

Settings: General treatment settings (antenatal) and specialist substance use programmes: Outpatient

Intervention: Cognitive behavioural therapy

Comparison: Control (usual care or brief advice)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Cognitive Behavioural Therapy				
Maternal treatment retention Participants retained after 6 weeks of treatment or participants attending at least one session Follow-up: 6–24 weeks	**919 per 1000**	**846 per 1000** (781 to 928)	**RR 0.92** (0.85 to 1.01)	275 (2 studies)	⊕⊕◯◯ LOW[1,2]	
Maternal substance use % days used drugs or alcohol in past month measured at delivery Follow-up: mean 12 weeks[3]		The proportion of days with drug or alcohol use in the intervention group was **1% higher** (5.05 lower to 7.05 higher)		163 (1 study)	⊕⊕◯◯ LOW[4]	Mixed effects negative binomial regression test for group by time interaction found no significant differences between groups at delivery and 3 mnths pp
Low birthweight < 2500g Medical records	**202 per 1000**	**146 per 1000** (73 to 289)	**RR 0.72** (0.36 to 1.43)	160 (1 study)	⊕⊕◯◯ LOW[4,5]	3 women had an unknown birthweight and were not included in the analysis
Preterm birth < 37 weeks From medical records	**202 per 1000**	**101 per 1000** (47 to 221)	**RR 0.5** (0.23 to 1.09)	163 (1 study)	⊕⊕◯◯ LOW[4,5]	
Infant birth defects	See comment	See comment	Not estimable	—	See comment	Not measured
Infant custody	See comment	See comment	Not estimable	—	See comment	Not measured
Infant head circumference	See comment	See comment	Not estimable	—	See comment	Not measured

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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 Risk of bias: Rated as Serious: Lack of reporting of sequence generation and allocation concealment in O'Neill 1996 and the loss-to-follow up > 10% resulted in down-grading for risk of bias. A likely lack of blinding for providers and participants in both trials may have introduced performance bias.

2 Indirectness: Rated as Serious. The measurement for treatment retention used in the analysis is a proxy measure for both trials. In O'Neill 1996 completion and availability for 6 week follow-up is used but not all sessions would have been attended as appointments were missed at an average of mean 2.9 (SD 6.45) with a range of 0–11. In Yonkers 2012 the proxy measure is attending at least one of 6 session during the entire study period which continued to 3 months postpartum.

3 Inclusion criteria was women of < 28 weeks pregnant. The mean duration of follow-up was calculated as from 28 weeks to delivery although women may have been in treatment for longer if enrolled before 28 weeks.

4 Risk of Bias: Rated as Serious. This well-conducted trial Yonkers 2012 was down-graded on the basis of a likely lack of blinding which may have introduced performance bias.

5 Imprecision: The event rate is very low < 300.

Author(s): Nandi Siegfried, Nicolas Clark

Date: 2013-08-01

Question: SHOULD COGNITIVE BEHAVIOURAL THERAPY VS CONTROL (USUAL CARE OR BRIEF ADVICE) BE USED IN PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE?

Settings: General treatment settings (antenatal) and specialist substance use programmes: Outpatient

Bibliography: Psychosocial interventions for pregnant or postpartum women with problematic substance use.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behavioural therapy	Control	Relative (95% CI)	Absolute	Quality	Importance
Maternal treatment retention (follow-up 6–24 weeks; assessed with: Participants retained after 6 weeks of treatment or participants attending at least one session)												
2	randomized trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	118/139 (84.9%)	125/136 (91.9%)	RR 0.92 (0.85 to 1.01)	74 fewer per 1000 (from 138 fewer to 9 more)	⊕⊕◯◯ LOW	CRITICAL
Maternal substance use (follow-up mean 12 weeks[3]; measured with: % days used drugs or alcohol in past month measured at delivery; better indicated by lower values)												
1	randomized trials	serious[4]	no serious inconsistency	no serious indirectness	serious	none	80	83	—	MD 1 higher (5.05 lower to 7.05 higher)	⊕⊕◯◯ LOW	CRITICAL
Low birthweight < 2500g (assessed with: medical records)												
1	randomized trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	11/76 (14.5%)	17/84 (20.2%)	RR 0.72 (0.36 to 1.43)	57 fewer per 1000 (from 130 fewer to 87 more)	⊕⊕◯◯ LOW	CRITICAL
Preterm birth < 37 weeks (assessed with: from medical records)												
1	randomized trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	8/79 (10.1%)	17/84 (20.2%)	RR 0.5 (0.23 to 1.09)	101 fewer per 1000 (from 156 fewer to 18 more)	⊕⊕◯◯ LOW	IMPORTANT
Infant birth defects – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cognitive behavioural therapy	Control	Relative (95% CI)	Absolute		
Infant custody – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant head circumference – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

[1] Risk of bias: Rated as Serious: Lack of reporting of sequence generation and allocation concealment in O'Neill 1996 and the loss-to-follow up > 10% resulted in down-grading for risk of bias. A likely lack of blinding for providers and participants in both trials may have introduced performance bias.

[2] Indirectness: Rated as Serious. The measurement for treatment retention used in the analysis is a proxy measure for both trials. In O'Neill 1996 completion and availability for 6 week follow-up is used but not all sessions would have been attended as appointments were missed at an average of mean 2.9 (SD 6.45) with a range of 0–11. In Yonkers 2012 the proxy measure is attending at least one of 6 session during the entire study period which continued to 3 months postpartum.

[3] Inclusion criteria was women of < 28 weeks pregnant. The mean duration of follow-up was calculated as from 28 weeks to delivery although women may have been in treatment for longer if enrolled before 28 weeks.

[4] Risk of Bias: Rated as Serious. This well-conducted trial Yonkers 2012 was down-graded on the basis of a likely lack of blinding which may have introduced performance bias.

[5] Imprecision: The event rate is very low < 300.

TABLE OF CHARACTERISTICS OF INCLUDED RCTs: 5 IN TOTAL

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Type of CM	Contigency	Randomized groups	Primary outcomes
INTERVENTION DURING PREGNANCY ONLY									
General treatment setting									
No trials were identified in general ante-natal or substance use programmes									
Specialized treatment setting									
Tuten 2012	USA	143 R 133 A	< 28 weeks	Current opioid dependence stabilized on methadone	Integrated pregnancy and substance use programme; Inpatient (1 wk); Outpatient (12 wks)	Vouchers exchangeable for on-site store items or gift certificate in local community	Opioid and cocaine-negative urine measured 3 days/wk	**Escalating CM:** Value of first $7.50 voucher increased by $1/day on specimen collection days until delivery or reaching capped amount of $42.50 **Fixed CM:** £25 voucher received for each drug-negative specimen **Control:** Yoked to escalating or fixed participant and received same voucher amount regardless of specimen	1. Drug abstinence (urine) 2. Opioid use (urine) 3. Cocaine use (urine) 4. Total amount of vouchers earned 5. Number of days in treatment
Jones 2001	USA	85 R	Not specified	Meeting methadone-maintenance eligibility requirements	Integrated pregnancy and substance use programme; Inpatient (7 days); Outpatient (7 days)	Vouchers exchangeable for merchandise and services purchased by research staff	Target behaviours and cocaine-negative urine, collected daily for 2 weeks, 3 times a wk per 3–4 wk	**Incentive:** In wk 1, US$5 voucher received for attendance of 4 hrs counselling during wk 1 with US$5 escalating vouchers per day if contingency met to a value of US$525 if all contingency met **Non-incentive:** Usual care within the comprehensive treatment programme	Not defined. 1. % participants leaving residential treatment 2. Mean full day attendance (residential, outpatient and combined) 3. Perfect treatment attendance (13 of 14 days) 4. Urine results
Carroll 1995	USA	20 R 14 A	< 28 weeks	Enrolled in methadone programme	Specialist methadone maintenance programme of Division of Substance Abuse; Outpatient (range from enrolment to delivery)	US$15 weekly	Three consecutive negative urine screens	**Enhanced treatment programme:** Standard treatment as below and weekly prenatal care and relapse prevention and contingency awards, child care during treatment **Standard treatment:** Daily methadone, weekly group counselling and 3 times weekly urine specimens	Primary not defined: MATERNAL 1. Urine results 2. % attendance at group 3. Groups attended 4. Weeks NEONATAL 1. Birthweight 2. Weeks gestation 3. Days in hospital

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Type of CM	Contigency	Randomized groups	Primary outcomes
INTERVENTION DURNG PREGNANCY AND AFTER DELIVERY									
General treatment setting									
No trials were identified in general ante-natal or substance use programmes									
Specialized treatment setting									
Jones 2011	USA	128 R 89 A	< 35 weeks	Self-reported heroin or cocaine use in past 30 days	Integrated pregnancy and substance use programme; Inpatient on assisted living unit (1 wk); Recovery housing (until one month post-delivery)	Housing, recreational activities and skills training to secure employment	Opioid and cocaine-negative urine specimens measured twice/wk	**Reinforcement-based Treatment:** Paid rent for recovery housing as available for up to 6 months on drug-negative urine; if positive, removed from housing and placed in alternative shelter until urine negative **Usual Care:** Participants informed of housing options, access to a telephone to call, but no payment was made to cover rent	MATERNAL 1. Days in treatment 1. Number of days in recovery housing 2. Heroin use (urine) 3. Cocaine use (urine) 4. Employment status 5. Illegal activity NEONATAL 1. Estimated Gestational Age at delivery 2. Prematurity < 37 wks 3. Birthweight 4. Number of days hospital after birth
Schottefeld 2011	USA	145 R 77 A	Pregnant (n = 64) and women with custody of young child (n = 81)	DSM IV criteria for cocaine dependence (excluded if using opioids)	Research Clinic setting (appears to be substance use focused); Outpatient (24 wks)	Vouchers redeemable for goods or services selected by the patient	Cocaine-negative urine tests measured twice/wk	**Community Reinforcement Approach (CRA) & CM:** Twice weekly CRA counselling session and vouchers of US$2.50 per negative test with bonus US$10.00 awarded after 3 consecutive negative specimens for 12 weeks; for 12 – 24 weeks variable voucher schedule **Community Reinforcement & Voucher control:** Twice weekly CRA counselling session and vouchers regardless of test yoked to CM participants **Twelve-step and CM:** Twice weekly individual sessions for 12 wks, then weekly for 12 – 24 wks; CM as for CRA & CM group **Twelve step and Voucher control:** Sessions as for Twelve-step and CM control as above	1. Maximum consecutive wks of cocaine abstinence 2. % cocaine-negative tests 3. % days using cocaine

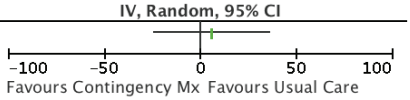
RCT – Randomized controlled trial
R – Number randomized
A – Number analysed

FOREST PLOTS OF CONTINGENCY MANAGEMENT COMPARISON

1 Contingency Managment versus Usual Care

1.1 Maternal % Urine positive for opiods

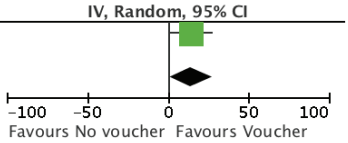
Study or Subgroup	Contingency Mx Mean	SD	Total	Usual Care Mean	SD	Total	Mean Difference IV, Random, 95% CI
Carroll 1995	30.9	33.9	7	25.3	23.4	7	5.60 [-24.91, 36.11]



1.2 Maternal % Urine negative for cocaine

Study or Subgroup	Contingency Mx Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Schottenfeld 2011	38.6	28.5	39	24.7	28.7	32	100.0%	13.90 [0.53, 27.27]
Total (95% CI)			39			32	100.0%	13.90 [0.53, 27.27]

Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)



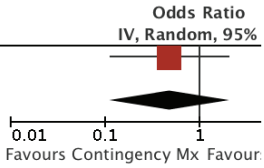
1.3 Maternal % Urine positive for cocaine

Study or Subgroup	Contingency Mx Mean	SD	Total	Usual Care Mean	SD	Total	Mean Difference IV, Random, 95% CI
Carroll 1995	39.4	33.9	7	39.8	35.6	7	-0.40 [-36.82, 36.02]

1.4 Maternal urine positive for any illegal drug: Logistic regression

Study or Subgroup	log[Odds Ratio]	SE	Contingency Mx Total	Usual Care Total	Weight	Odds Ratio IV, Random, 95% CI
Jones 2011	-0.73397	0.749909	47	42	100.0%	0.48 [0.11, 2.09]
Total (95% CI)			47	42	100.0%	0.48 [0.11, 2.09]

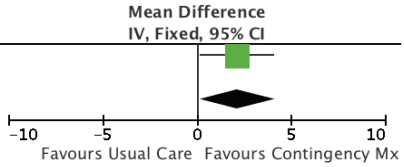
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



1.5 Maternal weeks of continuous cocaine abstinence

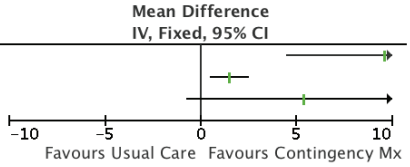
Study or Subgroup	Contingency Mx Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schottenfeld 2011	4.6	5.4	39	2.5	3	32	100.0%	2.10 [0.11, 4.09]
Total (95% CI)			39			32	100.0%	2.10 [0.11, 4.09]

Heterogeneity: Not applicable
Test for overall effect: Z = 2.07 (P = 0.04)



1.6 Maternal Retention in treatment

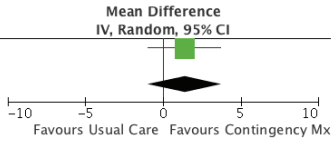
Study or Subgroup	Contingency Mx Mean	SD	Total	Usual Care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carroll 1995	14.7	5.9	7	5.1	3.6	7	9.60 [4.48, 14.72]
Jones 2001	12.1	2.3	44	10.6	2.4	36	1.50 [0.46, 2.54]
Schottenfeld 2011	25.3	13.7	39	19.9	12.8	32	5.40 [-0.78, 11.58]



1.8 Infant Gestational age at delivery - continuous data

Study or Subgroup	Contingency Mx Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Carroll 1995	39.1	1.7	7	37.7	2.7	7	100.0%	1.40 [-0.96, 3.76]
Total (95% CI)			7			7	100.0%	1.40 [-0.96, 3.76]

Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)



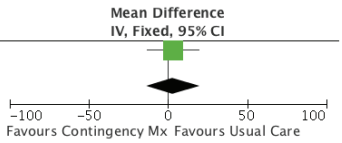
1.9 Infant Gestational age at delivery - Poisson regression

Study ID	Coningency Management Mean	Contingency Mx SE	Usual Care Mean	Usual Care SE	P value
Jones 2011	37.2	1.1	38.5	1.6	0.52

1.10 Infant days in hospital after birth - continuous data

Study or Subgroup	Contingency Mx Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Carroll 1995	41.3	15	7	38.1	16.7	7	100.0%	3.20 [-13.43, 19.83]
Total (95% CI)			7			7	100.0%	3.20 [-13.43, 19.83]

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)



CONTINGENCY MANAGEMENT COMPARED TO USUAL CARE FOR PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE

Patient or population: Pregnant or Postpartum women with problematic substance use
Settings: Residential, inpatient and outpatient
Intervention: Contingency Management
Comparison: Usual Care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual Care	**Contingency Management**				
Maternal % urine positive for opioids[1] Follow-up: 13–31 weeks	See comment	See comment	Not estimable[1]	14 (1 study)	⊕◯◯◯ VERY LOW[2,3]	The GRADE assessment is specific to this single trial. Results of other trials from which data could not be extracted are included in the footnotes.
Maternal % urine negative for cocaine[4] Follow-up: 24 weeks		The mean maternal % urine negative for cocaine in the intervention groups was **13.9 higher** (0.53 to 27.27 higher)		71 (1 study)	⊕◯◯◯ VERY LOW[5,6]	This trial also reported weeks of continuous cocaine abstinence & reported a statistically significant favourable effect of CM (F (1.141) = 7.76; p < 0.01)
Maternal % urine positive for cocaine[7] Follow-up: 13–31 weeks	See comment	See comment	Not estimable[7]	14 (1 study)	⊕◯◯◯ VERY LOW[2,3]	The GRADE assessment is specific to this single trial. Results of other trials from which data could not be extracted are included in the footnotes.
Maternal retention in treatment[8] Various proxy measures Follow-up: 2–24 weeks	See comment	See comment	Not estimable[8]	165 (3 studies)	⊕◯◯◯ VERY LOW[2,9,10,11]	Treatment duration was varying across trials and different proxy measures were used for retention e.g. no of prenatal visits. The results were thus not pooled.
Birthweight Grams	The mean birthweight ranged across control groups from **2942-2996 gm**	The mean birthweight in the intervention groups was **17.29 lower** (573.03 lower to 538.45 higher)		103 (2 studies)	⊕◯◯◯ VERY LOW[12,13,14]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Usual Care	Contingency Management				
Infant gestational age at delivery Weeks		The mean infant gestational age at delivery in the intervention groups was **1.4 higher** (0.96 lower to 3.76 higher)	14 (1 study)	14 (1 study)	⊕○○○ VERY LOW[2,3]	GA at delivery also reported in Jones 2011 (N = 89) by Poisson regression: GA on delivery: CM (Mean 37.2; SE 1.1); Usual Care (Mean: 38.5; SE 1.6); P = 0.52
Infant custody	See comment	See comment	Not estimable	—	See comment	None of the five included trials measured or reported this as an outcome.
Infant birth defects	See comment	See comment	Not estimable	—	See comment	None of the five included trials measured or reported this as an outcome.
Infant head circumference	See comment	See comment	Not estimable	—	See comment	None of the five included trials measured or reported this as an outcome.

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] Jones 2001 reported a significant effect of CM on the rate of opioid positive urine samples in day 8 - 14 (outpatient) (F (1.78) = 5.76; p =< 0.05) and this effect disappeared after vouchers were no longer provided after week 2. Jones 2011 reported that there was no statistically significant difference between heroin positive urines in the last 30 days between the groups. Tuten 2012 reported no statistically significant difference in the first opioid-positive assessment time point between the fixed combined with escalating voucher group compared with the control group (F(1,78.0) = 1.05; p = 0.31) and between the fixed and escalating groups (F(1,92.4) = 1.23; p = 0.27).

[2] Risk of Bias: Rated as Very serious. No reporting of randomization sequence, no blinding and high attrition.

[3] Imprecision: Rated as Very Serious. This is a very small trial (N = 20) with 14 analysed. The risk of imprecision is very high.

[4] Tuten 2012 reported no statistically significant differences in the the number of cocaine-negative urine tests between the combined fixed with escalating voucher group compared with the control group (F1,54.3) = 0.01; p = 0.91) and between the fixed and escalating voucher groups (F(1,88.7) = 0.09; p = 0.76).

[5] Risk of bias: Rated as Very Serious. The high rate of attrition and lack of blinding resulted in down-grading this trial.

[6] Imprecision: Rated as VERY SERIOUS. The 95% confidence interval is very wide.

[7] Jones 2001 reported a statistically significant favourable effect of CM on the rate of cocaine-positive urine from day 8 to 14 (F(1,78) - 7.05); p =< 0.05). This effect disappeared after the vouchers were stopped at the end of week 2. Jones 2011 reported no statistically significant effect between groups for cocaine-positive urine.

[8] The results from the three trials favoured contingency management over usual care for maternal retention in treatment. Carroll 1995 (N = 14 analysed) found no of prenatal visits was statistically significantly higher (CM: Mean = 14.7; SD: 5.9)(Usual Care: Mean = 5.1; SD: 3.6). In Jones 2001 (N = 80 analysed) participants in CM attended statistically significant more treatment days (CM: Mean = 12.1; SD: 2.3)(Usual Care: Mean = 10.6; SD: 2.4). In Schottenfeld 2011 (N = 71 analysed) participants in CM attended statistically significantly more therapy sessions (CM: Mean: 25.3; SD: 13.7)(Usual Care: Mean = 19.9; SD: 12.8).

[9] Risk of bias: Rated as Very Serious. Jones 2001 and Schottenfeld 2001 randomized adequately. However the lack of provider blinding across all three trials and the high attrition in two of the three trials, resulted in overall downgrading.

[10] Indirectness: Rated as Serious. Treatment duration was varying across trials and different proxy measures were used for retention e.g. no of prenatal visits versus no of groups attended

[11] Imprecision: Rated as Serious. This was difficult to rate as the measures were varying, but within each trial the 95% confidence intervals were large and so overall it was down-graded for imprecision.

[12] Risk of Bias: Rated as Very Serious. The high rate of attrition in Jones 2011 and Carroll 1995 resulted in the risk of bias rated as very serious. In addition, lack of blinding may result in a high risk of performance bias.

[13] Inconsistency: Rated as Serious. There was unexplained heterogeneity present.

[14] Imprecision: The confidence interval was wide and the overall sample size small.

Author(s): Nandi Siegfried, Nicolas Clark
Date: 2013-07-26
Question: SHOULD CONTINGENCY MANAGEMENT VS USUAL CARE BE USED IN PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE?
Settings: Residential, inpatient and outpatient
Bibliography: Psychosocial interventions for pregnant or postpartum women with problematic substance use.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Contingency Management	Usual Care	Relative (95% CI)	Absolute	Quality	Importance
Maternal % Urine positive for opioids[1] (follow-up 13–31 weeks; better indicated by lower values)												
1	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7	7	—[1]	not pooled[1]	⊕◯◯◯ VERY LOW	CRITICAL
Maternal % Urine negative for cocaine[4] (follow-up 24 weeks; better indicated by higher values)												
1	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	39	32	—	MD 13.9 higher (0.53 to 27.27 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Maternal % Urine positive for cocaine[7] (follow-up 13–31 weeks; better indicated by lower values)												
1	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7	7	—[7]	not pooled[7]	⊕◯◯◯ VERY LOW	CRITICAL
Maternal retention in treatment[8] (follow-up 2–24 weeks; measured with: Various proxy measures; better indicated by higher values)												
3	randomized trials	serious[2,9]	no serious inconsistency	serious[10]	serious[11]	none	90	75	—[8]	not pooled[8]	⊕◯◯◯ VERY LOW	CRITICAL
Birthweight (grams); better indicated by higher values)												
2	randomized trials	very serious[12]	serious[13]	no serious indirectness	serious[14]	none	54	49	—	MD 17.29 lower (573.03 lower to 538.45 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Infant gestational age at delivery (measured with: Weeks; better indicated by higher values)												
1	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7	7	—	MD 1.4 higher (0.96 lower to 3.76 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Custody of infant – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant birth defects – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant head circumference – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

[1] Jones 2001 reported a significant effect of CM on the rate of opioid positive urine samples in day 8 - 14 (outpatient) (F (1.78) = 5.76; p =< 0.05) and this effect disappeared after vouchers were no longer provided after week 2. Jones 2011 reported that there was no statistically significant difference between heroin positive urines in the last 30 days between the groups. Tuten 2012 reported no statistically significant difference in the first opioid-positive assessment time point between the fixed combined with escalating voucher group compared with the control group (F(1,78.0) = 1.05; p = 0.31) and between the fixed and escalating groups ((F(1,92.4) = 1.23; p = 0.27).

[2] Risk of Bias: Rated as Very serious. No reporting of randomization sequence, no blinding and high attrition.

[3] Imprecision: Rated as Very Serious. This is a very small trial (N = 20) with 14 analysed. The risk of imprecision is very high.

[4] Tuten 2012 reported no statistically significant differences in the the number of cocaine-negative urine tests between the combined fixed with escalating voucher group compared with the control group (F(1,54.3) = 0.01; p = 0.91) and between the fixed and escalating voucher groups ((F(1,88.7) = 0.09; p = 0.76).

[5] Risk of bias: Rated as Very Serious. The high rate of attrition and lack of blinding resulted in down-grading this trial.

[6] Imprecision: Rated as VERY SERIOUS. The 95% confidence interval is very wide.

[7] Jones 2001 reported a statistically significant favourable effect of CM on the rate of cocaine-positive urine from day 8 to 14 (F(1,78) - 7.05); p =< 0.05). This effect disappeared after the vouchers were stopped at the end of week 2. Jones 2011 reported no statistically significant effect between groups for cocaine-positive urine.

[8] The results from the three trials favoured contingency management over usual care for maternal retention in treatment. Carroll 1995 (N = 14 analysed) found no of prenatal visits was statistically significantly higher (CM: Mean = 14.7; SD: 5.9)(Usual Care: Mean = 5.1; SD: 3.6). In Jones 2001 (N = 80 analysed) participants in CM attended statistically significant more treatment days (CM: Mean = 12.1; SD: 2.3)(Usual Care: Mean = 10.6; SD: 2.4). In Schottenfeld 2011 (N = 71 analysed) participants in CM attended statistically significantly more therapy sessions (CM: Mean: 25.3; SD: 13.7)(Usual Care: Mean = 19.9; SD: 12.8).

[9] Risk of bias: Rated as Very Serious. Jones 2001 and Schottenfeld 2001 randomized adequately. However the lack of provider blinding across all three trials and the high attrition in two of the three trials, resulted in overall downgrading.

[10] Indirectness: Rated as Serious. Treatment duration was varying across trials and different proxy measures were used for retention e.g. no of prenatal visits versus no of groups attended

[11] Imprecision: Rated as Serious. This was difficult to rate as the measures were varying, but within each trial the 95% confidence intervals were large and so overall it was down-graded for imprecision.

[12] Risk of Bias: Rated as Very Serious. The high rate of attrition in Jones 2011 and Carroll 1995 resulted in the risk of bias rated as very serious. In addition, lack of blinding may result in a high risk of performance bias.

[13] Inconsistency: Rated as Serious. There was unexplained heterogeneity present

[14] Imprecision: The confidence interval was wide and the overall sample size small.

RISK OF BIAS IN EACH TRIAL INCLUDED IN THE CONTINGENCY MANAGEMENT COMPARISON

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Carroll 1995	?	?	−	?	−	?	+
Jones 2001	+	−	−	?	+	+	+
Jones 2011	+	+	−	?	−	?	+
Schottenfeld 2011	+	?	−	+	−	+	+
Tuten 2012	?	?	−	+	−	?	+

HOME VISITS during pregnancy and after birth for women with an alcohol or drug problem

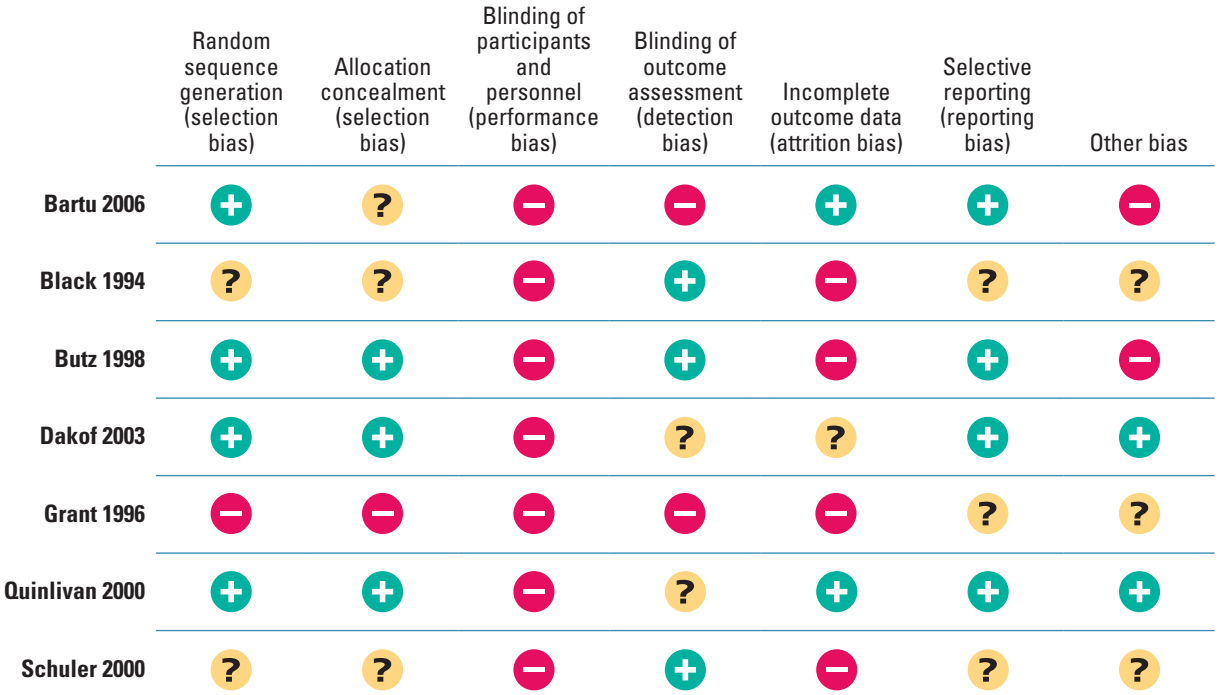
TABLE OF CHARACTERISTICS OF INCLUDED STUDIES: 6 RCTs & 1 QUASI-RCT

Trial ID	Country	N	Gestational age	Alcohol and drug use	Duration of visit	Frequency of visit	Home visitor	Visit content	Primary outcomes
INTERVENTION DURING PREGNANCY ONLY									
—	—	—	—	—	—	—	—	—	—
INTERVENTION AFTER DELIVERY ONLY									
RCT									
Bartu 2006	Australia	152	35–40 weeks at recruitment	Active use of illicit drugs	1–2 hours	1, 2, and 4 weeks pp; monthly for 6 months	Research midwife	Mother and infant well-being; parent craft; stress management; relaxation techniques; immunisation; Pap smear information; links to services	1. Duration of breast-feeding 2. Immunisation rates
Butz 1998	USA	204	During pregnancy	Self-reported use of opiates and/or cocaine in pregnancy OR positive urine in labour or infant		16 visits from birth to 18 months	Specialist midwives with experience in drug treatment services	Modelling of parent-child interaction; health monitoring of infant; parent education and skills training; used Hawaii Early Learning Profile and Carolina Preschool curriculum	1. Child Behaviour Checklist at 36 months
Dakof 2003	USA	103	PP	Positive cocaine urine of mother or infant	20 mins to 1 hour	1–4 per week for 8 weeks	Specialist midwives with experience in drug dependence treatment	Individual, family or case management sessions	1. Enrolment in treatment programme 2. 4 weeks and 90 day retention in treatment
Quinlivan 2000	Australia	136	At first antenatal appt	Alcohol and illicit drug use at beginning of pregnancy	1–4 hours	1 and 2 weeks pp and 1, 2, 4, and 6 mnths	Nurse midwife	Lactation and mothercraft education and advice; general and obstetric health surveillance; contraception and child health advice; information of D & A service; education on parenting skills; confirmed vaccination appts	1. Adverse neonatal outcomes 2. Knowledge about contraception 3. Vaccination 4. Breastfeeding
Schuler 2000	USA	227	PP	Positive urine at birth or history of recent drug use		Weekly from birth to 6 mnths, then biweekly to 18 months	Lay African American women	Goal of visits to increase maternal empowerment; enhance ability to manage self-identified problems using existing services; child component used Hawaii Early Learning Profile	1. Observed mother-infant interaction using Child Abuse Potential Inventory at 18 mnths 2. Bayley Scales of Infant Development at 18 mnths

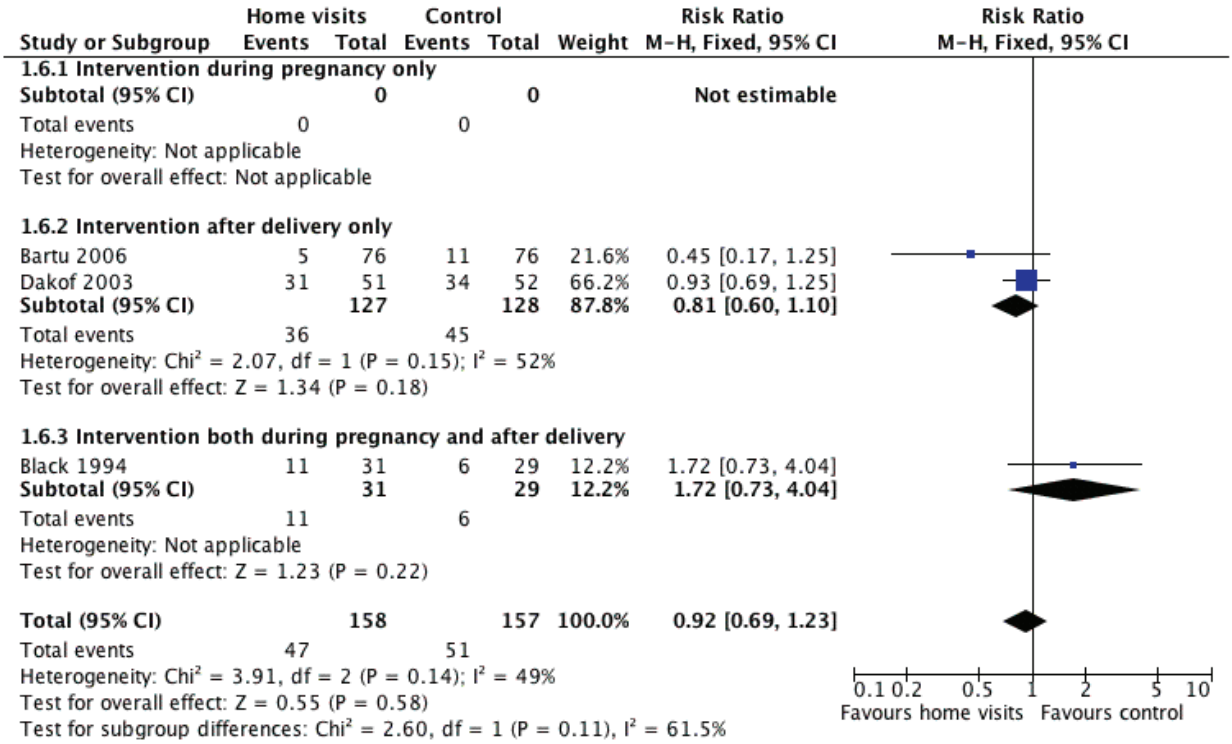
Trial ID	Country	N	Gestational age	Alcohol and drug use	Duration of visit	Frequency of visit	Home visitor	Visit content	Primary outcomes
Quasi-RCT									
Grant 1996	USA	66	PP	Self-report of heavy drug and/or alcohol use in pregnancy		Weekly for 6 weeks, then twice monthly for 3 years	para-professional advocates with similar life experiences	The Seattle Birth to 3 Years Program: link to care; parenting classes; therapeutic child care; substance abuse treatment programs	1. Bayley Scales of Infant Development at 3 years
INTERVENTION BOTH DURING PREGNANCY AND AFTER DELIVERY									
RCT									
Black 1994	USA	60	Prenatal	Self-reported cocaine or heroin use	1 hour	2 visits before birth; biweekly home visits until 18 mnths	Community health nurses	Formed alliance; addressed personal, family and environmental needs; facilitated child-parent interaction; information and advocacy for parents; used Hawaii Early Learning Profile and Carolina Preschool curriculum	1. Positive behaviours and attitudes in women 2. Child development

RCT – Randomized controlled trial
Quasi-RCT – A study which has a control group but where allocation is not performed randomly e.g. use of date of birth or allocation according to presentation schedule
PP – Postpartum

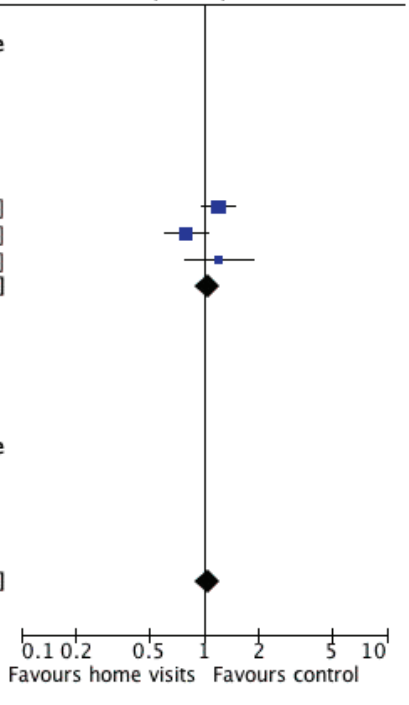
RISK OF BIAS IN EACH STUDY INCLUDED IN THE HOME VISITS COMPARISON



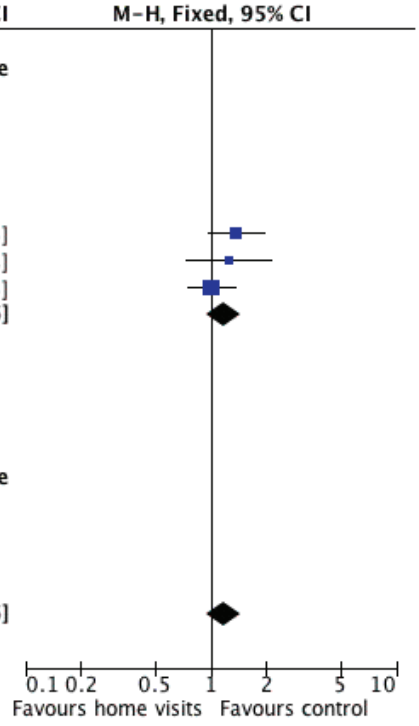
FOREST PLOTS OF HOME VISITS (FROM COCHRANE REVIEW SO NUMBERING NOT SEQUENTIAL)



Study or Subgroup	Home visits Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Intervention during pregnancy only						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.2 Intervention after delivery only						
Bartu 2006	55	71	42	65	40.2%	1.20 [0.96, 1.49]
Butz 1998	33	58	42	59	38.2%	0.80 [0.61, 1.05]
Schuler 2000	29	67	23	64	21.6%	1.20 [0.79, 1.85]
Subtotal (95% CI)		**196**		**188**	**100.0%**	**1.05 [0.89, 1.24]**
Total events	117		107			
Heterogeneity: $Chi^2 = 5.54$, df = 2 (P = 0.06); $I^2 = 64\%$						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.1.3 Intervention both during pregnancy and after delivery						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**196**		**188**	**100.0%**	**1.05 [0.89, 1.24]**
Total events	117		107			
Heterogeneity: $Chi^2 = 5.54$, df = 2 (P = 0.06); $I^2 = 64\%$						
Test for overall effect: Z = 0.55 (P = 0.58)						
Test for subgroup differences: Not applicable						



Study or Subgroup	Home visits Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Intervention during pregnancy only						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.2 Intervention after delivery only						
Bartu 2006	41	70	26	61	33.7%	1.37 [0.97, 1.95]
Butz 1998	21	58	17	59	20.4%	1.26 [0.74, 2.13]
Schuler 2000	39	67	37	64	45.9%	1.01 [0.75, 1.35]
Subtotal (95% CI)		**195**		**184**	**100.0%**	**1.18 [0.96, 1.46]**
Total events	101		80			
Heterogeneity: $Chi^2 = 1.92$, df = 2 (P = 0.38); $I^2 = 0\%$						
Test for overall effect: Z = 1.56 (P = 0.12)						
1.2.3 Intervention both during pregnancy and after delivery						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**195**		**184**	**100.0%**	**1.18 [0.96, 1.46]**
Total events	101		80			
Heterogeneity: $Chi^2 = 1.92$, df = 2 (P = 0.38); $I^2 = 0\%$						
Test for overall effect: Z = 1.56 (P = 0.12)						
Test for subgroup differences: Not applicable						



HOME VISITS DURING PREGNANCY AND AFTER BIRTH COMPARED TO NO HOME VISITS FOR WOMEN WITH AN ALCOHOL OR DRUG PROBLEM

Patient or population: Women with an alcohol or other substance use disorder
Settings: Community
Intervention: Home visits during pregnancy and after birth
Comparison: No home visits

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No home visits	Home visits during pregnancy and after birth				
Maternal retention in treatment Failure of retention in program at latest time measured	**325 per 1000**	**299 per 1000** (224 to 400)	**RR 0.92** (0.69 to 1.23)	315 (3 studies)	⊕◯◯◯ VERY LOW[1,2,3]	The GRADE assessment is specific to this single trial. Results of other trials from which data could not be extracted are included in the footnotes.
Maternal continued illicit drug use	**569 per 1000**	**598 per 1000** (507 to 706)	**RR 1.05** (0.89 to 1.24)	384 (3 studies)	⊕⊕◯◯ LOW[4,5,6]	This trial also reported weeks of continuous cocaine abstinence & reported a statistically significant favourable effect of CM (F (1.141) = 7.76; p < 0.01)
Maternal continued alcohol use	**435 per 1000**	**513 per 1000** (417 to 635)	**RR 1.18** (0.96 to 1.46)	379 (3 studies)	⊕⊕◯◯ LOW[4,6,7]	The GRADE assessment is specific to this single trial. Results of other trials from which data could not be extracted are included in the footnotes.
Infant birthweight	See comment	See comment	Not estimable		See comment	Not reported
Infant gestational age at delivery	See comment	See comment	Not estimable		See comment	Not reported
Infant custody	See comment	See comment	Not estimable		See comment	Not reported
Infant birth defects	See comment	See comment	Not estimable		See comment	Not reported
Infant head circumference	See comment	See comment	Not estimable		See comment	Not reported

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] The meta-analysis included three RCTs (Black 1994, Bartu 2006, and Dakof 2003). Two were judged to be at low risk of selection bias (although allocation concealment was unclear in Bartu 2006) and Black 1994 was judged to be at unclear risk of selection bias. All trials were judged to be at high risk of performance bias as blinding was not possible for the intervention. All trials were judged for this outcome (failure of retention in program) to be at high or unclear risk of detection bias. Attrition bias was a high risk for Black 1994 at 28% loss-to-follow-up.

[2] Heterogeneity is present (I-squared = 49%). There are multiple sources of heterogeneity including differences in the type of home visitor, frequency and duration of the home visit and differences in content of visit. These subgroups are explored in additional analyses and may explain some of the heterogeneity; however, given the uncertainty and extent of the heterogeneity, the analysis was downgraded for inconsistency.

[3] The sample size is small, and the event rate is less than 300.

[4] This meta-analysis includes three RCTs (Bartu 2006, Butz 1998 and Schuler 2000). Two trials were judged to be at low risk of selection bias and one was of unclear risk. All three trials were judged to be at high risk of performance bias as the visits could not be blinded. Two of three trials ensured outcome assessment was blinded reducing the risk of detection bias. Two trials had very high loss-to-follow-up (> 40%) at 18 months and are therefore at high risk of attrition bias.

[5] Heterogeneity is present (I-squared = 64%). As there is moderate heterogeneity, it may be more appropriate to use a random effects model. This provides a RR = 1.04 (95% CI: 0.78, 1.38). This does not differ qualitatively from the fixed effects model. However, there are multiple sources of heterogeneity including differences in the type of home visitor, frequency and duration of the home visit and differences in content of visit. These sub-groups are explored in additional analyses and may explain some of the heterogeneity; however, given the uncertainty and extent of the heterogeneity, the analysis was downgraded for inconsistency.

[6] The event rate is less than 300. However, given the relatively large event rate and narrow confidence interval, the analysis was not downgraded for imprecision.

[7] There was no statistical heterogeneity in the results. However, there are multiple potential causes of clinical heterogeneity including differences in the type of home visitor, frequency and duration of the home visit and differences in content of visit. These subgroups are explored in additional analyses but given the uncertainty regarding heterogeneity, the analysis was downgraded for inconsistency.

Author(s): Catherine Turnbull, David A Osborn
Date: 2013-01-23
Question: SHOULD HOME VISITS DURING PREGNANCY AND AFTER BIRTH VS NO HOME VISITS BE USED IN WOMEN WITH AN ALCOHOL OR DRUG PROBLEM?
Settings: Community
Bibliography: Turnbull C, Osborn DA. Home visits during pregnancy and after birth for women with an alcohol or drug problem. Cochrane Database of Systematic Reviews.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home visits during pregnancy and after birth	No home visits	Relative (95% CI)	Absolute	Quality	Importance
Maternal retention in treatment (assessed with: Failure of retention in program at latest time measured)												
3	randomized trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	47/158 (29.7%)	51/157 (32.5%)	RR 0.92 (0.69 to 1.23)	26 fewer per 1000 (from 101 fewer to 75 more)	⊕◯◯◯ VERY LOW	CRITICAL
Maternal continued illicit drug use												
3	randomized trials	serious[4]	serious[5]	no serious indirectness	no serious imprecision[6]	none	117/196 (59.7%)	107/188 (56.9%)	RR 1.05 (0.89 to 1.24)	28 more per 1000 (from 63 fewer to 137 more)	⊕⊕◯◯ LOW	CRITICAL
Maternal continued alcohol use												
3	randomized trials	serious[4]	serious[7]	no serious indirectness	no serious imprecision[6]	none	101/195 (51.8%)	80/184 (43.5%)	RR 1.18 (0.96 to 1.46)	78 more per 1000 (from 17 fewer to 200 more)	⊕⊕◯◯ LOW	CRITICAL
Infant birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Infant gestational age at delivery – not reported												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant custody – not reported												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home visits during pregnancy and after birth	No home visits	Relative (95% CI)	Absolute	Quality	Importance
Infant birth defects – not reported												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant head circumference – not reported												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

[1] The meta-analysis included three RCTs (Black 1994, Bartu 2006, and Dakof 2003). Two were judged to be at low risk of selection bias (although allocation concealment was unclear in Bartu 2006) and Black 1994 was judged to be at unclear risk of selection bias. All trials were judged to be at high risk of performance bias as blinding was not possible for the intervention. All trials were judged for this outcome (failure of retention in program) to be at high or unclear risk of detection bias. Attrition bias was a high risk for Black 1994 at 28% loss-to-follow-up.

[2] Heterogeneity is present (I-squared = 49%). There are multiple sources of heterogeneity including differences in the type of home visitor, frequency and duration of the home visit and differences in content of visit. These sub-groups are explored in additional analyses and may explain some of the heterogeneity; however, given the uncertainty and extent of the heterogeneity, the analysis was downgraded for inconsistency.

[3] The sample size is small, and the event rate is less than 300.

[4] This meta-analysis includes three RCTs (Bartu 2006, Butz 1998 and Schuler 2000). Two trials were judged to be at low risk of selection bias and one was of unclear risk. All three trials were judged to be at high risk of performance bias as the visits could not be blinded. Two of three trials ensured outcome assessment was blinded reducing the risk of detection bias. Two trials had very high loss-to-follow-up (> 40%) at 18 months and are therefore at high risk of attrition bias.

[5] Heterogeneity is present (I-squared = 64%). As there is moderate heterogeneity, it may be more appropriate to use a random effects model. This provides a RR = 1.04 (95% CI: 0.78, 1.38). This does not differ qualitatively from the fixed effects model. However, there are multiple sources of heterogeneity including differences in the type of home visitor, frequency and duration of the home visit and differences in content of visit. These sub-groups are explored in additional analyses and may explain some of the heterogeneity; however, given the uncertainty and extent of the heterogeneity, the analysis was downgraded for inconsistency.

[6] The event rate is less than 300. However, given the relatively large event rate and narrow confidence interval, the analysis was not downgraded for imprecision.

[7] There was no statistical heterogeneity in the results. However, there are multiple potential causes of clinical heterogeneity including differences in the type of home visitor, frequency and duration of the home visit and differences in content of visit. These sub-groups are explored in additional analyses but given the uncertainty regarding heterogeneity, the analysis was downgraded for inconsistency.

MOTIVATIONAL INTERVIEWING during pregnancy and after birth for women with an alcohol or drug problem

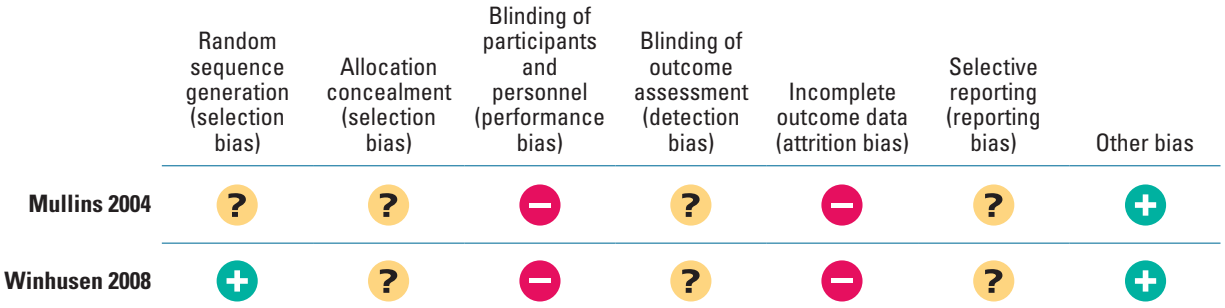
TABLE OF CHARACTERISTICS OF INCLUDED RCTs: 2 IN TOTAL

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
INTERVENTION DURING PREGNANCY ONLY								
General treatment settings								
No trials were identified from these settings.								
Specialist treatment settings								
Winhusen 2008	USA	200 R 200 A in ITT 171 A in evaluable sample	< 32 wks	Identified as needing substance abuse treatment via the Clinical Trials Network (CTN) site according to usual screening procedures used on site.	Outpatient. Multisite trial in four CTN sites: All provide comprehensive treatment programmes specifically for pregnant women abusing substances	1 month active treatment; 3 months follow-up	**Motivational enhancement therapy:** Three individual sessions based on brief motivational techniques of Miller & Rollnick. Three individual sessions: first scheduled for at trial entry (1.5–2 hrs) to establish rapport; second and third scheduled during the following month (each of 1 hr) to review and progress and develop change plan. Clinicians received 20 hours training with an MI expert. **Treatment-as-usual:** In addition to usual treatment offered in the programme, participants were offered at least 3 individual sessions with a clinician including the intake session. This was not based on MI techniques.	MATERNAL Primary: 1. Treatment utilization (ratio of treatment hrs attended to no. of hrs scheduled) 2. No. of wks in which one treatment session was attended 3. No. of wks until treatment drop-out Secondary: 1. Substance use a. Self-report b. Urine toxicology 2. University of Rhode Island Change Assessment (URICA) readiness score INFANT Nil
INTERVENTION AFTER PREGNANCY ONLY								
General treatment settings								
No trials were identified from these settings.								

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
Specialist treatment settings								
Mullins 2004	USA	71 R	Postpartum	Self-reported admission of drug use during pregnancy or positive toxicology screen at birth	Outpatient. Comprehensive, 12-month federal demonstration project providing free services for women who used illicit substances during pregnancy.	2 months	**Motivational Interviewing:** Three individual 1-hr sessions scheduled for at trial entry, 1 wk after entry, and 2 months after entry. No manual. Therapists instructed to utilise strategies consistent with participant's stage of change. **Educational Control:** At intake participants watched 30 min educational video on substance use, at 1 wk post-intake participants watched a similar video and at 2 months post-intake, participants received a supplementary 60-min home visit comprising case management.	MATERNAL 1. Attendance at study sessions 2. Frequency of attendance at weekly psychotherapy and substance abuse groups 3. Urine screen negative for all drugs INFANT Not applicable

RCT – Randomized controlled trial
R – Number randomized
A – Number analysed

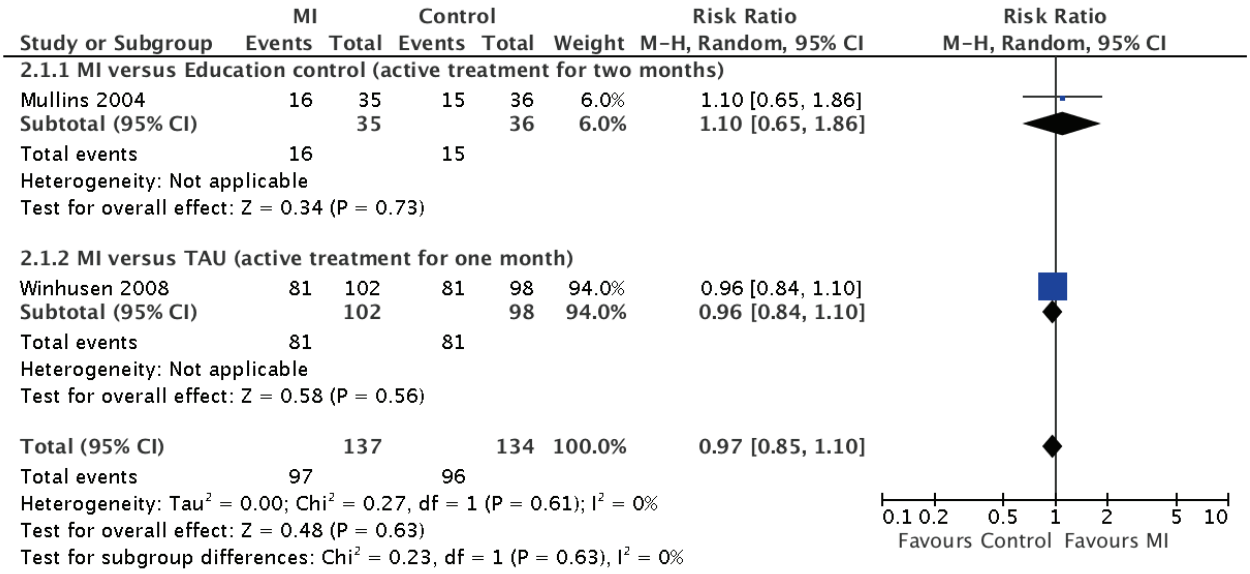
RISK OF BIAS IN EACH TRIAL INCLUDED IN THE MOTIVATIONAL INTERVIEWING COMPARISON



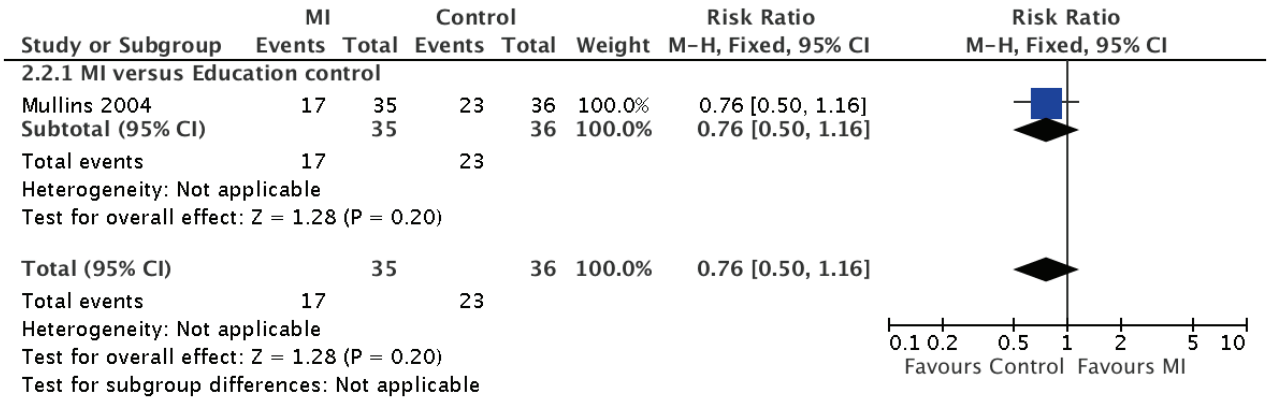
FOREST PLOTS OF MOTIVATIONAL INTERVIEWING COMPARISON

2 Motivational Interviewing versus Any Control

2.1 Maternal retention in treatment

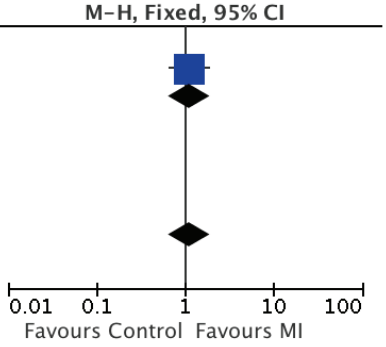


2.2 Frequency of attendance at study sessions in 1 week



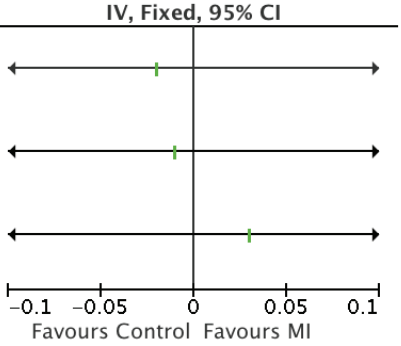
2.3 Frequency of attendance at study sessions in 8 weeks

Study or Subgroup	MI Events	MI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 MI versus Education control						
Mullins 2004	16	35	15	36	100.0%	1.10 [0.65, 1.86]
Subtotal (95% CI)		35		36	100.0%	1.10 [0.65, 1.86]
Total events	16		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
Total (95% CI)		35		36	100.0%	1.10 [0.65, 1.86]
Total events	16		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Not applicable						



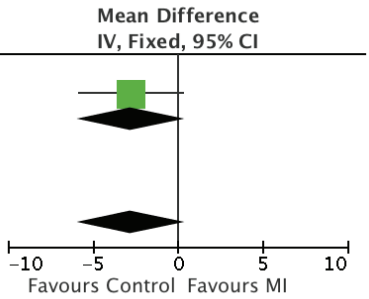
2.4 Group attendance ratio by study session attendance (MI versus Education Control only)

Study or Subgroup	MI Mean	MI SD	MI Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
2.4.1 Attended 1 study session							
Mullins 2004	0.27	0.33	35	0.29	0.24	36	-0.02 [-0.15, 0.11]
2.4.2 Attended 2 study sessions							
Mullins 2004	0.5	0.3	17	0.51	0.29	23	-0.01 [-0.20, 0.18]
2.4.3 Attended 3 study sessions							
Mullins 2004	0.67	0.26	16	0.64	0.31	15	0.03 [-0.17, 0.23]



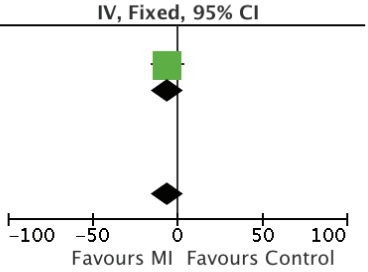
2.5 Treatment utilization: Mean scheduled hours attended in 4 weeks

Study or Subgroup	MI Mean	MI SD	MI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.5.1 MI versus TAU								
Winhusen 2008	6.2	10.9	97	9	11.4	97	100.0%	-2.80 [-5.94, 0.34]
Subtotal (95% CI)			97			97	100.0%	-2.80 [-5.94, 0.34]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.75 (P = 0.08)								
Total (95% CI)			97			97	100.0%	-2.80 [-5.94, 0.34]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.75 (P = 0.08)								
Test for subgroup differences: Not applicable								



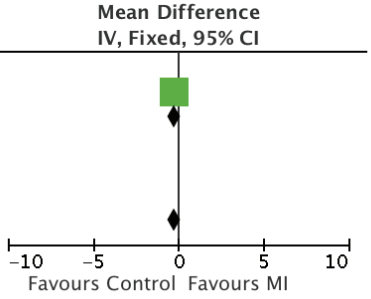
2.6 Days until treatment drop-out while pregnant

Study or Subgroup	MI Mean	MI SD	MI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.6.1 MI versus TAU								
Winhusen 2008	47.5	33.8	102	53.7	38	98	100.0%	-6.20 [-16.18, 3.78]
Subtotal (95% CI)			102			98	100.0%	-6.20 [-16.18, 3.78]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.22 (P = 0.22)								
Total (95% CI)			102			98	100.0%	-6.20 [-16.18, 3.78]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.22 (P = 0.22)								
Test for subgroup differences: Not applicable								



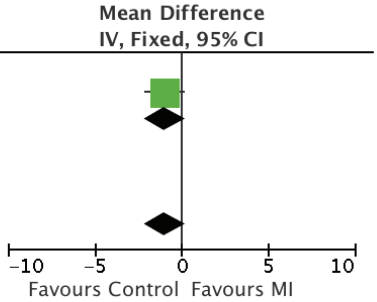
2.7 Number of weeks in which one treatment session was attended during first month

Study or Subgroup	MI Mean	MI SD	MI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.7.1 MI versus TAU								
Winhusen 2008	2.4	1.3	102	2.7	1.3	98	100.0%	-0.30 [-0.66, 0.06]
Subtotal (95% CI)			102			98	100.0%	-0.30 [-0.66, 0.06]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.63 (P = 0.10)								
Total (95% CI)			102			98	100.0%	-0.30 [-0.66, 0.06]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.63 (P = 0.10)								
Test for subgroup differences: Not applicable								



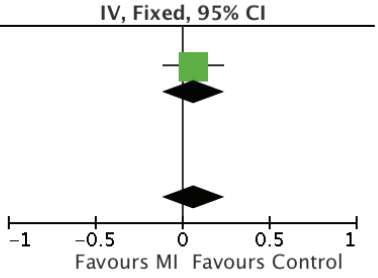
2.8 Number of weeks in which one treatment session was attended during three months follow-up

Study or Subgroup	MI Mean	MI SD	MI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.8.1 MI versus TAU								
Winhusen 2008	5	3.7	75	6	3.6	75	100.0%	-1.00 [-2.17, 0.17]
Subtotal (95% CI)			75			75	100.0%	-1.00 [-2.17, 0.17]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.68 (P = 0.09)								
Total (95% CI)			75			75	100.0%	-1.00 [-2.17, 0.17]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.68 (P = 0.09)								
Test for subgroup differences: Not applicable								



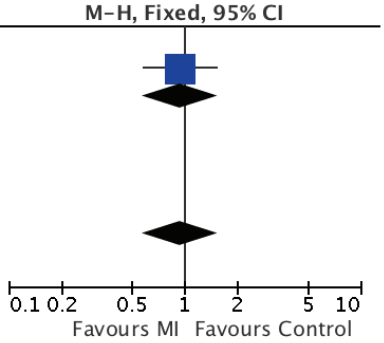
2.9 Mean proportion of negative urine screens at two months

Study or Subgroup	MI Mean	MI SD	MI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.9.1 MI versus Education control								
Mullins 2004	0.51	0.4	35	0.45	0.36	36	100.0%	0.06 [-0.12, 0.24]
Subtotal (95% CI)			35			36	100.0%	0.06 [-0.12, 0.24]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
Total (95% CI)			35			36	100.0%	0.06 [-0.12, 0.24]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.66 (P = 0.51)								
Test for subgroup differences: Not applicable								



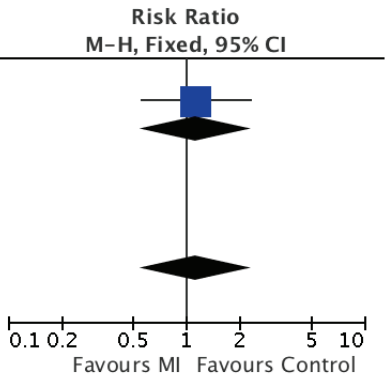
2.10 Proportion with positive urine toxicology in first month

Study or Subgroup	MI Events	MI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.10.1 MI vs TAU						
Winhusen 2008	22	85	24	87	100.0%	0.94 [0.57, 1.54]
Subtotal (95% CI)		85		87	100.0%	0.94 [0.57, 1.54]
Total events	22		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
Total (95% CI)		85		87	100.0%	0.94 [0.57, 1.54]
Total events	22		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
Test for subgroup differences: Not applicable						



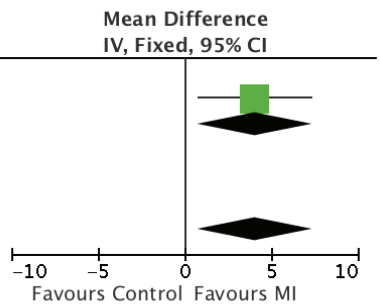
2.11 Proportion with positive urine toxicology at three month follow-up

Study or Subgroup	MI Events	MI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.11.1 MI vs TAU						
Winhusen 2008	13	78	12	81	100.0%	1.13 [0.55, 2.31]
Subtotal (95% CI)		78		81	100.0%	1.13 [0.55, 2.31]
Total events	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Total (95% CI)		78		81	100.0%	1.13 [0.55, 2.31]
Total events	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Test for subgroup differences: Not applicable						



2.12 Readiness to change – URICA scale: change from baseline to end of treatment

Study or Subgroup	MI Mean	MI SD	MI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.12.1 MI versus TAU								
Winhusen 2008	0.3	9.8	102	-3.7	13.7	98	100.0%	4.00 [0.69, 7.31]
Subtotal (95% CI)			102			98	100.0%	4.00 [0.69, 7.31]
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.37 (P = 0.02)								
Total (95% CI)			102			98	100.0%	4.00 [0.69, 7.31]
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.37 (P = 0.02)								
Test for subgroup differences: Not applicable								



MOTIVATIONAL INTERVIEWING COMPARED TO ANY CONTROL (TREATMENT-AS-USUAL OR EDUCATIONAL CONTROL) FOR PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE

Patient or population: Pregnant or postpartum women with problematic substance use

Settings: Outpatient in specialist substance use treatment programmes

Intervention: Motivational interviewing

Comparison: Any control (treatment-as-usual or educational control)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Any control (treatment-as-usual or Educational Control)	**Motivational Interviewing**				
Maternal retention in treatment Follow-up: 1–2 months	**716 per 1000**	**695 per 1000** (609 to 788)	**RR 0.97** (0.85 to 1.1)	271 (2 studies)	⊕⊕◯◯ LOW[1,2]	
Maternal substance use Mean proportion of negative urine screens Follow-up: mean 2 months		The mean maternal substance use in the intervention groups was **0.06 higher** (0.12 lower to 0.24 higher)		71 (1 study)	⊕⊕◯◯ LOW[3,4]	Winhusen 2008 (N = 200) measured proportion of positive urines in months 1 and 3. There were no statistically significant differences between the MI and TAU groups.
Infant birthweight	See comment	See comment	Not estimable		See comment	Not reported
Infant gestational age at delivery	See comment	See comment	Not estimable		See comment	Not reported
Infant custody	See comment	See comment	Not estimable		See comment	Not reported
Infant birth defects	See comment	See comment	Not estimable		See comment	Not reported
Infant head circumference	See comment	See comment	Not estimable		See comment	Not reported

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] Risk of Bias: Serious. Both trials were unblinded so the risk of performance bias is high. Attrition bias is also likely to be present due to the loss-to-follow-up.
[2] Imprecision: Rated as Serious. The number of events is less than 300.
[3] Risk of Bias: Serious. The trial was unblinded so the risk of performance bias is high. Attrition bias is also likely to be present due to the differential loss-to-follow-up between the groups.
[4] Imprecision: Rated as Very Serious. The sample size is very small.

Author(s): Nandi Siegfried, Nicolas Clark

Date: 2013-07-31

Question: SHOULD MOTIVATIONAL INTERVIEWING VS ANY CONTROL (TREATMENT-AS-USUAL OR EDUCATIONAL CONTROL) BE USED IN PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE?

Settings: Outpatient in specialist substance use treatment programmes

Bibliography: Psychosocial interventions for pregnant or postpartum women with problematic substance use.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Motivational Interviewing	Any control (treatment-as-usual or Educational Control)	Relative (95% CI)	Absolute	Quality	Importance
Maternal retention in treatment (follow-up 1–2 months)												
2	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	97/137 (70.8%)	96/134 (71.6%)	RR 0.97 (0.85 to 1.1)	21 fewer per 1000 (from 107 fewer to 72 more)	⊕⊕◯◯ LOW	CRITICAL
Maternal substance use (follow-up mean 2 months; measured with: Mean proportion of negative urine screens; better indicated by lower values)												
1	randomized trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	35	36	—	MD 0.06 higher (0.12 lower to 0.24 higher)	⊕⊕◯◯ LOW	CRITICAL
Infant birthweight – not measured												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Infant gestational age at delivery – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant custody – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant birth defects – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant head circumference – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

1 Risk of Bias: Rated as Serious. Both trials were unblinded so the risk of performance bias is high. Attrition bias is also likely to be present due to the loss-to-follow-up.
2 Imprecision: Rated as Serious. The number of events is less than 300.
3 Risk of Bias: Rated as Serious. The trial was unblinded so the risk of performance bias is high. Attrition bias is also likely to be present due to the differential loss-to-follow-up between the groups.
4 Imprecision: Rated as Very Serious. The sample size is very small.

THERAPEUTIC WORKPLACE during pregnancy and after birth for women with an alcohol or drug problem

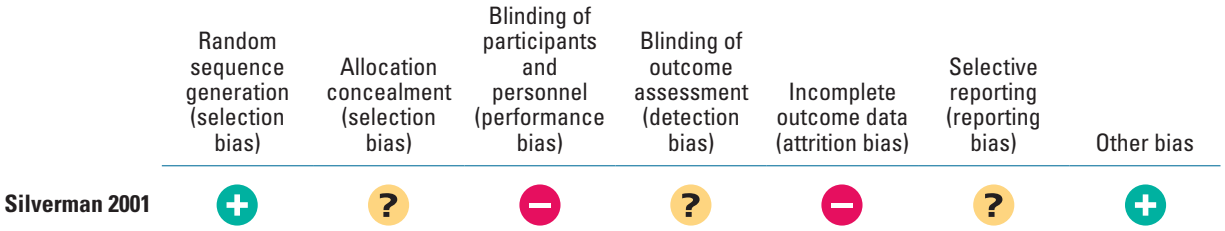
TABLE OF CHARACTERISTICS OF INCLUDED RCTs: 1 IN TOTAL

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
INTERVENTION DURING PREGNANCY ONLY								
General treatment settings								
No trials were identified from these settings.								
Specialist treatment settings								
Silverman 2001	USA	40	Not stated	On methadone programme and at least one urine sample positive for cocaine or opiates during 6 weeks prior to screening	Outpatient. Comprehensive treatment programme specifically for pregnant women abusing substances	24 weeks	**Therapeutic Workplace:** Salary is linked to abstinence to maintain entrance to the workplace. Participants earned base-pay vouchers according to a schedule of escalating reinforcement. A participant received a voucher worth US$7 on the first day that she provided a drug-free (negative for opiates and cocaine) urine sample and completed a 3-hr work shift. The vouchers increased by US$0.50 for each consecutive successful day, to a maximum of US$27 per day. If a participant either provided a drug-positive urine sample or failed to attend the workplace on a scheduled workday, the value of the next day's voucher was reset back to $7. **Usual care:** Participants received all the standard services available as part of the comprehensive treatment programme	MATERNAL 1. Urine- screen negative for cocaine, opiates and both 2. Treatment retention INFANT None
INTERVENTION DURING AND AFTER PREGNANCY ONLY								
General treatment settings								
No trials were identified from these settings.								
Specialist treatment settings								
No trials were identified from these settings.								

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
INTERVENTION AFTER PREGNANCY ONLY								
General treatment settings								
No trials were identified from these settings.								
Specialist treatment settings								
No trials were identified from these settings.								

RCT – Randomized controlled trial
R – Number randomized
A – Number analysed

RISK OF BIAS IN EACH TRIAL INCLUDED IN THE THERAPEUTIC WORKPLACE COMPARISON



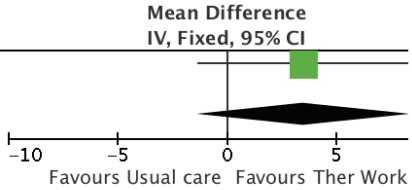
FOREST PLOTS OF THERAPEUTIC WORKPLACE COMPARISON

1 Therapeutic Workplace versus Usual Care

1.1 Treatment Retention: Mean weeks of treatment

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Silverman 2001	18.6	7.2	20	15.1	8.4	20	100.0%	3.50 [-1.35, 8.35]
Total (95% CI)			20			20	100.0%	3.50 [-1.35, 8.35]

Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)



1.2 Percentage of opiate-negative urine during 24 weeks of treatment (missing data assumed to be positive

Study ID	Therapeutic Workplace Mean SE	Usual Care Mean SE	t (38)	P value
Silverman 2001	52:8	33:6	2.04	0.05

1.3 Percentage of cocaine-negative urine during 24 weeks of treatment (Missing data assumed to be positive)

Study ID	Therapeutic Workplace Mean; SE	Usual Care Mean; SE	t (38)	P value
Silverman 2001	54:9	32:6	2.08	0.04

THERAPEUTIC WORKPLACE VERSUS USUAL CARE FOR PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE

Patient or population: Pregnant women with problematic substance use

Settings: Specialist substance use treatment setting: Outpatient

Intervention: Therapeutic Workplace versus Usual Care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Therapeutic Workplace versus Usual Care				
Treatment retention Mean weeks of treatment Follow-up: 24 weeks		The mean treatment retention in the intervention groups was **3.5 higher** (1.35 lower to 8.35 higher)		40 (1 study)	⊕◯◯◯ VERY LOW[1,2]	
Maternal substance use Urine-negative for opioids Follow-up: 24 weeks	See comment	See comment		40 (1 study)	⊕◯◯◯ VERY LOW[1,3]	There was a statistically significant difference favouring the Therapeutic Workplace group over Usual Care for urines negative for opioids.
Maternal substance use Urine-negative for cocaine Follow-up: 24 weeks	See comment	See comment		40 (1 study)	⊕◯◯◯ VERY LOW[1,3]	There was a statistically significant difference favouring the Therapeutic Workplace group over Usual Care for urines negative for cocaine.
Birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Infant gestational age at delivery	See comment	See comment	Not estimable	—	See comment	Not reported
Infant custody	See comment	See comment	Not estimable	—	See comment	Not reported
Infant birth defects	See comment	See comment	Not estimable	—	See comment	Not reported
Infant head circumference	See comment	See comment	Not estimable	—	See comment	Not reported

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] Risk of bias: Rated as Very Serious. There was no blinding which may introduce performance bias. Detection bias is less likely as the primary outcome was objectively measured: urine screens. The high rate of attrition across the study period and the differential between the groups resulted in a very serious risk of bias rating.

[2] Imprecision: Rated as Very Serious. The confidence interval is very wide and the sample size is very small (N = 40).

[3] Imprecision: Rated as Serious. The data is presented as a t test and 95% Confidence intervals (CI) are not reported so imprecision cannot be interpreted from the CI. The very small sample size of the participants (N = 40) indicates that imprecision is likely, despite this measurement being for 24 weeks of urine specimens per each participant.

Author(s): Nandi Siegfried, Nicolas Clark
Date: 2013-07-31
Question: THERAPEUTIC WORKPLACE VERSUS USUAL CARE FOR PREGNANT OR POSTPARTUM WOMEN WITH PROBLEMATIC SUBSTANCE USE
Bibliography: Psychosocial interventions for pregnant or postpartum women with problematic substance use.

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Therapeutic Workplace versus Usual Care	Control	Relative (95% CI)	Absolute	Quality	Importance
Treatment retention (follow-up 24 weeks; measured with: Mean weeks of treatment; better indicated by higher values)												
1	randomized trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	20	—	MD 3.5 higher (1.35 lower to 8.35 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Maternal substance use (follow-up 24 weeks; measured with: Urine-negative for opioids; Better indicated by lower values)												
1	randomized trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	—	MD 23% less (p=0.05)	⊕◯◯◯ VERY LOW	CRITICAL
Maternal substance use (follow-up 24 weeks; measured with: Urine-negative for cocaine; Better indicated by lower values)												
1	randomized trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	—	MD 26% less (p=0.04))	⊕◯◯◯ VERY LOW	CRITICAL
Birthweight – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant gestational age at delivery – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant custody – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant birth defects – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT
Infant head circumference – not measured												
0	—	—	—	—	—	none	—	—	—	—		IMPORTANT

[1] Risk of bias: Rated as Very Serious. There was no blinding which may introduce performance bias. Detection bias is less likely as the primary outcome was objectively measured: urine screens. The high rate of attrition across the study period and the differential between the groups resulted in a very serious risk of bias rating.
[2] Imprecision: Rated as Very Serious. The confidence interval is very wide and the sample size is very small (N = 40).
[3] Imprecision: Rated as Serious. The data is presented as a t test and 95% Confidence intervals (CI) are not reported so imprecision cannot be interpreted from the CI. The very small sample size of the participants (N = 40) indicates that imprecision is likely, despite this measurement being for 24 weeks of urine specimens per each participant.

Evidence Profile 3: Detoxification or quitting programmes for alcohol and other substance dependence in pregnancy

Evidence question:

For pregnant women with alcohol or other substance dependence, do detoxification or quitting programmes result in better maternal, fetal or infant outcomes compared to treatment-as-usual, maintenance treatment (in the case of opioids), or other methods of detoxification?

Selection criteria for the systematic review:

Study design: RCTs

Population: Pregnant women with alcohol or other substance dependence.

Interventions: Detoxification, either inpatient or outpatient.

Control: Non-detoxification, delayed detoxification, gradual detoxification, maintenance treatment (in the case of opioids), treatment-as-usual.

Outcomes: The following outcomes were selected by the guidelines group:

Outcome	Importance (0-9)
Maternal: Substance use	8.11
Maternal: Withdrawal	8.00
Maternal: Retention in substance use treatment	8.00
Infant: Neonatal Abstinence Syndrome	7.56
Infant: Gestational age at delivery	7.11
Infant: Birthweight	7.00
Infant: Spontaneous abortion	6.78

EVIDENCE TO RECOMMENDATIONS TABLE

Detoxification or quitting programmes for alcohol and other substance dependence in pregnancy

There were no randomized clinical trials identified by the systematic literature search on this evidence profile, hence the GRADE profile is based on a narrative review of the literature.

Summary of evidence

A withdrawal syndrome requiring pharmacological treatment in pregnancy can be said to occur for three substances: benzodiazepines, alcohol and opioids. The withdrawal syndrome associated with the cessation of other substances (such as psychostimulants) has not been considered severe enough to justify the routine use of psychotropic medication. For those pregnant women for whom medication-assisted withdrawal is successful, there does not appear to be any evidence of fetal distress during detoxification, nor any increased, no increased risk of fetal demise or premature delivery (Dashe et al., 1998). However, the nature and extent of withdrawal of the fetus from opioids or other substances is largely unknown, because there have been no methods developed to measure such withdrawal directly, and there is insufficient information available to distinguish the effects of fetal withdrawal from fetotoxicity.

Benzodiazepines

Medication-assisted withdrawal for benzodiazepines typically consists of a gradual withdrawal regimen with the goal of having the women benzodiazepine-free at the time of delivery, or later in the postpartum period. Withdrawal from benzodiazepines has typically been managed by transfer to a long-acting benzodiazepine (e.g. diazepam) followed by a gradual dose reduction, with the goal of being benzodiazepine-free at birth, or earlier if possible, without provoking significant withdrawal symptoms for the pregnant woman. There are no reliable data regarding the relative success or failure of such an approach in pregnant women, although the general belief is that relapse to use is common, particularly if the taper is too fast or too short.

Alcohol

Medication-assisted withdrawal for alcohol use in pregnant women typically uses a benzodiazepine, often diazepam, as primary pharmacotherapy. There are no reliable data related to outcome following detoxification during the different trimesters.

Opioids

Medication-assisted withdrawal from opioids typically involves tapered doses of methadone over a period of 3 to 14 days. Withdrawal from opioids is typically managed by tapered doses of methadone. The safety profile of methadone is well known but both conflicting and incomplete. Methadone maintenance pharmacotherapy has been found superior to detoxification in terms of treatment retention and heroin use (Mattick, Breen, Kimber, & Davoli, 2009). During pregnancy, methadone-maintenance pharmacotherapy has been found superior to detoxification for treatment retention, attending more obstetrical visits, and more often delivering at the program hospital (Jones et al., 2008).

Although there are considerable data regarding the failure of medication-assisted withdrawal for opioids, there are few data specific to trimester.

EVIDENCE TO RECOMMENDATIONS TABLE

Benefits and harms	
Benefits	• Pregnancy presents a unique opportunity to support women to reduce and ideally cease alcohol and/or illicit substance use (Chang et al., 1992) • Depending on the substance of use, medication-assisted withdrawal *that results in continued non-use of substances following medication-assisted withdrawal* is considered to be superior to usual care in terms of: – reduction in harmful consumption – reduction in risk to the fetus – increase in birthweight – improved general health of pregnant women – improved maternal psychological well-being – less risk of fetotoxicity – improved perinatal outcomes (e.g. reduction in preterm births, increased overall birthweights, reduction in number of low-birthweight infants – reductions in congenital defects or anomalies noting that: a meta-analysis by Enato et al. (2011) suggests that benzodiazepines are unrelated to an increased risk of major congenital abnormalities. However, research on the longer-term effects of benzodiazepines on the child exposed to benzodiazepines is largely lacking. • Improved general health of pregnant women • Improved maternal psychological well-being • Shorter hospitalizations, lower peak neonatal abstinence syndrome scores, and less likelihood of withdrawal treatment for neonates of mothers who had successfully completed medication-assisted withdrawal than for neonates of mothers who had been unsuccessful (Stewart, 2013) • Medication-assisted withdrawal has been associated with a significantly lower mean NAS peak score, a significantly lower mean amount of morphine to treat NAS, significantly fewer days medicated for NAS, significantly fewer number of days in the hospital relative to methadone, and significantly lower mean amount of morphine to treat NAS and significantly fewer days medicated for NAS than buprenorphine (Lund et al., 2012)
Harms	• The success of medication-assisted withdrawal during pregnancy is generally considered to be poor, with estimates of failure as low as 41% (Dashe et al., 1998) and as high as 96% (e.g., Luty et al., 2003). Failure rate is difficult to estimate precisely, because some authors have defined failure as failure to complete detoxification, while others have defined failure as return to substance use. This failure is associated with a number of negative outcomes, including increased fetal exposure to illicit substances and other maternal risk behaviors, reduced compliance with obstetrical care, and poorer neonatal birth parameters (Jones et al., 2008; summarized in Kaltenbach et al., 1998). • High risk of relapse to opioids following opioid detoxification (see above) • High risk of relapse to benzodiazepines following detoxification • Often stressful short-term symptoms associated with reduction or cessation of alcohol or substance use • Little development of coping skills • Increased risk of fetal stress (depending on the substance) • Increased risk of fetal morbidity or mortality, including miscarriage and stillbirth • Possible development of depression or anxiety as a result of cessation or reduction of alcohol or illicit substance use • Possible risk of switching from one substance to another substance • Damage to relationships/loss of employment

EVIDENCE TO RECOMMENDATIONS TABLE

Values and preferences	
In favour: **Pregnant woman**	• Increased personal contact and support • Opportunity to be substance free • Belief that it will lead to a healthier baby • Belief in positive response from family/society
Health-care worker	• Opportunity to intervene and assist with achievement of substance-free status • Opportunity to support health of fetus
Community	• Possible reduction of crime in the community • Possible reduction of STI risk in the community • Possible positive responses from some health-care providers, partners, family and co-workers
Against: **Pregnant woman**	• Fear of stigmatization for needing detoxification or for refusing detoxification in favour of maintenance medication treatments (being seen as 'weak-willed') • Dislike approach, sense of coercion • Fear of negative responses from partners, family and co-workers
Health-care worker	• Resent time and resources used • Do not believe treatment is appropriate or effective
Community	• Resent resources spent on detoxification programmes • Partner/family/employer may resent time and commitment to detoxification
Costs and feasibility	
Costs	• Trained staff and sustainable detoxification programme required • Financial implications for woman-care of other children, time lost from work
Feasibility (including economic consequences)	• Inconvenient for women • Likely to fail any other goal beyond being drug-free at the completion of detoxification

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Enato E, Moretti M, Koren G. The fetal safety of benzodiazepines: an updated meta-analysis. *J Obstet Gynaecol Can* 2011;33:46-8.

Jones HE, O'Grady KE, Malfi D, et al. Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. *Am J Addict* 2008;17:372-86.

Kaltenbach K, Finnegan L. Prevention and treatment issues for pregnant cocaine-dependent women and their infants. *Ann N Y Acad Sci* 1998;846:329-34.

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Luty J, Nikolaou V, Bearn J. Is opiate detoxification unsafe in pregnancy? *J Subst Abuse Treat* 2003;24:363-7.

Mattick RP, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2009:CD002209.

Stewart RD, Nelson DB, Adhikari EH, et al. The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy. *Am J Obstet Gynecol* 2013;209:267 e1-5.

Draft recommendations:

- Pregnant women dependent on alcohol, amphetamine type stimulants, cocaine, cannabis, volatile agents, (everything except opioids and benzodiazepines), should be advised and encouraged to cease their alcohol or other substance use, and provided with the opportunity to do so in a safe and supportive manner, both for the health of the pregnant woman and to reduce the possibility of damage to the fetus.
- Pregnant women dependent on opioids should be advised to use opioid-agonist maintenance treatment (such as methadone or buprenorphine) rather than to attempt opioid detoxification.
- Pregnant patients with benzodiazepine-use disorder should be transferred to a long-acting benzodiazepine (e.g., diazepam) and undergo a gradual dose reduction, with the goal of being benzodiazepine-free at birth, if possible. Psychosocial treatment should serve as an integral component of any dose-reduction strategy.
- Pregnant women who wish to undergo detoxification should be invited to withdraw from substance use in an inpatient or hospital facility to increase the chances of successful completion of substance withdrawal and to monitor the health of the fetus.
- The health of the fetus should be monitored during detoxification by fetal heart monitoring, and by the monitoring of fetal movements. If there are signs of fetal distress associated with the detoxification, then medication should be used to reduce the severity of withdrawal and the process of withdrawal should be slowed or temporarily halted.
- Withdrawal symptoms from the cessation of alcohol consumption should be managed with a long-acting benzodiazepine, titrated to the severity of withdrawal.
- Psychotropic medication should not be routinely used in pregnant women to assist detoxification from stimulants (including cocaine), cannabis and volatile agents, but should be reserved for specific symptoms which emerge.
- Given the high risk of relapse in opioid dependence, detoxification from opioids should be advised only for carefully selected patients. Such pregnant women who make an informed choice to cease opioid use should be supported to do so either with gradual tapering of opioids in an ambulatory treatment setting or with more rapid tapering in a residential treatment facility.

Final recommendations:

RECOMMENDATION 4

Health-care providers should, at the earliest opportunity, advise pregnant women dependent on alcohol or drugs to cease their alcohol or drug use and offer, or refer to, detoxification services under medical supervision where necessary and applicable.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Pregnant women dependent on alcohol or drugs who agree to undergo detoxification should be offered the supported withdrawal from substance use in an inpatient or hospital facility, if medically indicated.
- Detoxification can be undertaken at any stage in pregnancy, but at no stage should antagonists (such as naloxone, or naltrexone – in the case of opioid withdrawal) be used to accelerate the detoxification process.
- Equal attention should be paid to the health of mother and fetus during detoxification and treatment adjusted accordingly.
- The exceptions to this recommendation are opioid and benzodiazepine dependence, which are covered by recommendations 5 and 6 separately.
- It was decided that this recommendation should be strong, despite the very low quality of evidence of the effectiveness of the health-care intervention because there is clear evidence of harm to the fetus of ongoing maternal substance use, and the benefit to both mother and fetus of ceasing alcohol and/or substance use under medical supervision strongly outweighs any potential harms.

RECOMMENDATION 5

Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available rather than to attempt opioid detoxification.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Opioid maintenance treatment in this context refers to either methadone maintenance treatment or buprenorphine maintenance treatment.
- Pregnant patients with opioid dependence who wish to undergo detoxification should be advised that relapse to opioid use is more likely following medication-assisted withdrawal than while undertaking opioid maintenance treatment.
- Such medication-assisted withdrawal from opioids should be attempted only in an inpatient unit, using a gradual reduction in methadone or buprenorphine doses. Inpatient care should also be considered for the initiation and optimization of maintenance treatment.
- Psychosocial treatment should be an integral component of such treatment.
- Pregnant women who fail to complete medication-assisted withdrawal should be offered opioid agonist pharmacotherapy.
- It was decided that this recommendation should be strong despite the low quality of evidence of effectiveness from randomized controlled trials, as the rate of relapse to opioid use following detoxification has been shown to be high and the risks of harm to both mother and fetus from failed detoxification are catastrophic compared to the very low risks of harm from opioid maintenance treatment.

RECOMMENDATION 6

Pregnant women with benzodiazepine dependence should undergo a gradual dose reduction, using long-acting benzodiazepines.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Long-acting benzodiazepines should only be used for as short a time as is medically feasible in managing benzodiazepine withdrawal.
- Psychosocial interventions should be offered throughout the period of benzodiazepine withdrawal.
- Inpatient care should be considered in the withdrawal management of pregnant women with benzodiazepine dependence.
- It was decided that this recommendation should be strong despite the very low quality of evidence of effectiveness because ongoing benzodiazepine use in pregnancy is associated with significant risk of harm. At the same time, abrupt cessation of benzodiazepines can result in a severe withdrawal syndrome including seizures and psychosis. This leaves gradual reduction as the only practicable alternative. Significant clinical experience indicates that this approach is feasible and safe. Hence the GDG was in agreement that the benefits of gradual dose reduction outweigh the harms of both ongoing use and abrupt cessation.

RECOMMENDATION 7

Pregnant women who develop withdrawal symptoms following the cessation of alcohol consumption should be managed with the short-term use of a long-acting benzodiazepine.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Management of alcohol withdrawal usually also includes administration of thiamine.
- Alcohol withdrawal management may be facilitated by the use of an alcohol withdrawal scale such as the CIWA-Ar.
- Inpatient care should be considered in the withdrawal management of pregnant women with alcohol dependence.
- Alcohol withdrawal can be a severe and even life-threatening condition, provoking seizures and delirium. Evidence from non-pregnant populations has demonstrated the effectiveness of long-acting benzodiazepines for preventing seizures and delirium in alcohol withdrawal. Given the severity of alcohol withdrawal, and the lack of significant harm from short-term benzodiazepine use, and the evidence supporting the use of benzodiazepines in the management of alcohol withdrawal in the general population, the GDG decided that this recommendation should be strong despite the low quality of evidence in pregnant women.

RECOMMENDATION 8

In withdrawal management for pregnant women with stimulant dependence, psychopharmacological medications may be useful to assist with symptoms of psychiatric disorders but are not routinely required.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Except for the management of acute intoxication, withdrawal management in amphetamine-type stimulants (ATS) dependence or cocaine dependence does not include psychopharmacological medications as a primary approach to treatment in pregnant patients. There is no evidence that medication-assisted withdrawal would benefit pregnant women with these respective disorders.
- Inpatient care should be considered in the withdrawal management of pregnant women with stimulant dependence.
- It was decided that this recommendation should be strong despite the very low quality of evidence because the harms to mother and fetus of ongoing use of psychostimulants use have been shown to be high. The risks of providing short-term appropriate non-teratogenic medications for short-term management of psychologically distressing symptoms in pregnancy are very low. Therefore, the potential benefits of this approach strongly outweigh the harms of providing psychopharmacological treatment of symptoms, if required, during psychostimulant withdrawal.

Factors in considering the strength of the recommendations (recommendations 4–8):

Factor	Decision
Is there high or moderate quality evidence? The higher the quality of evidence, the more likely is a strong recommendation.	**No**
Is there certainty about the balance of benefits versus harms and burdens? In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms? In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?	**Yes**
Are the expected values and preferences clearly in favour of the recommendation?	**Yes**
Is there certainty about the balance between benefits and resources being consumed? In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed? In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?	**Yes**

Research gaps

- What type of benzodiazepine tapers work best for which types of patients?
- What medications are the safest and most effective for mother and fetus being withdrawn from alcohol?
- What intensity of fetal monitoring is needed to determine the relative safety of detoxification during pregnancy?
- What are the best withdrawal-severity assessment tools to measure withdrawal in pregnant women?
- What are the best ways to manage withdrawal from cocaine, cannabis, amphetamine, alcohol or volatile solvents in pregnant women?

Evidence profile 4: Pharmacological treatment (maintenance and relapse prevention) for alcohol and other substance dependence in pregnancy

Evidence question:

In pregnant women dependent on alcohol or other substances, does pharmacological treatment (either maintenance or relapse prevention) result in better maternal, fetal or infant outcomes than no pharmacological treatment or other pharmacological treatment?

Study selection criteria for the systematic review:

Study design: RCTs

Population: Pregnant women dependent on alcohol or other substances.

Interventions: Any pharmacotherapy used for agonist maintenance treatment (such as methadone or buprenorphine in opioid dependence) or relapse prevention treatment (such as naltrexone in opioid or alcohol dependence).

Control: No pharmacotherapy or other pharmacotherapy.

Outcomes: The outcomes of interest were:

Outcome	Importance (0-9)
Maternal: Substance use	8.11
Maternal: Withdrawal Severity	8.00
Maternal: Retention in substance use treatment	8.00
Infant: Neonatal Abstinence Syndrome	7.56
Infant: Gestational age at delivery	7.11
Infant: Birthweight	7.00
Infant: Spontaneous abortion	6.78

EVIDENCE TO RECOMMENDATIONS TABLE

Pharmacological treatment (maintenance and relapse prevention) for alcohol and other substance dependence in pregnancy

Summary of evidence

- Siegfried and Clark (2013) have performed systematic reviews of psychopharmacological treatments: methadone versus buprenorphine and a single study of methadone compared to slow-release morphine for pregnant women with a substance use disorder. See GRADE tables and summary of findings tables (below) for full details. Pharmacotherapy has been shown to be successful in the treatment of opioid use disorder. Methadone and buprenorphine have similar efficacy. Methadone appears to result in better maternal retention in treatment. Buprenorphine is associated with a number of better neonatal outcomes, specifically increased birthweight, reduced prematurity, and possibly a milder NAS. There is a lack of data on the safety and efficacy of the buprenorphine/naloxone combination in pregnancy.
- Psychosocial interventions in addition to pharmacotherapy have been shown to be superior to pharmacotherapy alone (Amato et al., 2011).
- There was no evidence found on the use of medications for relapse prevention for alcohol dependence in pregnancy (acamprosate, disulfiram, nalmefene, naltrexone).
- There was no RCT evidence on the use of naltrexone in relapse prevention from opioid dependence in pregnancy.
- There was no evidence found on the use of benzodiazepine maintenance for benzodiazepine dependence in pregnancy.

EVIDENCE TO RECOMMENDATIONS TABLE

Benefits and harms	
Benefits	• Pregnancy presents a unique opportunity to support women to reduce and ideally cease alcohol and/or illicit substance use • Although research in this area is extremely limited, given the history of exclusion of women from pharmacotherapy trials, and depending on the substance of use, pharmacotherapeutic interventions (specifically opioid agonist treatment in opioid dependence) are thought to be superior to usual care (e.g., Rayburn & Bogenschutz, 2004) in terms of: – reduction in harmful consumption – reduction in risk to the fetus – increase in birthweight – increase in the detection of harmful use and referral to treatment – improved general health of pregnant women – improved maternal psychological well-being – less risk of fetotoxicity – improved perinatal outcomes (e.g., reduction in preterm births, increased overall birthweights, reduction in number of low-birthweight infants) – reductions in congenital defects or anomalies
Harms	• Unpleasant side effects due to the pharmacological intervention or uncovered withdrawal from alcohol or substance use • Possible development of depression or anxiety as a result of cessation or reduction of alcohol or illicit substance use • Methadone and buprenorphine both reduce additional opioid use in pregnancy, but the neonate often develops a withdrawal syndrome referred to as neonatal abstinence syndrome (NAS) • Possible risk of drug substitution • Increased risk of fetotoxicity • Possible increased risk of congenital defects and anomalies related to exposure to the pharmacological intervention (particularly for acamprosate, naltrexone, nalmefene, disulfiram, benzodiazepines)
Values and preferences	
In favour: **Pregnant woman**	• May value increased personal contact and support • May value positive responses from partners, family and co-workers • May value stability of substance supply • May value increased psychosocial support
Health-care worker	• May value opportunity to intervene • May value opportunity for improved monitoring of health of mother and child
Community	• Partners/employers may value increased stability • May value potential for reduced crime/STI
Against: **Pregnant woman**	• Stigmatization when identified as drinking alcohol or using illicit substances during pregnancy • Stigmatization for being in need of drug treatment • Little development of coping strategies • Little commitment to behaviour change • Fear of negative responses from partners, family and co-workers • Resentment of intensive time and resources required for treatment
Health-care worker	• Ideological objection to maintenance treatment • Anxiety about ability to manage complex interactions with substance users • Dislike working with population considered difficult
Community	• May consider resource use inappropriate • Ideological objection to maintenance of substance use/or failure to withdraw • Employers/partners /families may resent extra time devoted to management

EVIDENCE TO RECOMMENDATIONS TABLE

Costs and feasibility	
Costs	• Potentially substantial additional cost beyond costs of detoxification, depending on the medication • Trained professional staff and sustainable programme required
Feasibility (including economic consequences)	• Inconvenient for women, particularly maintenance treatment requiring daily dosing • There are some suggestions in the literature that pregnant and postpartum women maintained on opioid agonists may have pain management needs different from those of non-opioid-agonist-maintained women (Jones et al., 2009; Höflich et al., 2012) • Requires patient monitoring to ensure patient continues taking her medication • A comprehensive care model in which pharmacotherapy is part of a women-centred, trauma-informed programme would be the best model of care – and also the costliest

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Jones HE, Martin PR, Heil SH, Stine SM, Kaltenbach K, Selby P, Coyle MG, O'Grady KE, Arria AM, Fischer G. Treatment of Opioid Dependent Pregnant Women: Clinical and Research Issues. *J Subst Abuse Treat.* 2008 October; 35(3): 245–259

Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. *Am J Obstet Gynecol* 2004;191:1885-97.

Draft recommendations:

- Pharmacotherapy is not recommended for routine treatment of dependence on amphetamine-type stimulants, cannabis, cocaine, or volatile agents in pregnant patients
- Medications for the treatment of alcohol dependence (acamprosate, naltrexone and disulfiram) should generally not be used in pregnancy.
- Pregnant patients with benzodiazepine dependence should undergo a gradual taper.
- Pregnant patients with an opioid use disorder should be encouraged to commence opioid agonist pharmacotherapy with either methadone or buprenorphine, in preference to detoxification, or detoxification followed by naltrexone.

Final recommendations:

RECOMMENDATION 9

Pharmacotherapy is not recommended for routine treatment of dependence on amphetamine-type stimulants, cannabis, cocaine or volatile agents in pregnant patients.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- For pregnant patients who use cannabis, amphetamine-type stimulants, cocaine, and volatile agents, the focus of treatment should be on psychosocial interventions.
- The recommendation was considered conditional given the complete lack of research on this issue.

RECOMMENDATION 10

Given that the safety and efficacy of medications for the treatment of alcohol dependence has not been established in pregnancy, an individual risk benefit analysis should be conducted for each woman.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- Pregnant patients with alcohol dependence should be offered psychosocial interventions.
- The recommendation was considered conditional given the complete lack of research on this issue.

RECOMMENDATION 11

Pregnant patients with opioid dependence should be advised to continue or commence opioid maintenance therapy with either methadone or buprenorphine.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Pregnant patients with opioid dependence should be encouraged to commence opioid agonist pharmacotherapy, which should be combined with psychosocial interventions.
- 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.
- Regardless of the choice of medication, psychosocial interventions should be an integral component of treatment.
- Opioid-dependent pregnant patients who wish to receive opioid antagonist pharmacotherapy should be discouraged from such a choice.
- It was decided that this recommendation should be strong despite the low quality of evidence as the rate of relapse to opioid use following detoxification is high and the risks of harm from failed detoxification are catastrophic compared to the small risks of harm from opioid maintenance treatment.

Factors in considering the strength of the recommendations (recommendations 9–11):

Factor	Recommendations 9 & 10	Recommendation 11
Is there high or moderate quality evidence? The higher the quality of evidence, the more likely is a strong recommendation.	**No**	**No**
Is there certainty about the balance of benefits versus harms and burdens? In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms? In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?	**No**	**Yes**
Are the expected values and preferences clearly in favour of the recommendation?	**Yes**	**Yes**
Is there certainty about the balance between benefits and resources being consumed? In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed? In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?	**Yes**	**Yes**

Research recommendations

- A potential case registry of pregnancies exposed to different substances, including psychotropic medication used for the treatment of substance use disorders in pregnancy, which can help explore the potential risks and benefits of pharmacotherapy in substance use disorders in pregnancy.
- The optimal treatment with methadone and buprenorphine in pregnancy (including further dose/response studies).
- Safety of pharmacotherapy for alcohol dependence in pregnancy.

Summary of findings and GRADE tables

METHADONE vs BUPRENORPHINE during pregnancy for women with opioid dependence

TABLE OF CHARACTERISTICS OF INCLUDED RCTs: 3 IN TOTAL

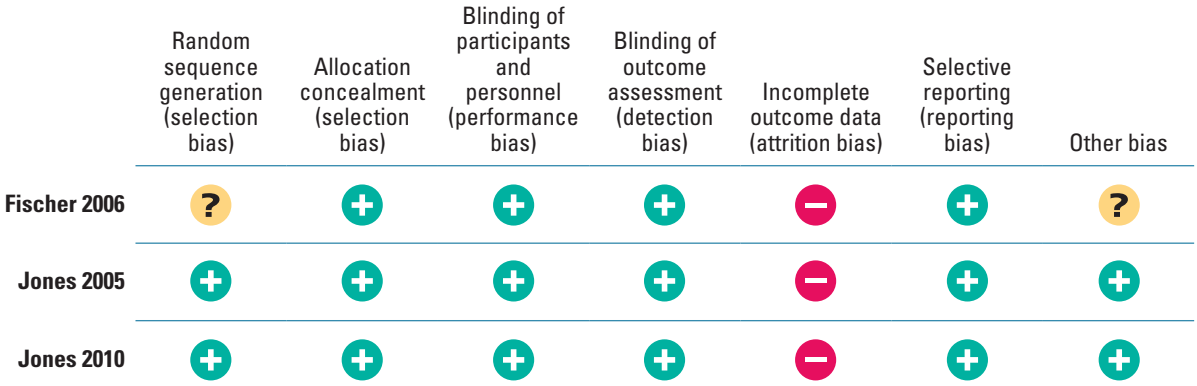
Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting	Randomized groups	Primary outcomes
INTERVENTION DURING PREGNANCY ONLY							
General treatment settings							
No trials were identified from these settings.							
Specialist treatment settings							
Jones 2005	USA, single centre	30 R 20 A	16–30 wks	Opioid-dependent pregnant women (DSM IV) with opioid-positive urine at treatment entry and reported use of opiates at least 4 of 7 days in the week prior to treatment entry	Resident (inpatient) unit of the Center for Addiction and Pregnancy (CAP), a multidisciplinary treatment programme. Women had access to an array of services including case management, group and individual counseling, obstetrical care, psychiatric evaluation and treatment, general medical management, and on-site child care and paediatric care.	Upon treatment admission, all participants received methadone (standard of care for opioid-dependent patients at CAP) for 3–5 days until signing written informed consent. Following consent and during medical screening, participants were switched from daily methadone to an equivalent dose of immediate-release morphine divided into four daily doses. Once medically cleared and randomized, participants were switched from their individualized dose of immediate-release morphine onto an equivalent dose of double-blind study medication. Medications were administered double-blind and double-dummy (i.e., each dosing day 12 sublingual tablets followed by 40 ml of oral liquid were administered). The first dose of double-blind medication was given at least 6 hours after the last immediate-release morphine and was split and separated by 2 hours. **Buprenorphine:** Participants were started with a dose of buprenorphine ranging from 4–24 mg. A participant assigned to active buprenorphine received 12 sublingual buprenorphine HCl (SubutexTM 2 mg) tablets followed by 40 ml of placebo liquid. Dose conversion was derived from first converting immediate-release morphine into methadone milligrams and then an equivalent buprenorphine dose was selected based on clinical experience and literature demonstrating similar outcomes for 8mg of buprenorphine and 60 mg of methadone. On the subsequent 2 days, doses of buprenorphine were systematically increased on an individual basis (2–4 mg of buprenorphine/day) that was dependent on patient report and clinician assessment until day 4 when patients achieved an individual stabilization dose. **Methadone:** Participants were started on the first day with a total dose of methadone which ranged from 20–60 mg. A participant assigned to active methadone received 12 sublingual placebo tablets followed by her dose of methadone HCl (20–100 mg) in 40 ml liquid. The dose conversion ratio used for the transition was 6 mg morphine for every 1mg methadone. On the subsequent 2 days, doses of methadone were systematically increased on an individual basis (5–10 mg methadone/day) that was dependent on patient report and clinician assessment until day 4 when patients achieved an individual stabilization dose. **Co-interventions:** Voucher payments for providing an ethanol-negative breath sample and a urine sample free of opioid, cocaine, benzodiazepines, THC, barbiturates, amitryptilines, amphetamines, clonazepams, doxepins, PCP, phenothiazines, and propoxyphene. Participants earned a US$7.50 voucher for their first drug-negative breath and urine sample, and vouchers for subsequent consecutive drug-negative samples increased by US$1. Maximum possible earnings were US$ 1200.	INFANT • Number of neonates requiring morphine drops for NAS • Peak NAS score measured by 19-item modified Finnegan Scale • Total amount of morphine drops administered to treat NAs • Total days of neonatal hospital stay from delivery until discharge from the hospital

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting	Randomized groups	Primary outcomes
Fischer 2006	Austria, single centre	18 R 14 A	24–29 wks	Opioid-dependent diagnosed by DSM IV with positive opioid urine toxicology on screening	Addiction clinic of the Medical University Vienna: treatment provided as outpatient, but admitted for at least 3 days during induction period	Participants were admitted to the clinic for a minimum of 3 days induction. All participants were maintained on oral slow-release morphine hydrochloride. Participants received a mean daily dose of 330.56mg (range: 90–600mg) over 24 hours; the final dose of slow-release morphine (mean: 164.44mg SD: 95.50; range: 30–460mg) a mean of 17 hours prior to the first dose of medication. **Buprenorphine:** Participants were started on 8 mg buprenorphine at the onset of moderate withdrawal symptoms on day 1 (Wang score between 5 and 10). Participants who received more than 400mg/day of oral slow-release morphine, commenced treatment with 12 mg buprenorphine. Doses were titrated for 5 days according to a predefined titration algorithm: day 1 dosing was followed by 12 mg buprenorphine if withdrawal was present. Dose titration increments to 16, 20 and 24 mg per day were available during buprenorphine induction. Participants received placebo syrup comprising 30mg dextramethorphan oral solution taste-matched to methadone. Doses of buprenorphine were between 8 and 24 mg/day throughout the study. **Methadone:** Participants were started on 40 mg methadone at the onset of moderate withdrawal symptoms on day 1 (Wang score between 5 and 10). Participants who received more than 400mgday of oral slow-release morphine, commenced treatment with 55 mg methadone. Doses were titrated for 5 days according to a predefined titration algorithm: day 1 dosing was followed by 55 mg methadone if withdrawal was present. Dose titration increments to 70, 85 and 100 mg per day were available during induction onto methadone (depending on clinical status). Participants received sub-lingual placebo tablets to taste-matched to buprenorphine. Doses of methadone ranged between 40 and 100 mg/day throughout the study. **Co-interventions:** All participants received food vouchers as compensation (the maximum amount possible was the equivalent of 1000 euros for 20 weeks participation).	Outcomes were not clearly defined as PRIMARY or SECONDARY. MATERNAL: • Frequency and amount of additional opioids used by the mother as measured by urine toxicology • Frequency and amount of use of other substances of abuse by the mother as measured by urine toxicology • Retention in treatment as measured by completion of the study INFANT : • Severity and duration of the NAS as measured by the Finnegan Scale

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting	Randomized groups	Primary outcomes
Jones 2010	USA and Austria, multi-centre (8 sites)	175 R 131 A	6–30 wks	Opioid-dependent women (current via DSM IV criteria or have a history of opioid dependence and be at risk of relapse) and provide an opioid-positive urine sample	University hospital setting on an outpatient basis, but women were admitted for at least 3 days in a residential or inpatient setting during induction onto double-blind study medication. Women had access to an array of services including case management, group and individual counseling, obstetric care, psychiatric evaluation and treatment, general medical management, and access to child care and pediatric care. Neonates were hospitalized for a minimum of 4 days and assessed for NAS for at least 10 days.	Before randomization, all participants received rapid-release morphine sulfate as inpatients to achieve medical stabilization and to ease the transition to the double-blind medication. A blinded individualised dosing schedule was used to implement dose-unit increases or decreases with dose adjustments of 2mg for buprenorphine and 5 or 10 mg for methadone. Dose adjustments were based on clinical decisions, participant request, urine toxicology and self-reported withdrawal symptoms. **Buprenorphine:** Daily seven tablets (three in the size of an 8-mg tablet and four in the size of a 2-mg tablet) to place under the tongue for 5 minutes, or until the tablets dissolved. Each tablet contained buprenorphine or placebo. A flexible dose range of 2 to 32 mg of buprenorphine in sublingual tablets was estimated to be equivalent to 20 to 140 mg of methadone on the basis of previously published data from clinical trials. After receiving these tablets, participants received liquid containing methadone placebo. Oral methadone placebo was given in the same fixed volume and included the same flavour-masking concentrates as the active drug concentrate. **Methadone:** Daily seven tablets of placebo buprenorphine followed by methadone dose in liquid preparation diluted to provide the dose in a fixed volume (e.g., 40 ml at U.S. sites and 50 ml in Vienna). **Co-interventions:** Monetary vouchers in exchange for providing urine samples that were negative for opioids (other than buprenorphine and methadone), other illicit drugs, and misuse of prescription medications.	INFANT: • Number of neonates requiring treatment for NAS • Peak NAS score • Total amount of morphine needed for NAS treatment • Length of hospital stay • Head circumference

RCT – Randomized controlled trial
R – Number randomized
A – Number analysed

RISK OF BIAS IN EACH TRIAL INCLUDED IN THE METHADONE VS BUPRENORPHINE COMPARISON



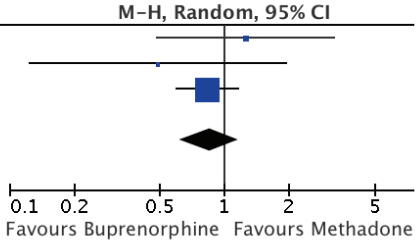
FOREST PLOTS OF METHADONE VS BUPRENORPHINE COMPARISON

1 BUPRENORPHINE vs METHADONE

1.1 Neonatal Abstinence Syndrome requiring treatment

Study or Subgroup	Buprenorphine Events	Total	Methadone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2006	5	8	3	6	10.5%	1.25 [0.48, 3.28]
Jones 2005	2	9	5	11	5.1%	0.49 [0.12, 1.95]
Jones 2010	27	57	41	72	84.4%	0.83 [0.59, 1.17]
Total (95% CI)		74		89	100.0%	0.84 [0.62, 1.15]
Total events	34		49			

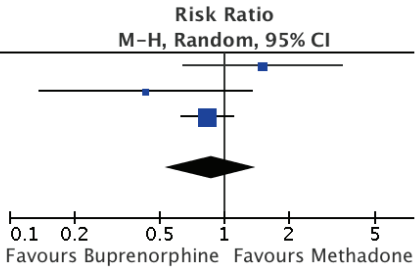
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.26$, df = 2 (P = 0.53); $I^2 = 0\%$
Test for overall effect: Z = 1.06 (P = 0.29)



1.2 Neonatal Abstinence Syndrome requiring treatment Intention to treat analysis

Study or Subgroup	Buprenorphine Events	Total	Methadone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2006	6	9	4	9	22.7%	1.50 [0.63, 3.56]
Jones 2005	3	15	7	15	14.7%	0.43 [0.14, 1.35]
Jones 2010	40	86	50	89	62.6%	0.83 [0.62, 1.11]
Total (95% CI)		110		113	100.0%	0.86 [0.53, 1.40]
Total events	49		61			

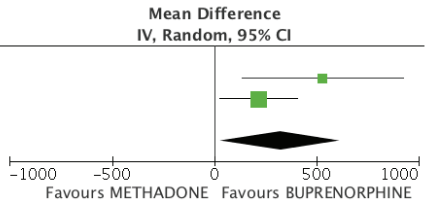
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 3.09$, df = 2 (P = 0.21); $I^2 = 35\%$
Test for overall effect: Z = 0.61 (P = 0.54)



1.3 Birth weight

Study or Subgroup	Buprenorphine Mean	SD	Total	Methadone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fischer 2006	2,820	0	8	2,820	0	6		Not estimable
Jones 2005	3,530.4	460.19	8	3,001.8	400.32	11	34.0%	528.60 [131.54, 925.66]
Jones 2010	3,093.7	552.91	58	2,878.5	566.47	73	66.0%	215.20 [22.50, 407.90]
Total (95% CI)			**74**			**90**	**100.0%**	**321.85 [30.81, 612.88]**

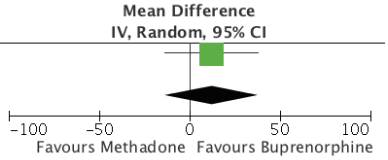
Heterogeneity: Tau² = 23756.19; Chi² = 1.94, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 2.17 (P = 0.03)



1.4 Time in hours to onset of NAS

Study or Subgroup	Buprenorphine Mean	SD	Total	Methadone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fischer 2006	72	35.2	8	60	11.3	6	100.0%	12.00 [−14.01, 38.01]
Total (95% CI)			**8**			**6**	**100.0%**	**12.00 [−14.01, 38.01]**

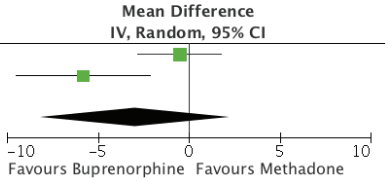
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



1.5 Duration of treatment for NAS in days

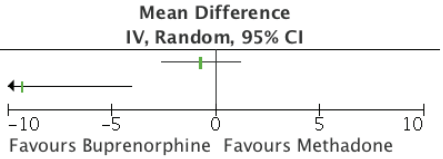
Study or Subgroup	Buprenorphine Mean	SD	Total	Methadone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fischer 2006	4.8	2.9	8	5.3	1.5	6	53.8%	−0.50 [−2.84, 1.84]
Jones 2010	4.1	7.55	57	9.9	13.58	72	46.2%	−5.80 [−9.50, −2.10]
Total (95% CI)			**65**			**78**	**100.0%**	**−2.95 [−8.13, 2.23]**

Heterogeneity: Tau² = 11.55; Chi² = 5.63, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 1.12 (P = 0.26)



1.6 Mean cumulative dose of morphine in mg required to manage NAS

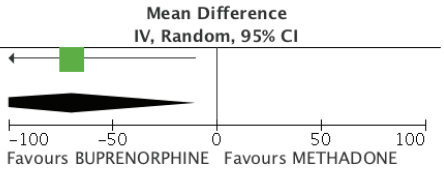
Study or Subgroup	Buprenorphine Mean	SD	Total	Methadone Mean	SD	Total	Mean Difference IV, Random, 95% CI
Fischer 2006	2	2	8	2.71	1.68	6	−0.71 [−2.64, 1.22]
Jones 2010	1.1	5.28	57	10.4	22.06	72	−9.30 [−14.58, −4.02]



1.7 Total number of morphine drops administered

Study or Subgroup	Buprenorphine Mean	SD	Total	Methadone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jones 2005	23.6	57.9	9	93.1	77.94	11	100.0%	−69.50 [−129.10, −9.90]
Total (95% CI)			**9**			**11**	**100.0%**	**−69.50 [−129.10, −9.90]**

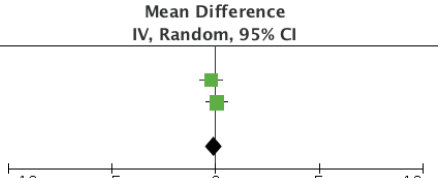
Heterogeneity: Not applicable
Test for overall effect: Z = 2.29 (P = 0.02)



1.8 APGAR at 1 min

Study or Subgroup	Buprenorphine Mean	SD	Total	Methadone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fischer 2006	8.5	0	8	8.5	0	6		Not estimable
Jones 2005	8.1	0.51	8	8.3	0.8	11	46.8%	−0.20 [−0.79, 0.39]
Jones 2010	8.1	1.52	58	8	1.71	73	53.2%	0.10 [−0.45, 0.65]
Total (95% CI)			**74**			**90**	**100.0%**	**−0.04 [−0.44, 0.36]**

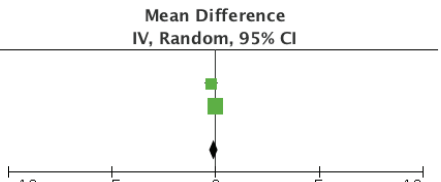
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



1.9 APGAR at 5 min

Study or Subgroup	Buprenorphine Mean	SD	Total	Methadone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fischer 2006	10	0	8	10	0	6		Not estimable
Jones 2005	8.7	0.42	8	8.9	0.3	11	39.6%	−0.20 [−0.54, 0.14]
Jones 2010	9	0.76	58	9	0.85	73	60.4%	0.00 [−0.28, 0.28]
Total (95% CI)			**74**			**90**	**100.0%**	**−0.08 [−0.29, 0.14]**

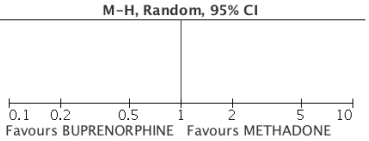
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)



1.10 Infant toxicology positive at delivery

Study or Subgroup	Buprenorphine Events	Buprenorphine Total	Methadone Events	Methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
Jones 2005	0	9	0	11		Not estimable
Total (95% CI)		**9**		**11**		**Not estimable**
Total events	0		0			

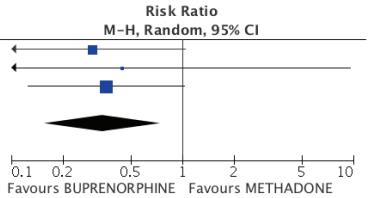
Heterogeneity: Not applicable
Test for overall effect: Not applicable



1.11 Premature delivery before week 37

Study or Subgroup	Buprenorphine Events	Buprenorphine Total	Methadone Events	Methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2006	2	8	5	6	38.9%	0.30 [0.09, 1.05]
Jones 2005	0	8	1	11	6.4%	0.44 [0.02, 9.69]
Jones 2010	4	58	14	73	54.7%	0.36 [0.13, 1.03]
Total (95% CI)		**74**		**90**	**100.0%**	**0.34 [0.16, 0.74]**
Total events	6		20			

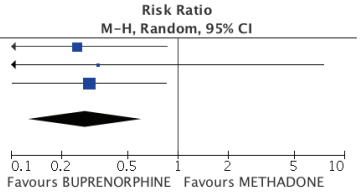
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.71 (P = 0.007)



1.12 Premature delivery before week 37 Intention to treat analysis

Study or Subgroup	Buprenorphine Events	Buprenorphine Total	Methadone Events	Methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2006	2	9	8	9	39.9%	0.25 [0.07, 0.87]
Jones 2005	0	15	1	15	6.3%	0.33 [0.01, 7.58]
Jones 2010	4	86	14	89	53.8%	0.30 [0.10, 0.86]
Total (95% CI)		**110**		**113**	**100.0%**	**0.28 [0.13, 0.61]**
Total events	6		23			

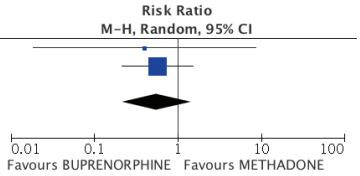
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 3.19 (P = 0.001)



1.13 Maternal toxicology positive at delivery

Study or Subgroup	Buprenorphine Events	Buprenorphine Total	Methadone Events	Methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
Jones 2005	0	9	1	11	9.5%	0.40 [0.02, 8.78]
Jones 2010	5	57	11	72	90.5%	0.57 [0.21, 1.56]
Total (95% CI)		**66**		**83**	**100.0%**	**0.55 [0.21, 1.43]**
Total events	5		12			

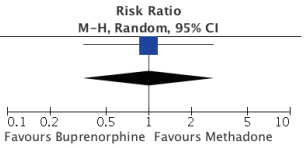
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)



1.14 Number of women who nursed their infants

Study or Subgroup	Buprenorphine Events	Buprenorphine Total	Methadone Events	Methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2006	4	8	3	6	100.0%	1.00 [0.35, 2.88]
Total (95% CI)		**8**		**6**	**100.0%**	**1.00 [0.35, 2.88]**
Total events	4		3			

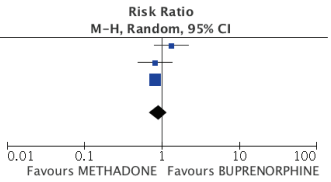
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



1.15 Maternal retention in trial (proxy measure for retention in treatment)

Study or Subgroup	Buprenorphine Events	Buprenorphine Total	Methadone Events	Methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2006	8	9	6	9	19.6%	1.33 [0.80, 2.23]
Jones 2005	9	15	11	15	19.8%	0.82 [0.49, 1.37]
Jones 2010	58	86	73	89	60.6%	0.82 [0.69, 0.98]
Total (95% CI)		**110**		**113**	**100.0%**	**0.90 [0.70, 1.17]**
Total events	75		90			

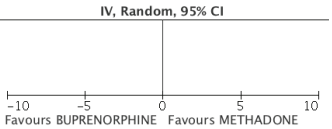
Heterogeneity: Tau² = 0.02; Chi² = 3.06, df = 2 (P = 0.22); I² = 35%
Test for overall effect: Z = 0.76 (P = 0.45)



1.16 Maternal withdrawal

Study or Subgroup	Buprenorphine Mean	Buprenorphine SD	Buprenorphine Total	Methadone Mean	Methadone SD	Methadone Total	Weight	Mean Difference IV, Random, 95% CI
Fischer 2006	0	0	0	0	0	0		Not estimable
Jones 2005	0	0	8	0	0	10		Not estimable
Total (95% CI)			**8**			**10**		**Not estimable**

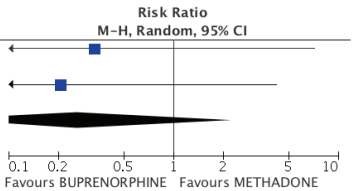
Heterogeneity: Not applicable
Test for overall effect: Not applicable



1.17 Spontaneous abortion

Study or Subgroup	Buprenorphine Events	Buprenorphine Total	Methadone Events	Methadone Total	Weight	Risk Ratio M-H, Random, 95% CI
Fischer 2006	0	9	1	9	49.1%	0.33 [0.02, 7.24]
Jones 2005	0	15	0	15		Not estimable
Jones 2010	0	86	2	89	50.9%	0.21 [0.01, 4.25]
Total (95% CI)		**110**		**113**	**100.0%**	**0.26 [0.03, 2.26]**
Total events	0		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)



BUPRENORPHINE COMPARED TO METHADONE FOR MATERNAL SUBSTANCE DEPENDENCE

Patient or population: Maternal substance dependence
Settings: Residential and clinic-based
Intervention: Buprenorphine
Comparison: Methadone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Methadone	**Buprenorphine**				
Maternal toxicology positive at delivery Urine screening	**145 per 1000**	**80 per 1000** (30 to 207)	**RR 0.55** (0.21 to 1.43)	149 (2 studies)	⊕⊕◯◯ LOW[1,2]	Jones 2010 applied Poisson regression with OR = 0.5 (95% CI: 0.1, 2.7). RevMan OR = 0.53 (95% CI: 0.17, 1.63). Meta-analysis was deemed appropriate.
Maternal withdrawal Wang Withdrawal Scale	See comment	See comment	Not estimable	0 (2 studies)	⊕◯◯◯ VERY LOW[3,4]	Jones 2005 reported no difference (F 0.67(df 1,16); p = 0.426); Fischer 2006 provided overall sample means but reported no differences between groups in text
Maternal retention in substance treatment – Retention in trial (proxy measure) Follow-up: 14-28 days post-partum	**796 per 1000**	**653 per 1000** (565 to 757)	**RR 0.90** (0.70 to 1.17)	223 (3 studies)	⊕⊕⊕◯ MODERATE[5,6]	
Birthweight		The mean birthweight in the intervention groups was **321.85 gm higher** (30.81 gm to 612.88 gm higher)		164 (3 studies)	⊕⊕◯◯ LOW[5,7]	
Premature delivery before week 37 Intention to treat (ITT) analysis	**230 per 1000**	**74 per 1000** (37 to 150)	**RR 0.28** (0.13 to 0.61)	223 (3 studies)	⊕⊕◯◯ LOW[5,7]	Jones 2010 applied Poisson regression with OR = 0.3 (95% CI: 0.1, 2.0). RevMan OR = 0.32 (95% CI: 0.12, 0.85). Meta-analysis using ITT was deemed appropriate.
Neonatal Abstinence Syndrome requiring treatment Intention to treat (ITT) analysis	**540 per 1000**	**464 per 1000** (286 to 756)	**RR 0.86** (0.53 to 1.4)	223 (3 studies)	⊕⊕◯◯ LOW[2,5]	Jones 2010 applied Poisson regression with OR = 0.7 (95% CI: 0.2, 1.8). RevMan OR = 0.83 (95% CI: 0.62, 1.11). Meta-analysis using ITT was deemed appropriate.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Methadone	**Buprenorphine**				
Spontaneous abortion	**27 per 1000**	**0 per 1000** (0 to 0)	Not estimable	223 (3 studies)	⊕◯◯◯ VERY LOW[5,9]	There were zero events in the buprenorphine group and 3 events in the methadone group.

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] Risk of Bias: Both trials (Jones 2005 and Jones 2010) were well-conducted with appropriate randomization and blinding. However, the high rate of attrition in Jones 2010 and the magnitude of the differential between the groups (18% in methadone and 33% in the buprenorphine groups) results in the overall risk of bias rated as serious
[2] Imprecision: The event rate is low and the confidence interval is wide.
[3] Risk of Bias: Attrition was high and poses a serious risk of bias.
[4] Imprecision: Two trial reported withdrawal data (Jones 2005 and Fischer 2006). Trial samples sizes were very small (18 in each trial) and there is a high likelihood of imprecision in the results although confidence intervals are not reported for the estimates.
[5] Risk of Bias: All three trials were well-conducted but attrition was high in all three trials. In the larger trial (Jones 2010) the magnitude of the differential attrition between the groups (18% in methadone and 33% in the buprenorphine groups) results in the overall risk of bias rated as serious.
[6] Indirectness: Retention in the trial was deemed a suitable proxy measure for retention in substance use treatment. The evidence was not downgraded for indirectness.
[7] Imprecision: The confidence interval is wide and the sample size is less than 400 (GRADE guideline for assessing continuous data)
[8] Imprecision: Event rate was very low and the confidence interval was wide.
[9] Imprecision: Event rate is very low and the confidence interval is very wide.

Author(s): Nandi Siegfried, Nicolas Clark
Date: 2013-07-21
Question: SHOULD BUPRENORPHINE VS METHADONE BE USED IN MATERNAL SUBSTANCE DEPENDENCE?
Settings: Residential and clinic-based
Bibliography: Siegfried N, Clark N. Psychopharmacological treatment for maternal substance dependence.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buprenorphine	Methadone	Relative (95% CI)	Absolute		
Maternal toxicology positive at delivery (assessed with: Urine screening)												
2	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/66 (7.6%)	12/83 (14.5%)	RR 0.55 (0.21 to 1.43)	65 fewer per 1000 (from 114 fewer to 62 more)	⊕⊕◯◯ LOW	CRITICAL
Maternal withdrawal (assessed with: Wang Withdrawal Scale)												
2	randomized trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	—	—	not pooled	not pooled	⊕◯◯◯ VERY LOW	CRITICAL
Maternal retention in substance treatment (assessed with: Retention in trial (proxy measure)												
3	randomized trials	serious[5]	no serious inconsistency	no serious indirectness[6]	no serious imprecision	none	75/110 (68.2%)	90/113 (79.6%)	RR 0.90 (0.70 to 1.17)	143 fewer per 1000 (from 40 fewer to 231 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Birthweight (better indicated by higher values)												
3	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[7]	none	74	90	—	MD 321.85 higher (30.81 to 612.88 higher)	⊕⊕◯◯ LOW	CRITICAL
Premature delivery before week 37 Intention to treat (ITT) analysis												
3	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[8]	none	8/110 (7.3%)	26/113 (23%)	RR 0.28 (0.13 to 0.61)	156 fewer per 1000 (from 81 fewer to 193 fewer)	⊕⊕◯◯ LOW	CRITICAL
Neonatal Abstinence Syndrome requiring treatment Intention to treat (ITT) analysis												
3	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	49/110 (44.5%)	61/113 (54%)	RR 0.86 (0.53 to 1.4)	76 fewer per 1000 (from 254 fewer to 216 more)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buprenorphine	Methadone	Relative (95% CI)	Absolute		
Spontaneous abortion												
3	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[9]	none	0/110 (0%)	3/113 (2.7%)	—	27 fewer per 1000 (from 27 fewer to 27 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

1 Risk of Bias: Both trials (Jones 2005 and Jones 2010) were well-conducted with appropriate randomization and blinding. However, the high rate of attrition in Jones 2010 and the magnitude of the differential between the groups (18% in methadone and 33% in the buprenorphine groups) results in the overall risk of bias rated as serious

2 Imprecision: The event rate is low and the confidence interval is wide.

3 Risk of Bias: Attrition was high and poses a serious risk of bias.

4 Imprecision: Two trial reported withdrawal data (Jones 2005 and Fischer 2006). Trial samples sizes were very small (18 in each trial) and there is a high likelihood of imprecision in the results although confidence intervals are not reported for the estimates.

5 Risk of Bias: All three trials were well-conducted but attrition was high in all three trials. In the larger trial (Jones 2010) the magnitude of the differential attrition between the groups (18% in methadone and 33% in the buprenorphine groups) results in the overall risk of bias rated as serious.

6 Indirectness: Retention in the trial was deemed a suitable proxy measure for retention in substance use treatment. The evidence was not downgraded for indirectness.

7 Imprecision: The confidence interval is wide and the sample size is less than 400 (GRADE guideline for assessing continuous data)

8 Imprecision: Event rate was very low and the confidence interval was wide.

9 Imprecision: Event rate is very low and the confidence interval is very wide.

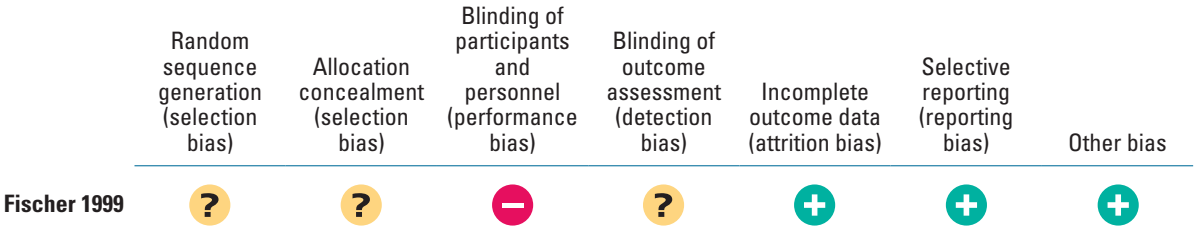
METHADONE vs SLOW-RELEASE MORPHINE during pregnancy for women with opioid dependence

TABLE OF CHARACTERISTICS OF INCLUDED RCTs: 1 IN TOTAL

Trial ID	Country	N	Gestational age	Alcohol and drug use	Setting (duration)	Study duration	Randomized groups	Primary outcomes
INTERVENTION DURING PREGNANCY ONLY								
General treatment settings								
No trials were identified from these settings.								
Specialist treatment settings								
Fischer 1999	Austria	24 R 24 A	Pregnancy and gestational age not stated for inclusion criteria; baseline EGA mean in methdadone 19.86 (SD: 5.55) wks; morphine: 23.46 (SD: 8.49) wks	Opioid dependence (DSM IV) or polysubstance use	Outpatient. Specialist comprehensive psychiatric, obstetric and medical programme for substance dependence	From intake to post delivery – specific duration not reported	**Methadone:** Participants were started on a flexible dosing schedule with a 10 day induction period. Methadone solution was administered once a day. Participants received take-home doses for those days when they did not attend the clinic and on weekends. After the induction period doses were stabilized until week 32 when a small dosage increase was noted. At delivery, the mean methadone dose was 53.48 +/- 25.11mg (range: 13–120mg) **Slow-release morphine:** Participants were started on a flexible dosing schedule with a 10 day induction period. Slow-release morphine tablets were taken twice daily. Participants received take-home doses for those days when they did not attend the clinic and on weekends. After the induction period doses were stabilized until week 32 when a small dosage increase was noted. At delivery, the mean morphine dose was 300.43 +/- 137.46mg (range: 60–660mg).	No primary outcome clearly delineated. MATERNAL 1. Substance use a. Visible Injecting sites b. Urine Screens INFANT 1. Substance use a. Visible Injecting sites b. Urine Screens 2. Severity and duration of the NAS as measured by the Finnegan Scale 3. Duration of hospitalization for NAS 4. Birthweight 5. Gestational age at birth 6. Head circumference 7. Length

RCT – Randomized controlled trial
R – Number randomized
A – Number analysed

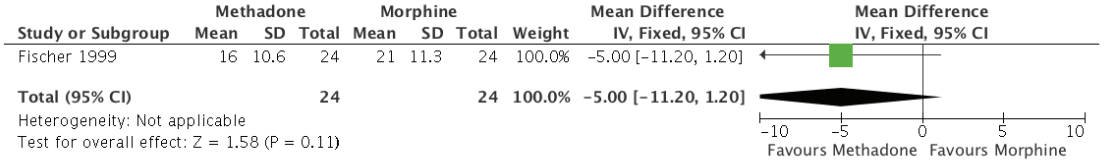
RISK OF BIAS IN EACH TRIAL INCLUDED IN THE METHADONE VS MORPHINE COMPARISON



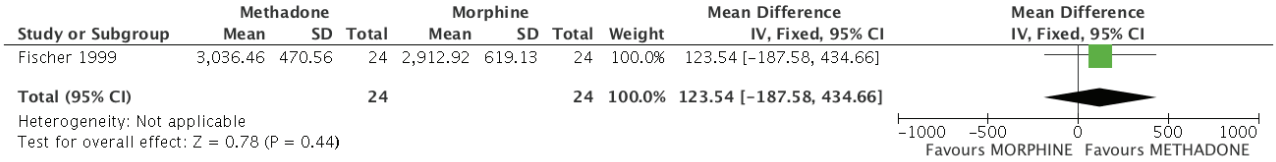
FOREST PLOTS OF METHDAONE VS MORPHINE COMPARISON

2 METHADONE vs SLOW-RELEASE MORPHINE

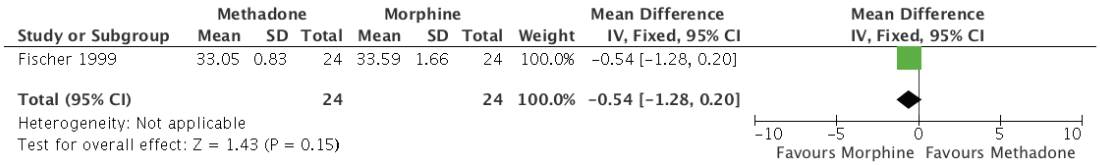
2.1 Mean duration of Neonatal Abstinence Syndrome in days



2.2 Infant birth weight



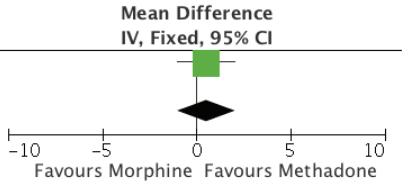
2.3 Infant Head Circumference



2.4 Infant length (cm)

Study or Subgroup	Methadone Mean	SD	Total	Morphine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fischer 1999	48.75	1.98	24	48.22	3.37	24	100.0%	0.53 [-1.03, 2.09]
Total (95% CI)			**24**			**24**	**100.0%**	**0.53 [-1.03, 2.09]**

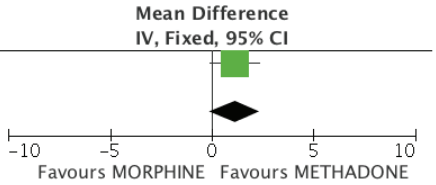
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



2.5 Estimated Gestational age at delivery

Study or Subgroup	Methadone Mean	SD	Total	Morphine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fischer 1999	38.92	1.74	24	37.79	2.55	24	100.0%	1.13 [-0.11, 2.37]
Total (95% CI)			**24**			**24**	**100.0%**	**1.13 [-0.11, 2.37]**

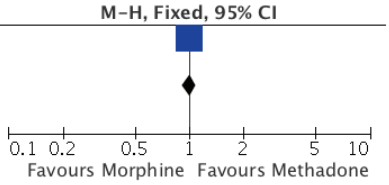
Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)



2.6 Maternal Retention in Treatment

Study or Subgroup	Methadone Events	Total	Morphine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fischer 1999	24	24	24	24	100.0%	1.00 [0.92, 1.08]
Total (95% CI)		**24**		**24**	**100.0%**	**1.00 [0.92, 1.08]**
Total events	24		24			

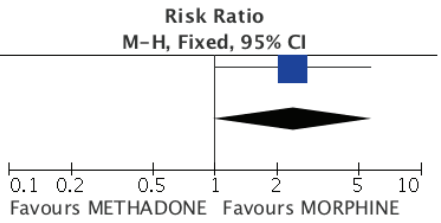
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



2.7 Maternal substance use (proxy measure is identification of Injection sites)

Study or Subgroup	Methadone Events	Total	Morphine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fischer 1999	12	24	5	24	100.0%	2.40 [1.00, 5.77]
Total (95% CI)		**24**		**24**	**100.0%**	**2.40 [1.00, 5.77]**
Total events	12		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)



METHADONE COMPARED TO SLOW-RELEASE MORPHINE FOR PREGNANT OR POSTPARTUM WOMEN WITH OPIOID DEPENDENCE

Patient or population: Pregnant or postpartum women with opioid dependence
Settings: Outpatient in specialist substance use treatment setting
Intervention: Methadone
Comparison: Slow-release Morphine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Slow-release Morphine	**Methadone**				
Maternal substance use Proxy measure for opioid use is identification of injection sites	**208 per 1000**	**500 per 1000** (208 to 1000)	**RR 2.4** (1 to 5.77)	48 (1 study)	⊕○○○ VERY LOW[1,2,3]	Statistically significantly fewer benzodiazepines were consumed by women in the morphine group compared with the methadone group. Cocaine use was low for both.
Maternal withdrawal	See comment	See comment	Not estimable	—	See comment	Not reported
Maternal retention in treatment – Proxy measure of retention in trial	**1000 per 1000**	**1000 per 1000** (920 to 1000)	**RR 1** (0.92 to 1.08)	48 (1 study)	⊕⊕○○ LOW[1,4]	No women were lost from the trial.
Infant birthweight in grams		The mean infant birthweight in the intervention groups was **123.54 higher** (187.58 lower to 434.66 higher)		48 (1 study)	⊕⊕○○ LOW[1,5]	
Infant prematurity Estimated gestational age at delivery in weeks		The mean infant prematurity in the intervention groups was **1.13 higher** (0.11 lower to 2.37 higher)		48 (1 study)	⊕⊕○○ LOW[1,5,6]	Methadone group EGA at delivery range 36–42 wks and Morphine EGA at delivery range 31–41 wks. N of premature delivery was not reported.
Neonatal Abstinence Syndrome (NAS) Mean duration of NAS in days		The mean neonatal abstinence syndrome (nas) in the intervention groups was **5 lower** (11.2 lower to 1.2 higher)		48 (1 study)	⊕⊕○○ LOW[1,7]	No reported statistical differences between groups for consumption of phenobarbitone or intensity of NAS. N for numbers with NAS in each group was not reported.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Slow-release Morphine	Methadone				
Spontaneous abortion	See comment	See comment	Not estimable	48 (1 study)	⊕⊕◯◯ LOW[1,6]	No women experienced a spontaneous abortion in the trial

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] Risk of Bias: Rated as Serious. Lack of reporting results in the randomization process being marked as unclear. The lack of blinding is a high risk due to the possible presence of performance and detection bias.
[2] Indirectness: Rated as Serious. Illicit opioid use could not be determined by urinalysis so identification of injection sites served as a proxy measure.
[3] Imprecision: Rated as Serious. The event rate is low and the confidence interval is wide.
[4] Indirectness: The proxy measure of retention in the trial is used to indicate treatment retention. The report states that women participated actively in the treatment programme but no comparison between groups is provided.
[5] Indirectness: The number of premature births was not reported. The range of EGA indicates that there were some premature < 37 week births.
[6] Imprecision: Rated as Serious: There is a likelihood of imprecision due to the small overall sample size.
[7] Imprecision: Rated as Serious: The confidence interval is wide.

Author(s): Nandi Siegfried, Nicolas Clark
Date: 2013-08-02
Question: SHOULD METHADONE vs SLOW-RELEASE MORPHINE BE USED IN PREGNANT OR POSTPARTUM WOMEN WITH OPIOID DEPENDENCE?
Settings: Outpatient in specialist substance use treatment setting
Bibliography: Siegfried N, Clark N. Psychopharmacological treatment for pregnant or postpartum women with problematic substance use.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methadone	Slow-release Morphine	Relative (95% CI)	Absolute		
Maternal substance use (assessed with: Proxy measure for opioid use is identification of injection sites)												
1	randomized trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12/24 (50%)	5/24 (20.8%)	RR 2.4 (1 to 5.77)	292 more per 1000 (from 0 more to 994 more)	⊕◯◯◯ VERY LOW	CRITICAL
Maternal withdrawal – not reported												
1	—	—	—	—	—	none	—	—	—	—		CRITICAL
Maternal Retention in Treatment (assessed with: Proxy measure of retention in trial)												
1	randomized trials	serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	24/24 (100%)	24/24 (100%)	RR 1 (0.92 to 1.08)	0 fewer per 1000 (from 80 fewer to 80 more)	⊕⊕◯◯ LOW	CRITICAL
Infant birthweight in grams (better indicated by higher values)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	24	24	—	MD 123.54 higher (187.58 lower to 434.66 higher)	⊕⊕◯◯ LOW	CRITICAL
Infant prematurity (measured with: Estimated gestational age at delivery in weeks; better indicated by higher values)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness[6]	serious[7]	none	24	24	—	MD 1.13 higher (0.11 lower to 2.37 higher)	⊕⊕◯◯ LOW	CRITICAL
Neonatal Abstinence Syndrome (NAS) (measured with: Mean duration of NAS in days; better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	24	24	—	MD 5 lower (11.2 lower to 1.2 higher)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methadone	Slow-release Morphine	Relative (95% CI)	Absolute		
Spontaneous abortion												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	0/24 (0%)	0/24 (0%)	—	—	⨁⨁◯◯ LOW	CRITICAL

[1] Risk of Bias: Rated as Serious. Lack of reporting results in the randomization process being marked as unclear. The lack of blinding is a high risk due to the possible presence of performance and detection bias.
[2] Indirectness: Rated as Serious. Illicit opioid use could not be determined by urinalysis so identification of injection sites served as a proxy measure.
[3] Imprecision: Rated as Serious. The event rate is low and the confidence interval is wide.
[4] Indirectness: The proxy measure of retention in the trial is used to indicate treatment retention. The report states that women participated actively in the treatment programme but no comparison between groups is provided.
[5] Imprecision: Rated as Serious. The sample size is very small N = 48 and the confidence interval is wide.
[6] Indirectness: The number of premature births was not reported. The range of EGA indicates that there were some premature < 37 week births.
[7] Imprecision: Rated as Serious: There is a likelihood of imprecision due to the small overall sample size.
[8] Imprecision: Rated as Serious: The confidence interval is wide.

Evidence profile 5: Breastfeeding

Evidence question:

In the management of postpartum women using alcohol or drugs or with substance use disorders, does encouraging breastfeeding result in better maternal or infant outcomes than not encouraging breastfeeding, discouraging breastfeeding (recommending breast milk substitutes), or recommending intermittent use of breast milk substitutes following periods of substance use?

Study selection criteria for the systematic review:

Study design: RCTs

Population: Postpartum women using alcohol or drugs or with substance use disorders.

Interventions: Encouraging breastfeeding.

Control: Not encouraging breastfeeding (treatment-as-usual), discouraging breastfeeding (recommending breast milk substitutes), or recommending short-term use of breast milk substitutes for periodic substance use.

Outcomes: The following outcomes were of interest:

Outcome	Importance (0–9)
Infant: Weight gain	7.78
Infant: Attachment	7.56
Infant: Failure to thrive	7.44
Infant: Neurobehaviour (lethargy, sedation, irritability)	7.44
Infant: Neonatal Abstinence Syndrome	7.22
Infant: Infections	7.11
Infant: Feeding issues	7.00
Maternal: Bonding with child	6.89
Maternal: Substance use	6.33
Maternal: Well-being	6.22
Infant: Death	6.00
Maternal: Mastitis	5.11
Termination of maternal rights (e.g. baby taken into care)	4.11

EVIDENCE TO RECOMMENDATIONS TABLE

Breastfeeding with maternal alcohol and/or other substance dependence

There were no randomized controlled trials identified for this evidence profile. The evidence summary is based on a narrative review of the evidence.

Summary of evidence (see the longer narrative review of evidence following this table)

- Enhanced maternal-infant attachment through breastfeeding (Luijk et al., 2012) is especially important, particularly for women feeling guilty about their prenatal drug use and those with lack of self-confidence in parenting skills.
- Breastfeeding and/or breast milk may reduce the incidence and/or severity of neonatal abstinence syndrome in opioid exposed infants (McQueen et al., 2012).
- Evidence of decreased stress response (Mezzacappa et al., 2005) and increased vagal tone, indicating better autonomic regulation, in lactating versus non-lactating women is salient for drug dependent women. Stress can be a major factor in the development of psychiatric symptoms, and has been linked to relapse to substance abuse (Sinha, et al. 2007) Further maternal dysregulation of the stress and reward systems is associated with drug seeking and neglectful parenting behaviors (Rutherford et al., 2011).
- For alcohol, binge alcohol, tobacco and cannabis use, breastfeeding rates rebound substantially in the postpartum period compared with use during pregnancy (National Survey on Drug Use and Health, combined data from 2002-2007).
- Depression correlates with substance use, and new mothers with postpartum depression may be at high risk for substance use or return to substance use (Chapman & Wu, 2013).
- Maternal psychopathology is more common in substance dependent women than in the general population (Fitzsimons et al., 2007) and is not infrequently related to poor judgment, enhancing the physical risk to the breastfed infant. Maternal somnolence, lack of adequate sleep-wake cycling, or decreased reaction times due to psychoactive medication or drug use may additionally result in infant injury. Women with substance use disorders are more likely to minimize risks, have less self-control, and less regard for their own and other people's safety in situations that can be risky for the breastfed infant, further enhancing the possibility of harm.
- Breastfed infants necessarily accompany their mothers and require attention more frequently than the non-breastfed infant. For women who are medically or psychiatrically unstable, have continued drug use, or live in environments that are unsafe or chaotic, this translates to increased infant exposures to violence, maternal drug seeking/drug trade, or maternal prostitution. Due to brain changes that are associated with drug use, drug dependent women often view normal infant cues as stressful instead of rewarding (Rutherford et al., 2011).
- Women who are regular cocaine or amphetamines/methamphetamines users and unstable should be advised against breastfeeding. Mothers who use these stimulants infrequently may be candidates for breastfeeding, provided that they express and throw away the milk after using, have a supplementary feeding plan in place, and do not breastfeed for 24 hours after use. Mothers need to be advised that these substances have been found in the breast milk, and has been shown to cause toxicity in the infant.
- There is insufficient information regard breastfeeding during cannabis use, although it has been found in breast milk. Its effects on the infant are unknown.
- Two small sample size reports have noted that women prescribed methadone may want to consider weaning their children off breast milk gradually to reduce the risk of developing withdrawal symptoms (Malpas & Darlow, 1999; Isemann et al., 2010).

Benefits and harms

Benefits	• Pregnancy and the immediate postpartum period represents an ideal time for mother-child bonding and breastfeeding may increase this bonding • Breastfeeding represents the single best way for a mother to feed her child • Breastfeeding is likely to lead to better short- and long-term child development outcomes • Breastfeeding may serve as a protective factor from many illnesses • Breastfeeding may help protect babies from developing allergies • Breastfeeding may boost a child's intelligence • Breastfeeding may protect a child from obesity • Breastfeeding may lower a baby's risk of SIDS • Breastfeeding can reduce maternal stress level and risk of postpartum depression • Breastfeeding is less costly, more hygienic and easier to deliver than other feeding methods

EVIDENCE TO RECOMMENDATIONS TABLE

Harms	• Potential higher risk of difficulties bonding due to neonatal withdrawal symptoms • Short and long term risks of the child being exposed via breast milk to varying amounts of substances consumed by the mother. These risks depend on the substance consumed by the mother, with little data available for several substances (e.g., hallucinogens, volatile agents). The most harmful exposures are alcohol (>50gms in one occasion) • Risk that a mother who is using sedative substances may inadvertently suffocate the child • Greater risk exposure of breastfed child to chaotic lifestyle harms such as violence, maternal drug seeking/ prostitution. • Maternal psychopathology may enhance risk to breast fed child
Values and preferences	
In favour: **Mother**	• More convenient, less costly means of feeding child • Value support from HCW for breastfeeding
Health-care worker	• Value breastfeeding for reduction in gastrointestinal and other childhood infectious disease • Value breastfeeding for potential to reduce NAS • Value breastfeeding as optimal means of child nutrition
Community	• Value breast feeding as means of superior child development • Possible positive responses from partners, family and co-workers
Against: **Mother**	• Fatigue, irritability, poor bonding may make breastfeeding undesirable • Lifestyle-need to seek drugs/engage in prostitution may make breastfeeding undesirable • Physical effects – painful enlarged breasts, poor lactation – may make breast feeding undesirable to mother • May believe breastfeeding will harm infant
Health-care worker	• May believe mother is incapable of breastfeeding • May believe mother is likely to smother infant • May find time and commitment needed to support mother burdensome • May believe infant is at risk from mother's substance use
Community	• Partners/family/employers may believe breast feeding is inappropriate and actively oppose it
Costs and feasibility	
Feasibility (including economic consequences)	• Managing breastfeeding in women who use alcohol requires support, trust and clear advice: e.g. women who use alcohol should be discouraged from breastfeeding for 2 hours after consuming one drink, and 4 to 8 hours after consuming more than one drink in a single sitting. • The availability of safe and affordable breast milk substitutes, including access to clean water, sterilizing equipment, the affordability of breast milk substitutes and the age of the infant/child needs to be considered and balanced against risks of breastfeeding. • Breastfeeding itself imposes little additional cost beyond providing basic services to the mother and child. However, trained staff and a sustainable programme is needed to support breastfeeding and bonding and teach and support mother with care of the infant. • A comprehensive care model in which there is a focus on the mother-infant dyad and is part of a women-centred, trauma-informed programme would be the best model of care – and also the costliest.

Draft recommendations:

- The decision to breastfeed should take into account the specifics risks and benefits of breastfeeding compared to alternatives in each case. In most instances, the benefits will outweigh the risks of breastfeeding and in this situation women with a substance use disorders should be encouraged to breastfeed with appropriate support and precautions.
- Skin-to-skin contact is important regardless of feeding choice and needs to be actively encouraged for the mother who is fully conscious and aware and able to respond to her baby's needs.
- Mothers who are stably maintained on opioid agonist medication, either methadone or buprenorphine, should be encouraged to breastfeed.
- Mothers who are stably maintained on opioid antagonist medication, such as naltrexone, should be discouraged from breastfeeding because naltrexone does pass into breastmilk, and naltrexone has been shown to cause tumors in animal studies.

Final recommendations:

RECOMMENDATION 12

A. Mothers with substance use disorders should be encouraged to breastfeed unless the risks clearly outweigh the benefits.

B. Breastfeeding women using alcohol or drugs should be advised and supported to cease alcohol or drug use; however, substance use is not necessarily a contraindication to breastfeeding.

Strength of recommendation: Conditional **Quality of evidence: Low**

Remarks:

- A risk assessment should take into account the risks of exposure to alcohol and drugs in breast milk, HIV status, the specific pattern of substance use in each case, the availability of safe and affordable breast milk substitutes, as well as access to clean water, sterilizing equipment, and the age of the infant/child. Heavy daily alcohol consumption, such as in alcohol dependence, would constitute high risk to the infant, for example, and in the presence of safe breast milk alternatives, it would be preferable not to breastfeed.
- The message to breastfeeding women who have used alcohol and drugs, to cease using alcohol and drugs while breastfeeding should be given in such a way that it does not undermine the potential benefits of breastfeeding.
- It is possible to reduce the risk of exposure through breastfeeding by altering the timing of breastfeeding, or by the use of temporary alternatives, such as stored (frozen) breast milk or breast milk substitutes where they are available and can be safely used. Women who use alcohol intermittently should be discouraged from breastfeeding for 2 hours after consuming one standard drink (10 g of pure alcohol), and 4 to 8 hours after consuming more than one drink in a single occasion. Breastfeeding advice for women with HIV should also take into consideration the risk of HIV transmission (refer to WHO guidelines on breastfeeding and HIV).
- Mothers of infants with a neonatal withdrawal syndrome should be offered appropriate breastfeeding information and support.
- This recommendation was considered conditional because the different values and preferences of women and the lack of strong evidence of harms of low levels of substance use in pregnancy.

RECOMMENDATION 13

Skin-to-skin contact is important regardless of feeding choice and needs to be actively encouraged for the mother with a substance use disorder who is able to respond to her baby's needs.

Strength of recommendation: **Strong** Quality of evidence: **Low**

Remarks:

- It was decided that the recommendation should be strong despite the very low quality evidence as the risk of harm is minimal, it consumes no resources, the values and preferences were in favour of the recommendation, and there was considered to be certainty about the balance between benefits and harms.

RECOMMENDATION 14

Mothers who are stable on opioid maintenance treatment with either methadone or buprenorphine, should be encouraged to breastfeed unless the risks clearly outweigh the benefits.

Strength of recommendation: **Strong** Quality of evidence: **Low**

Remarks:

- Women prescribed opioids such as methadone and buprenorphine and wishing to stop breastfeeding may wean their children off breast milk gradually to reduce the risk of developing withdrawal symptoms.
- It was decided that the recommendation should be strong, as, despite the low quality of evidence of effect, it was considered highly likely that the benefit of avoiding withdrawal symptoms in the infant strongly outweighed any potential harms. The values and preferences expressed by end-users surveyed were strongly in favour of the recommendation and there was certainty about the balance between benefits and resources being consumed.

Factors in considering the strength of the recommendations (recommendations 12–14):

Factor	Decision
Is there high or moderate quality evidence? The higher the quality of evidence, the more likely is a strong recommendation.	**No**
Is there certainty about the balance of benefits versus harms and burdens? In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms? In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?	**Yes**
Are the expected values and preferences clearly in favour of the recommendation?	**Yes**
Is there certainty about the balance between benefits and resources being consumed? In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed? In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?	**Yes**

Breastfeeding and substance use/misuse: A review of the evidence and estimates of risks associated with individual substances

Lauren M. Jansson

Both licit and illicit substance use remain a significant problem among women of childbearing age. The 2007 National Survey on Drug Use and Health (NSDUH) revealed that among pregnant women aged 15 to 44 years, 5.2 percent used illicit drugs in the past month in the US. Although the prevalence of prescribed opioid pain relievers/narcotic analgesics, such a hydrocodone and oxycodone, among pregnant women is not well known, there is growing evidence that misuse of opioid pain relievers/narcotic analgesics is increasing internationally (RADARs system report 2012; Maxwell & McCance-Katz, 2009). In the US, the incidence of NAS and maternal opioid use has tripled between 2000 and 2009 (Patrick et al., 2012). Adolescents are a particular concern; in 2010-11, among young pregnant women between 15 and 17 years the rate of illicit drug use was 20.9% and smoking rates are higher in pregnant vs non-pregnant teens in this group (NIDA). Other substance use during pregnancy is also of significant concern throughout the world: In Barcelona, 11% of meconium tested was positive for drugs of abuse in a random survey of 175 newborns (Concheiro et al., 2012); 14% of Canadian women report alcohol use during their last pregnancy in 2005 (Health Canada, 2005), and worldwide, the incidence on fetal alcohol syndrome is 1:2000 live births (Sachdeva et.al., 2009).

Breast milk is well-known as optimal nutrition for the newborn. There are myriad other recognized benefits from breast milk and lactation that are likely to provide a particular benefit to the drug dependent dyad who are, in general, at higher risk for many acute and chronic physical and psychological conditions. These include reduced infections in the neonate, a diminution of certain chronic health conditions in later life, such as Types I and II diabetes and obesity, and improved cognition and brain development (Isaacs et al., 2010). Breastfeeding is an analgesic for newborns (Gray, et al., 2002) and there is some evidence that breast milk and/or breastfeeding can ameliorate the incidence or severity of neonatal abstinence syndrome (NAS, or withdrawal, typically found in opioid exposed infants after delivery) (Welle-Strand et al., 2013, McQueen, 2011). Mothers also have significant health benefits, such as reduced incidence of breast and ovarian cancer, decreased stress response (Mezzacappa et al., 2005) and increased vagal tone, indicating better autonomic regulation, in lactating vs non-lactating women. This may be a particularly salient benefit for drug dependent women, as stress can be a major factor in the development of psychiatric symptoms, and has been linked to relapse to substance abuse (Sinha, et al. 2007) and maternal dysregulation of the stress and reward systems is associated with drug seeking and neglectful parenting behaviors (Rutherford et al., 2011). Enhanced maternal-infant attachment (Luijk et al., 2012) may be another especially important benefit, particularly for women who may harbor guilt in regards to their prenatal drug use and lack of self-confidence in parenting skills.

Despite the significant and specific benefits of breast milk and breastfeeding for the substance exposed dyad, when considering lactation among this high risk population, there must necessarily be a discussion regarding the risk: benefit ratio of this practice, and several risk factors must be considered. These factors stem from: 1) maternal functioning, 2) infant functioning, and 3) toxicities associated with the substance(s) used.

1. The substance dependent mother

Substance dependent women may have health or other conditions that can increase the risk to the breast fed infant. These include HIV or other infections, poor nutrition, and psychiatric disorders that require psychotropic medications with known toxicity. Research has indicated that the mother's decision to breastfeed does not necessarily reflect a lifestyle including drug abstinence that would preclude toxic exposures in her offspring (Frank et al., 1992). Drug dependent women frequently use more than one substance (illicit and/or licit), and the incidence of concurrent alcohol use and cigarette smoking is high. Exposure to alcohol or drugs can significantly impair the mother's judgment and ability to care for the baby, and for chronic drug users, repetitive exposures increase this risk and lead to brain changes that enhance this risk. For women who are able to achieve abstinence during pregnancy, relapse to substance use after delivery is a significant concern. For alcohol, binge alcohol, tobacco and cannabis use, rates rebound substantially in the postpartum period compared with use during pregnancy (National Survey on Drug Use and Health, combined data from 2002-2007). Some women relapse on substances that are not usually detected in the urine toxicology tests that are part of the regular screening for drug use in treatment programs or hospitals (e.g. clonidine, some benzodiazepines). In most

societies, pregnant and parenting drug dependent women are usually under considerable social pressure to deny substance use, making detection of perinatal substance dependence both important and problematic. Depression correlates with substance use, and new mothers with postpartum depression may be at high risk for substance use or return to substance use (Chapman & Wu, 2013). Additionally, substance using and/or dependent women frequently display some behaviors or conditions that can be harmful for the breastfed infant independently or in addition to the drug exposure per se. Maternal psychopathology is more common in substance dependent women than in the general population (Fitzsimons et al., 2007) and is not infrequently related to poor judgment, enhancing the physical risk to the breastfed infant. Maternal somnolence, lack of adequate sleep-wake cycling, or decreased reaction times due to psychiatric medication may additionally result in infant injury. Women with substance use disorders are more likely to minimize risks, have less self-control, and less regard for their own and other people's safety in situations that can be risky for the breastfed infant, further enhancing the possibility of harm.

2. The substance exposed infant

The risks associated with substances in breast milk to the infant are also influenced by factors beyond what is known about the pharmacokinetics of the drug. Certain drugs may accumulate in the infant due to reduced clearance or immature metabolic pathways (AAP, 2013). Specific genotypes may provide increased vulnerability, such as those associated with ultra-rapid metabolism of codeine (Berlin, et al., 2009). The substance exposed infant, particularly the opioid exposed infant, may undergo NAS after birth, which can entail significant morbidity and prolonged pharmacotherapeutic treatment. Infants with NAS may be particularly difficult to breastfeed due to symptoms of the disorder, such as hypertonicity, suck-swallow incoordination, or other feeding difficulties (Jansson et.al., 2004), which can lead to failure to thrive for infants relying solely on breast milk for nutrition in addition to maternal frustration or feelings of guilt or inadequacy which can lead to depression or relapse. An important consideration is that the breastfed infant, as opposed to the infant receiving formula, necessarily accompanies his mother and requires attention more frequently. For women who are medically or psychiatrically unstable, have continued drug use, or live in environments that are unsafe and/or chaotic, this translates to increased infant exposures to harmful situations. Infants in these situations can be at risk for exposure to violence, maternal drug seeking/drug trade, or maternal prostitution. Due to brain changes that are associated with drug use, drug dependent women often view normal infant cues as stressful instead of rewarding (Rutherford et al., 2011), and this can additionally lead to situations of infant neglect and/or abuse.

3. Substances and breast milk/breastfeeding

Risks of breastfeeding in substance dependent women include direct toxicities of the substances transmitted into breast milk and ingested by the infant, as well as secondary exposures resulting in additional toxicities to the infant due to maternal substance use or the environment in which the substance dependent woman lives. Drugs with long half lives are more likely to accumulate in human milk, and drugs with high bioavailability are more easily absorbed by the infant (Hale, 2004). Illicit substances can be cut with dangerous and unknown adulterants. Vaporized substances can provide a secondary exposure to the infant; for example, there are over 450 compounds in THC smoke, many of which are toxic; 6 to 53% of Δ^9-THC is released into the air during smoking by side stream (Huestis et al., 1992). For women living in poor environments, as many drug dependent women are, additional environmental exposures such as heavy metals, insecticides, inhaled aromatic hydrocarbons, etc. should be considered (Erlin & van den Anker, 2012).

There exists sparse literature on the subject of substances of abuse and transmission into breast milk in total, as this research is, in general, fraught with ethical and practical dilemmas, and is additionally difficult to perform. There is a near absence of literature on long term effects of exposures via breast milk. Most clinical trials in this arena explore the issues of lactation and medications used to treat opioid dependence. The large majority of literature in the area of illicit substance use and lactation consists primarily of case reports. All suffer from small numbers. While any discussion of individual substances of abuse is somewhat artificial in this population of women due to the high prevalence of poly-substance use, individual substances and toxicities related to infant exposures via breast milk are considered below. Estimates of risk for each substance are included, but it is important to note that most are largely author opinion based on a review and synthesis of available literature.

Cocaine:
Both the parent drug and the metabolite are present in milk, and high concentrations are expected due to the chemical nature of cocaine (Bailey, 1998), which can result in significant exposures (Winecker et al., 2001). There is considerable variability in the concentrations of cocaine reported in breast milk, and cocaine is not consistently detected in the breast milk of known users, so analysis of breast milk is not a sensitive method of exposure. For a 4 kg infant feeding every 3 hours, the blood concentration of cocaine can reach 200ng/mL comparable to an adult blood cocaine concentration measured after administration of 1.5 mg/kg intranasal or 16 mg IV dose of cocaine (Winecker et al., 2001). Newborns are particularly sensitive to cocaine because metabolism of cocaine to benzoylecgonine, its principal metabolite, is delayed due to immaturity of the cholinesterase system. Intoxication in the breastfed infant of the intranasal cocaine using mother has been reported (Chasnoff et al., 1987) as has intoxication in an infant whose mother used cocaine for nipple soreness (Chaney et al., 1988). Guidelines have been developed for the lactating cocaine occasionally using woman (Sarkar et al., 2005). A 24-hour period of breastfeeding abstinence has been recommended for women who occasionally use cocaine (Cressman, 2012).

Estimate of risk: Due to the immaturity of the newborn's ability to metabolize cocaine ingested via breast milk, high concentrations are possible, and reported intoxications, risks of lactation in chronically cocaine using, or cocaine dependent, women are significant. It is likely that the risks associated with lactation in heavy or chronic cocaine users outweigh benefit when safe alternatives to breastfeeding are available. In non dependent or intermittent users the risk is lower, and can be further reduced by a 24-hours cessation in breastfeeding (when safe and affordable alternatives to breastfeeding are available).

Methamphetamine:
Methamphetamine undergoes demethylation to amphetamine which is the active metabolite. Amphetamines often contain other substances with unpredictable effects. Amphetamines are concentrated in breast milk and 2.8 to 7.5 times maternal plasma (ACOG, 2011) and infant symptoms, including irritability and agitation (AAP, 2001) and infant death (Ariagno et al., 1995) have been reported. In one study, two women taking street methamphetamine (doses unknown) intravenously had drug levels measures in plasma and breast milk. Calculated infant doses were 16.7 and 42.2 mcg/kg/day of methamphetamine and 0.8 and 2.5 mcg/kg/day of amphetamine (Bartu, et al., 2009), which are less that therapeutic doses of equipotent dextroamphetamine for older children with ADHD.

Estimate of risk: Accurate information regarding the safety of methamphetamine abuse/misuse is unavailable.

Cannabis:
Δ^9-THC is the main compound in cannabis, and it is very fat soluble, and it persists in the body fat of users and can be released over long periods of time depending on extent of use. There are many compounds, most toxic, in Δ^9-THC smoke. It appears that active components of cannabis are excreted into breast milk in small quantities. There is some concern about cannabis' effect of neurotransmitters, CNS development and endo-cannabinoid functions in the infant exposed via breast milk (Fernandez-Ruiz, et.al., 2004; Schuel, et.al.,2002). Δ^9-THC is concentrated to a milk/plasma ratio of 8 in breast milk in heavy users, secreted into breast milk and absorbed and metabolized by the infant (THC metabolites are found in infant feces) (Perez-Reyes & Wall, 1982). In one feeding the infant could ingest 0.8% of the weight adjusted maternal intake of one joint (Bennett, 1997). Cannabis exposure via breast milk in the first month of infant life was associated with decreased motor development, but not growth or intellectual development, at one year (Astley & Little, 1990), and infant effects, such as sedation, growth delay (Hale & Hartman, 2006) low tone and poor sucking (Liston, 1998) have been described. Two studies (Astley & Little, 1990; Tennes, et.al., 1985) found that occasional cannabis use during breastfeeding did not have any discernable effects on breastfed infants. However, because an important phase of brain growth occurs in the period just after birth, THC could theoretically alter brain cell metabolism (Garry et al., 2009) and hence development. Among chronic THC users, 50% report "impaired control over their use", and THC use itself is associated with a wide range of psychiatric conditions (Hall & Degenhardt, 2004), which implies an additional risk to the breastfed infant of the THC using mother.

Estimate of risk: Due to the potentially high concentrations of THC in breast milk of chronic/heavy users and toxicities present in smoke, the potential for altered development in exposed infants, and frequently altered sensorium of heavily using mothers, there is a significant risk. It is likely that the risks associated with lactation in heavy or chronic THC users outweigh benefit when safe alternatives to breastfeeding are available. However,

small amounts of available literature regarding light or occasional use point to little effect on the infant. It may be, in the case of light or infrequent maternal THC use, that the benefits of breast milk/breastfeeding, with appropriate supports for infant care during period of maternal use, may outweigh risk in certain circumstances. In cases of heavy cannabis use the risk is greater and it may be safer not to breastfeed when safe and affordable alternatives are available.

Benzodiazepines:
Benzodiazepines are frequently prescribed to drug dependent women, and also frequently abused/misused. Based on relatively small numbers, adverse event rates of 0–50% have been reported for various agents (17% alprazolam, 22% diazepam, and 50% clonazepam). These events include lethargy, irritability, poor weight gain and apnea. No adverse events have been reported for other agents (oxazepam, lorazepam, or temazepam) (Rubin et al., 2004). When used as an adjunctive medication, there exists the potential for drug-drug interactions and increased risk for CNS depression (for example, the opioid analgesic morphine and anxiolytic diazepam when taken together potentiate CNS depression) but use alone may present minimal risk. In one study among 124 benzodiazepine prescribed women, adverse outcomes, specifically sedation, was reported in 1.6% of infants. Benzodiazepine use in the postpartum period that is prescribed is usually compatible with breastfeeding (Kelly et al., 2012).

Estimate of risk: While it has been found that prescribed benzodiazepine use is usually compatible with lactation, there is no available literature on benzodiazepine abuse/misuse and breastfeeding. Particularly in women who are polydrug dependent, where the potential exists for drug synergy to produce untoward effects in the infant, the risks are significant and it would appear that the risk of lactation in this population would outweigh benefit, when safe alternatives to breastfeeding are available.

Alcohol:
There are many international beliefs that alcohol (particularly beer) intake improves breastfeeding success (Koletzka & Lehner, 2000) and that alcohol will increase milk yield and relax both the mother and the infant (Menella, 2002). Despite these beliefs, the opposite is true. Alcohol blocks the release of oxytocin, resulting in decreased milk yield and milk ejection reflex (Bowen & Tumbach, 2011). Alcohol exposure via breast milk can alter the infant's milk intake by decreased milk production and increased infant sucking, which may be compensatory (Giglia et al., 2006). Animal research has found that alcohol changes the structure of the mammary gland in rats, leading to impaired mammary gland function during the first few days of lactation (Steven et al., 1989). Early cessation of breastfeeding has been associated with a high frequency of alcohol consumption during lactation, even after controlling for confounders (Howard & Lawrence, 1998). Animal models have demonstrated diminished infant growth (Detering et al., 1979; Hekmatpanah et al., 1994; Vilaro et al., 1985). Alcohol enters breast milk by passive diffusion and reflects maternal blood levels within 30-60 minutes after ingestion (Lawton, 1985, Kesaniemi, 1974, Mennella & Beauchamp, 1993); for heavy drinkers, alcohol levels are higher in breast milk than in blood (Lawton et al., 1985). The infant brain is extremely sensitive to alcohol even in small quantities, and the small quantities ingested during lactation are accumulated in the infant because it is metabolized and excreted more slowly than in adults (Little et al., 1989). Alterations in infant sleep-wake cycles (Menella & Gerrish, 1998), development (Little et al., 1990), and infant growth (Backstrand et al., 2004) have been reported. There has been reported a strong inverse linear relationship between chronic exposure of ethanol in breast milk and the psychomotor developmental index on the Bayley Scales of infant development at one year (Little et al., 1989). Alcohol intake by lactating mothers recommended as "safe" for non-lactating women may have a negative effect on infant development and behavior (Giglia et al., 2006). The Institute of Medicine National Academy of Sciences (1991) concluded that alcohol consumption by lactating women in excess of 0.5 g/kg of maternal weight may be harmful to the infant. The American Academy of Pediatrics advises breastfeeding mothers to avoid alcohol consumption in general (AAP, 2005).

Estimate of risk: Lower levels of alcohol use (i.e. 1 standard drink per day) are unlikely to cause significant short or long term problems in the nursing infant, especially if the mother waits 2 to 2.5 hours per drink before nursing, and the risks are likely to be less than not breastfeeding. Daily heavy use of alcohol (i.e. more than 2 drinks per day) may affect infants negatively; alcohol appears to be eliminated from breast milk more slowly and there is a decrease in the length of time that mothers breastfeed their infants, resulting in significant risk. Chronically alcohol dependent women, or women who binge drink heavily represent a high risk to the infant, and breastfeeding is high risk and not recommended.

Opioids:
The first reports of problems with maternal opioid use and nursing were in 1985, when 4 infants became apneic after breastfeeding from mothers prescribed codeine every 4-6 hours (Davis & Bhutan, 1985). For codeine, 39 adverse events and 1 infant death (Koren et al., 2006) have been reported (Hendrickson et al., 2012). Infant toxicities may be related to a duplication of the CYP2D6 gene, causing mothers to be ultra-rapid metabolizers of codeine to morphine, leading to high plasma and milk levels (Madadi et al., 2009). Since there is no tangible method of assessing cytochrome phenotypes, codeine is not advised in nursing mothers. Other opioids may be equally unsafe. Twenty percent of oxycodone using mothers report neonatal CNS depression after breast feedings (Lam, 2012). One toddler death in a methadone misusing opioid naïve breastfeeding mother has been described (West et al., 2009). Heroin transfers into breast milk and is converted to morphine. Morphine, in acceptable doses and used in the short term for pain control, is safe for breastfeeding women (Wittels et al., 1990; Hendrickson et al., 2012), however, heroin using women frequently consume larger (or unknown) doses making this practice dangerous (D'Appolito, 2013).

In general, agents used for the treatment of opioid dependence are likely to be compatible with breastfeeding. Maternal methadone and buprenorphine maintenance in opioid dependent pregnant woman are associated with improved maternal and neonatal outcomes in the context of comprehensive drug treatment and prenatal care. Methadone is distributed into breast milk in low concentrations, there are low ratios of milk to plasma concentrations (~0.4) and calculated theoretic infant doses are low (0.038-0.0152 mg/day) (Jansson et al., 2008; Bogen et al., 2011). Additionally, concentrations in infant plasma at two weeks of age are low (2.2 – 8.1 ng/mL), making breastfeeding among stable and otherwise abstinent methadone maintained women recommended (Jansson et al., 2004) regardless of maternal methadone dose, as dose is unrelated to milk concentrations (Jansson et al., 2008). Reports on buprenorphine exposure via breast milk are somewhat limited. Buprenorphine is excreted into human milk and achieves a level similar to that in maternal plasma (Johnson, 2001). Extant literature finds low concentrations and low calculated theoretic infant doses (Ilett et al., 2012, Lindemalm et al., 2009); in addition this agent is poorly bioavailable, making it likely that breastfeeding should be encouraged in otherwise abstinence, stable buprenorphine maintained women. It is unlikely that either agent, when delivered to the breastfeeding infant from a medically maintained mother, would be present in substantial amounts necessary to prevent or ameliorate neonatal abstinence syndrome. There is a single report of a naltrexone maintained woman with low concentrations of naltrexone in breast milk and low calculated infant dose. Naltrexone is concentrated in breast milk at a milk:plasma ratio of 1.9 (Chan et al., 2004).

Estimate of risk: Opioid dependent women using heroin or misusing prescription opioid containing medications in a way that results in cycles of intoxication and withdrawal are likely to present a significant risk to their breastfed infant, and therefore this practice is discouraged. Prescribed oxycodone for lactating women has also been found to be unsafe. Prescribed morphine for pain control in the postpartum period is low risk and compatible with lactation. Breastfeeding in methadone and buprenorphine maintained and otherwise abstinent women women is low risk should be encouraged if they meet other criteria.

Conclusions

Advising the substance using woman on breastfeeding can present a dilemma to the treating practitioner. A complete and thorough evaluation of the dyad in the perinatal period would consider several factors, including:

- maternal medical and psychiatric status;
- maternal drug use and substance abuse treatment histories and medication requirements;
- maternal family and community support systems;
- maternal plans for postpartum health and psychiatric care, substance abuse treatment and pediatric care;
- access to and capacity to afford breastmilk substitutes, access to clean water and capacity to sterilize feeding equipment.

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Evidence profile 6: Management of infants exposed to alcohol and other psychoactive substances

Evidence question

Does the identification and treatment of neonates with disorders due to alcohol or drug exposure in utero result in better maternal, neonatal or infant outcomes, compared to treatment-as-usual or other forms of treatment of neonatal disorders due to alcohol or drug exposure in utero?

Study selection criteria for the systematic review:

Study design: RCTs

Population: Neonates with disorders due to alcohol or drug exposure in utero such as neonatal substance withdrawal and fetal alcohol syndrome.

Interventions: Systematic methods of identification and treatment of disorders due to alcohol and drug exposure in utero, including medication for neonatal withdrawal.

Control: Treatment-as-usual, non systematic identification, other treatments of disorders due to alcohol or drug exposure in utero.

Outcomes: The following outcomes were of interest:

Outcome	Importance (0–9)
Infant: Death	8.22
Infant: Treatment failure	8.11
Infant: Seizures	8.11
Infant: Total length of hospital stay	7.78
Infant: Weight gain	7.78
Infant: Days to regain birthweight	7.67
Infant: Duration of withdrawal treatment	7.67
Infant: Attachment	6.44
Maternal: Bonding with child	6.44
Infant: Infections	5.89

EVIDENCE TO RECOMMENDATIONS TABLE

Identification and treatment of neonatal disorders due to exposure to alcohol or drugs in utero – including pharmacotherapy (opioids and/or barbiturates) and/or supportive treatment (swaddling, skin to skin care) for neonatal withdrawal

Summary of evidence

- Osborn et al. (2013) conducted a Cochrane review in which they evaluated (1) the contribution of opioids in addition to supportive therapy; (2) opioids compared to phenobarbitone; (3) opioids compared to diazepam; (4) buprenorphine compared to an opium solution; (5) oral morphine compared to tincture of opium in the treatment of neonatal withdrawal/neonatal abstinence syndrome (NWS/NAS). **See accompanying GRADE tables for evaluation of treatment effect against critical outcomes.** The small size and risk of bias in the studies evaluated means the evidence of treatment effect is very uncertain.
- Protocols for the management of NAS have seen significant development over the past 40+ years. Initial NAS treatment guidelines were weight-based, and tables for treatment with phenobarbital and paregoric were published (Finnegan et al., 1975). Current treatment follows similar practices. Either an opioid such as morphine sulfate or tincture of opium, or a sedative, typically phenobarbital, predominate, with infrequent use of a benzodiazepine. A measure of NAS such as the Finnegan scale is typically used to guide treatment initiation, maintenance, and weaning. Because there is neither a uniform assessment method to measure NAS nor an established treatment protocol, and health-care practices and costs worldwide are not uniform, it is difficult to state with any precision how NAS is treated across the globe. Moreover, the availability of opioids as a treatment for NAS varies worldwide, further complicating the ability to make general statements regarding NAS treatment. Patrick and colleagues (Patrick et al., 2012) found that, between 2000 and 2009, per 1,000 hospital live births, prenatal exposure to opioids increased from 1.2 to 5.6 and the incidence of NAS increased from 1.2 to 3.4. Hospital charges for discharges with NAS increased more than 46% during this same 10-year period.
- An opioid probably confers greater benefit than either phenobarbitone or diazepam as first-line pharmacotherapy for NAS (Osborne et al., 2013). Buprenorphine may prove to be an effective alternative front-line pharmacotherapy for NAS (Kraft et al., 2008).Buprenorphine may be superior to methadone in the reduction in NAS severity and time in treatment for NAS [Jones et al. (2005), Fischer et al. (2006), and Jones et al. (2010)].
- Jones et al. (2012a,b) reviewed the comparative efficacy studies of buprenorphine versus methadone. Regardless of whether the study was a randomized controlled trial, prospective study, or case report, there is clear evidence that prenatal buprenorphine exposure is related to NAS, and that such NAS may be less frequent, less severe, and/or of shorter duration. However, conclusions are limited in regard to NAS due to the fact that most studies fail to adequately define and/or measure NAS and/or specify a treatment protocol.
- There is limited experience with opioid antagonists in pregnancy outside of its investigation in Australia (Hulse et al., 2000, 2001, 2003, 2004; Hulse & O'Neil, 2002). Rapid opioid detoxification using sedation followed by naltrexone, as well as oral and implantable formulations of naltrexone, has been investigated. In all cases, there have been no reports of adverse fetal effects, and neonatal birth parameters were within normal limits. However, maternal outcomes were not reported and relapse to maternal opioid use was evident. Neonatal outcomes following prenatal exposure to implanted naltrexone were within normal limits, with some suggestion of a lower risk of prematurity and a higher 1-minute Apgar scores in naltrexone than methadone-exposed neonates. The small samples sizes and limited focus on outcomes suggest caution in the interpretation of the results of these studies; however, findings do not indicate that prenatal naltrexone exposure results in an increased risk for poor neonatal outcomes.
- A rooming-in approach may help reduce the need for NAS pharmacotherapy, NICU admissions, and length of stay for term infants (Abrahams et al., 2007; Abrahams et al., 2010; Hodgson and Abrahams, 2012). Feeding on demand and swaddling may be sufficient to treat mild withdrawal symptoms (Kieviet et al. (2012)).
- Early identification of Fetal Alcohol Syndrome (FAS) is feasible and can increase the uptake of early intervention programmes for children with FAS and their families, enabling children with FAS to reach their full potential (Bertrand, Floyd & Weber, 2005).

EVIDENCE TO RECOMMENDATIONS TABLE

Benefits and harms	
Benefits	• Pregnancy and the immediate postpartum period represents an ideal time for mother-child bonding, an opportunity to develop basic parenting skills. • Considerable research (e.g., Hudak & Tan, 2012) has found pharmacotherapy for NAS yields these benefits: – Less risk of seizures – Less risk of neonatal morbidity and mortality – Improved outcomes (e.g. weight gain, maternal bonding – provided mother and child are allowed to be together) – Possible reduction in congenital anomalies • In non-opioid-agonist maintained postpartum women, immediate and uninterrupted skin-to-skin contact at birth, and rooming-in during the postpartum period is beneficial for establishing maternal-child bonding (Dumas 2013). • Early identification of Fetal Alcohol Syndrome (FAS) can improve the chances that children with FAS will reach their full potential.
Harms	• Risk of adverse neonatal response to pharmacological agent. Buprenorphine may have less adverse impact than methadone on fetal neurobehaviour (Jansson et al., 2012; Salisbury et al., 2012). • Jones et al (2010) found there may be a higher incidence of non-serious maternal adverse events, particularly non-serious maternal cardiovascular events, associated with methadone than buprenorphine. They found no differences in between the two medications for neonatal adverse events. • Early identification of Fetal Alcohol Syndrome (FAS) may stigmatize children and their mothers.
Values and preferences	
In favour: **Mother**	• Value care to support health of baby • Value opportunity to have baby more settled after withdrawal, ultimately easier to look after • Value opportunity to bond with, and learn to care, for baby • Value greater chance of normal neonatal development
Health-care worker	• Value opportunity to intervene in care of compromised neonate • Value opportunity to support mother with bonding, breastfeeding, childcare • Value opportunity to monitor health of fragile neonate
Community	• Value better neonatal outcomes-healthier, developmentally normal children • Partners, family co-workers value chance of healthier, developmentally normal baby
Against: **Mother**	• Stigmatization as person who 'made her baby dependent to drugs or alcohol' • Anxiety about negative responses from partners, family and co-workers • Resent longer hospital stay • Resent interference by hospital staff and other 'authorities'
Health-care worker	• Resent extra time and resources devoted to managing mother and infant with NAS • Negative view of mother's ability to care for child
Community	• Community may have punitive view-may demand incarceration of mother or removal of child • Community may consider extra resources needed to manage mother and child wasteful

EVIDENCE TO RECOMMENDATIONS TABLE

Costs and feasibility	
Feasibility (including economic consequences)	• Inconvenient for women because infant may need an extended stay in the hospital and/or outpatient pharmacotherapy • Potentially substantial additional cost beyond no treatment • Trained professional staff and sustainable programme required • Consistent and frequent monitoring of child • Requires long term patient monitoring to ensure patient continues taking her medication • A comprehensive care model in which pharmacotherapy is part of a women-centred, trauma-informed program would be the best model of care – and also the costliest

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Draft recommendations:

- Infants of all opioid-dependent mothers should be monitored for NAS.
- Hospitals providing obstetrical care should have a protocol in place for identifying, assessing, monitoring and intervening using non-pharmacological and pharmacological methods for neonates prenatally exposed to opioids.
- Pharmacological treatment of infants with NAS due to opioids should be initiated according to a validated NAS treatment protocol.
- Non-pharmacological treatments including low lights, quiet environment, swaddling and skin to skin contact should be used with all prenatally opioid exposed neonates.
- An opioid should be used as initial treatment for infants with NAS symptoms severe enough to need intervention due to opioid withdrawal.
- If there has been concurrent use of other drugs in pregnancy, particularly benzodiazepines, and symptoms of NAS are not adequately suppressed by an opioid alone, phenobarbitone may be indicated as an additional therapy. If opioids are unavailable, phenobarbitone may be used as an alternative therapy.
- If an infant has signs of NAS and reaches the treatment threshold and the drugs used by the mother are unknown, or are sedatives, or the infant was born to a mother intoxicated with alcohol, then phenobarbitone may be a preferable initial treatment.
- Mothers of infants at risk of NAS should receive appropriate breastfeeding information and support, parenting support and assessment, and should be taught settling techniques. Women and their partners/ support persons should also receive information about safe sleeping practices, especially if using sedative substances.

Final recommendations:

RECOMMENDATION 15

Health-care facilities providing obstetric care should have a protocol in place for identifying, assessing, monitoring and intervening, using non pharmacological and pharmacological methods, for neonates prenatally exposed to opioids.

Strength of recommendation: Strong **Quality of evidence: Low**

Remarks:

- Evidence of a dose-response relationship between opioid maintenance treatment and neonatal withdrawal syndrome has been inconsistent, which implies that all infants should be assessed.
- Infants exposed to opioids during pregnancy should remain in the hospital at least 4-7 days following birth and be monitored for neonatal withdrawal symptoms using a validated assessment instrument which should be first administered 2 hours after birth and then every 4 hours thereafter.
- Non- pharmacological interventions including low lights, quiet environments swaddling and skin to skin contact should be used with all neonates prenatally exposed to alcohol and drugs.
- It was decided that the recommendation should be strong despite the low quality of evidence of effect, as the GDG agreed that the benefits of such an approach strongly outweighed any potential harms. The values and preferences of end-users were in favour of the recommendation and there was certainty that while resources would be consumed, the benefits strongly outweighed costs. There was a high value placed on identifying preventable suffering in affected neonates.

RECOMMENDATION 16

An opioid should be used as initial treatment for an infant with neonatal opioid withdrawal syndrome if required.

Strength of recommendation: Strong **Quality of evidence: Very low**

Remarks:

- Prolonged treatment of neonatal opioid withdrawal syndrome with opioids is generally not necessary and aiming for shorter treatment is preferable.
- Phenobarbital can be considered as an additional therapy if there has been concurrent use of other drugs in pregnancy, particularly benzodiazepines, and if symptoms of neonatal opioid withdrawal are not adequately suppressed by an opioid alone. If opioids are unavailable, phenobarbital can be used as an alternative therapy.
- Infants with signs of a neonatal withdrawal syndrome in the absence of known maternal opioid use should be fully assessed for possible benzodiazepine, sedative, or alcohol exposure.
- The strong recommendation to use opioids rather than phenobarbital despite the very low quality of evidence of effectiveness was based on vast clinical experience with opioids in the management of both adult and neonatal opioid withdrawal. There has only been very limited clinical experience with phenobarbital use. In addition, the values and preferences of end-users were in favour of the recommendation and the GDG agreed that there was certainty about the balance between benefits and resources being consumed.

RECOMMENDATION 17

If an infant has signs of a neonatal withdrawal syndrome due to withdrawal from sedatives, or alcohol, or the substance the infant was exposed to is unknown, then phenobarbital may be a preferable initial treatment option.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- Infants with signs of a neonatal withdrawal syndrome in the absence of known maternal opioid use should be fully assessed for possible benzodiazepine, sedative, or alcohol exposure.
- This recommendation was considered conditional because of the lack of high quality evidence and the lack of certainty of the balance between benefits and harms.

RECOMMENDATION 18

All infants born to women with alcohol use disorders should be assessed for signs of fetal alcohol syndrome.

Strength of recommendation: Conditional **Quality of evidence: Very low**

Remarks:

- Signs of fetal alcohol syndrome (FAS) include growth impairment, dysmorphic facial features (short palpebral fissures, smooth or flattened philtrum, thin upper lip) and central nervous system abnormalities, including microcephaly.
- When assessing such infants the following information should be recorded:
  - birthweight and length
  - head circumference
  - dysmorphic facial features
  - gestation
  - prenatal exposure to alcohol
  - follow-up of infants with signs of FAS should be provided
- This recommendation was considered conditional because of the lack of high quality evidence, and questions about the faesibility of implementation in all settings.

Factors in considering the strength of the recommendations (recommendations 15–18):

Factor	15 & 16	17	18
Is there high or moderate quality evidence? The higher the quality of evidence, the more likely is a strong recommendation.	**No**	**No**	**No**
Is there certainty about the balance of benefits versus harms and burdens? In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms? In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?	**Yes**	**No**	**Yes**
Are the expected values and preferences clearly in favour of the recommendation?	**Yes**	**No**	**Yes**
Is there certainty about the balance between benefits and resources being consumed? In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed? In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?	**Yes**	**Yes**	**No**

Summary of findings and GRADE tables

OPIATES AND SUPPORTIVE THERAPY COMPARED TO SUPPORTIVE THERAPY FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants

Settings: Hospital

Intervention: Opioid and supportive therapy

Comparison: Supportive therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Supportive therapy	**Opioid and supportive therapy**				
Death	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure Finnegan score	**118 per 1000**	**152 per 1000** (48 to 479)	**RR 1.29** (0.41 to 4.07)	80 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	Supportive treatment included pacifier, swaddling, close wrapping, small frequent feeds, and close skin contact by sling or other methods.
Seizures	See comment	See comment	Not estimable	—	See comment	Not reported
Total length of hospital stay Days in hospital		The mean total length of hospital stay in the intervention groups was **15 higher** (8.86 to 21.14 higher)		80 (1 study)	⊕◯◯◯ VERY LOW[1,2,4]	
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight		The mean days to regain birthweight in the intervention groups was **2.8 lower** (5.33 to 0.27 lower)		72 (1 study)	⊕◯◯◯ VERY LOW[1,2,5]	
Duration of treatment for NAS Days		The mean duration of treatment for nas in the intervention groups was **12.5 higher** (7.52 to 17.48 higher)	Not estimable	80 (1 study)	⊕◯◯◯ VERY LOW[1,2,4]	

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] This is reported as a quasi-randomized trial which allocated participants to groups using the last number of the participant's hospital number. Both random generation and allocation concealment were judged to be inadequate and there is thus a high risk of selection bias. There was no blinding of providers or parents so performance bias may be present. Blinding was unreported for short-term outcomes and the risk of detection bias is unclear. Long-term outcomes were not measured.
[2] Not applicable as results are from one study only.
[3] The sample size is small and the event rate is extremely low so imprecision is highly likely in the results.
[4] The sample size is small and the confidence interval is very wide.
[5] The sample size is small and the confidence interval is wide.

OPIATES COMPARED TO PHENOBARBITONE FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants
Settings: Hospital
Intervention: Opioid
Comparison: Phenobarbitone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Phenobarbitone	**Opiates**				
Death – not reported	See comment	See comment	Not estimable	—	See comment	
Treatment failure See footnote [1]	**279 per 1000**	**212 per 1000** (142 to 309)	**RR 0.76** (0.51 to 1.11)	302 (4 studies)	⊕⊕◯◯ LOW[2,3,4]	The meta-analysis included both randomized (RCT) and quasi-randomized controlled trials. GRADE assessment was done within the RCT study design.
Seizures	**113 per 1000**	**9 per 1000** (0 to 163)	**RR 0.08** (0 to 1.44)	111 (1 study)	⊕⊕◯◯ LOW[5,6,7]	As this was a RCT, the GRADE assessment was done within the RCT study design category.
Total length of hospital stay Days in hospital		The mean total length of hospital stay in the intervention groups was **2.54 lower** (7.06 lower to 1.98 higher)		106 (2 studies)	⊕◯◯◯ VERY LOW[8,9]	As this was a meta-analysis of two quasi-trials, the GRADE assessment was done within the observational study design category.
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight		The mean days to regain birthweight in the intervention groups was **1.4 lower** (3.47 lower to 0.67 higher)		71 (1 study)	⊕◯◯◯ VERY LOW[10,11]	As this was a quasi-trial, the GRADE assessment was done within the observational study design category.
Duration of treatment for NAS Days		The mean duration of treatment for nas in the intervention groups was **3.73 lower** (7.75 lower to 0.29 higher)		106 (2 studies)	⊕◯◯◯ VERY LOW[8,9]	As this was a meta-analysis of two quasi-trials, the GRADE assessment was done within the observational study design category.

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] Treatment failure defined by review as failure to reduce a standardised score of NAS from a clinically significant level to a clinically 'safe' level defined by author of the trial, or the use of additional pharmacological treatments for control of NAS.
[2] The meta-analysis combines results from two randomized controlled trials (Jackson 2004 and Madden 1977) and two quasi-randomized trials (Finnegan 1984 and Khoo 1995). Random generation and allocation concealment were lacking in three of the four studies and there is thus a risk of selection bias. Blinding of participants and providers was only performed in one study so performance and measurement bias may be present in the other studies. In Jackson 2004, infants randomly allocated to phenobarbitone tended to have been exposed to benzodiazepines and other classes of drugs compared with those randomized to morphine.
[3] Statistical heterogeneity was not present (I squared = 0%). Some clinical heterogeneity may be present as drug types and doses differed but it was not downgraded for unexplained inconsistency. The opiates and dosages used in the four studies were: Finnegan 1984 - Paregoric, dose not reported; Jackson 2004 - Morphine 50 microg/kg/dose four times a day with no titration; Khoo 1995 - Morphine 0.5mg/kg/day in 4–6 divided doses, titrated up to maximum 0.9mg/kg/day; Madden 1977 - Methadone 0.25mg 6 hourly increased every 6 hours to maximum 0.5mg 6 hourly
[4] The combined sample size is 302. The event rate is very low. Although the confidence interval is narrow, according to GRADE criteria for dichotomous data, event rates less than 300 are downgraded for imprecision.
[5] This RCT (Kandall 1983) was judged to be at unclear risk of selection bias as no method of random generation was reported. The randomized groups were very imbalanced (49 vs 62), increasing the likelihood of selection bias. Detection and performance bias may be present as no blinding was reported. Attrition was not reported and the risk of selective reporting was unclear.
[6] Not applicable as results are from one trial only.
[7] The sample size is small, the event rate very low (zero events in the opioid group) and the confidence interval is wide.
[8] The two studies (Khoo 1995 and Madden 1977) included in this meta-analysis are quasi-randomized trials. There is a high risk of selection bias as random generation and allocation concealment were inadequate. Blinding was not reported and there is thus an unclear risk of detection and performance bias. Both studies accounted for incomplete outcome data and attrition bias is thus a low risk. Selective reporting bias was unclear.
[9] The sample size is small and the confidence interval is very wide.
[10] This quasi-RCT (Khoo 1995) is at high risk of selection bias as random generation (use of last number of the participant's hospital number) and allocation concealment were judged to be inadequate. Blinding was not reported and performance and detection bias may be present.
[11] The sample size is small and the confidence interval is wide.

OPIOID COMPARED TO DIAZEPAM FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants
Settings: Hospital
Intervention: Opioid
Comparison: Diazepam

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Diazepam	**Opioid**				
Death	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure See footnote [1]	**389 per 1000**	**167 per 1000** (89 to 311)	**RR 0.43** (0.23 to 0.8)	86 (2 studies)	⊕◯◯◯ VERY LOW[2,3,4]	The meta-analysis included one quasi-trial (Finnegan 1984) and one RCT (Madden 1977). GRADE assessment was done within the RCT study design category.
Seizures	See comment	See comment	Not estimable	—	See comment	Not reported
Total length of hospital stay Days in hospital		The mean total length of hospital stay in the intervention groups was **2.33 higher** (1.79 lower to 6.45 higher)		33 (1 study)	⊕◯◯◯ VERY LOW[5,6,7]	Madden 1977 is an RCT and GRADE assessment was done within the RCT study design category.
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment for NAS Days		The mean duration of treatment for nas in the intervention groups was **1.56 higher** (1.59 lower to 4.71 higher)		33 (1 study)	⊕◯◯◯ VERY LOW[5,6,7]	Madden 1977 is an RCT and GRADE assessment was done within the RCT study design category.

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] Treatment failure defined by review as failure to reduce a standardised score of NAS from a clinically significant level to a clinically 'safe' level defined by author of the trial, or the use of additional pharmacological treatments for control of NAS.
[2] The risk of selection bias is high for the quasi-trial (Finnegan 1988) as random generation and allocation concealment were judged as inadequate. No method was reported in the Madden 1977 RCT. Blinding was lacking or unclear and performance and detection bias may be present. Both studies accounted for incomplete outcomes so attrition bias is a low risk.
[3] The meta-analysis reported here was conducted using a fixed effects model and a RR = 0.43 (95%CI: 0.23, 0.80) with Finnegan 1984 showing a statistically significant benefit of opiates over diazepam and Madden 1977 showing a benefit of diazepam over opiates. Clinical heterogeneity may explain this result as Finnegan compared Paregoric with diazepam and Madden compared methadone with diazepam. In this situation when heterogeneity is present, a random effects model is more appropriate. This would change the RR = 0.55 (95% CI: 0.10, 2.89) and is no longer statistically significant. The relatively large difference in results following sensitivity analyses reduces the robustness of the results. The assessment is downgraded for unexplained inconsistency.
[4] The sample size is very small with very few events.
[5] This RCT (Madden 1977) was judged to be at unclear risk of selection bias as no random generation or allocation concealment was reported. Blinding was not reported for the trial so performance and detection bias may be present. Incomplete outcome data was addressed so attrition bias was minimal.
[6] Not applicable as only one study included.
[7] The sample size is very small and the confidence interval is wide.

SUBLINGUAL BUPRENORPHINE COMPARED TO NEONATAL OPIUM SOLUTION FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants
Settings: Hospital
Intervention: Sublingual Buprenorphine
Comparison: Neonatal Opium Solution

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Neonatal Opium Solution	**Sublingual Buprenorphine**				
Death	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure Need for adjunctive treatment	**77 per 1000**	**308 per 1000** (39 to 1000)	**RR 4** (0.51 to 31.13)	26 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	Primary aim of this RCT was safety, tolerability and feasibility. Efficacy was a secondary goal. The report acknowledges that the RCT was not powered for this.
Seizures	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 3** (0.13 to 67.51)	26 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	One infant developed generalised seizures in the Buprenorphine group.
Total length of hospital stay Days		The mean total length of hospital stay in the intervention groups was **11 lower** (21.69 to 0.31 lower)		25 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment for NAS		The mean duration of treatment for nas in the intervention groups was **10 lower** (20.69 lower to 0.69 higher)		25 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] This RCT (Kraft 2009) was judged to be at low risk of selection bias. Random generation and allocation concealment were adequate as the sequence was generated centrally by the Hospital Investigational Drug Service. The study was not blinded and detection and performance bias may be present. All outcomes were accounted for and attrition bias was judged to be low. Selective outcome reporting was not present.
[2] Not applicable as only one study.
[3] The sample size is very small with very few events and the confidence interval is very wide.

MORPHINE COMPARED TO TINCTURE OF OPIUM (TO) FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants
Settings: Hospital
Intervention: Morphine
Comparison: Tincture of Opium (TO)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Tincture of Opium (TO)	**Morphine**				
Death	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure Mean Finnegan score: proxy measure for treatment failure	See comment	See comment		33 (1 study)	⊕◯◯◯ VERY LOW[1,2,3,4]	Mean maximum Finnegan score values for each group: Morphine: 15.4g and Tincture: 15.5g. No SD reported.
Seizures	See comment	See comment	Not estimable	—	See comment	Not reported
Total length of hospital stay Days in hospital	See comment	See comment		33 (1 study)	⊕⊕◯◯ LOW[1,2,4]	The mean duration of hospitalization in the Morphine = 37.5 days; range: 20-66) and in the Tincture of Opium group = 32.4 days; range: 17-55). Not significant.
Infant weight gain	See comment	See comment		33 (1 study)	⊕⊕◯◯ LOW[1,5]	Mean weight gain per day in the Morphine group = 18.9g and in Tincture of Opium = 24.9g (p = 0.24; 95% CI of mean difference: 15.9g, -4.1g).
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment for NAS Skewed data	See comment	See comment		0 (1 study)	⊕⊕◯◯ LOW[1,4]	The mean duration of treatment for NAS in the morphine group = 29.8 days; range: 10- 62; in the TO Opium group (26.9 days; range: 8- 51). Not significant.

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] This RCT (Langefeld 2005) was well-conducted with adequate random generation and allocation concealment, blinding (solutions identical in appearance and flasks were only identified with a number and name of the newborn) and no attrition nor selection reporting.
[2] Not applicable as only one study included.
[3] The report did not provide details of treatment failure, but reported mean maximum Finnegan score values for each group: Morphine: 15.4g and Tincture: 15.5g. No SD reported.
[4] The mean and ranges were reported, not standard deviations or a confidence interval of the difference. Based on the sample size being very small and the wide ranges, the results are judged to be very imprecise.
[5] The sample size is very small. As no variance estimates are reported for means, it is not possible to calculate the mean difference nor the variance. The mean weight gain per day is reported for each group, but not for the mean difference between the groups. However, a 95% confidence interval for the mean difference in weight gain per day between the groups (15.9; -4.1g) is reported.

SPECIFIC OPIOID COMPARED TO SPECIFIC SEDATIVE FOR TREATMENT FAILURE IN OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants

Settings: Hospital

Intervention: Specific opioid

Comparison: Specific sedative

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Specific sedative	Specific opioid				
Treatment failure – Paregoric versus phenobarbitone	**317 per 1000**	**174 per 1000** (95 to 320)	**RR 0.55** (0.3 to 1.01)	178 (2 studies)	⊕◯◯◯ VERY LOW[1,2,3]	
Treatment failure – Methadone versus phenobarbitone	**62 per 1000**	**56 per 1000** (4 to 817)	**RR 0.89** (0.06 to 13.08)	34 (1 study)	⊕◯◯◯ VERY LOW[4,5,6]	
Treatment failure – Morphine versus phenobarbitone	**403 per 1000**	**254 per 1000** (157 to 403)	**RR 0.63** (0.39 to 1)	149 (2 studies)	⊕⊕◯◯ LOW[3,7,8]	
Treatment failure – Paregoric versus diazepam	**800 per 1000**	**192 per 1000** (112 to 344)	**RR 0.24** (0.14 to 0.43)	85 (2 studies)	⊕◯◯◯ VERY LOW[1,9,10]	
Treatment failure – Methadone versus diazepam	**62 per 1000**	**0 per 1000** (0 to 0)	**RR 2.68** (0.12 to 61.58)	34 (1 study)	⊕◯◯◯ VERY LOW[4,5,6]	

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] This meta-analysis combined two quasi-trials (Finnegan 1984 and Kaltenbach 1986). It was unclear whether some of the infants reported in the study were also included in Finnegan 1984, and there is a risk of double-counting the participants. The studies allocated groups from envelopes designated according to the first letter of the last name. Allocation concealment was judged to be inadequate and selection bias may is a high risk. Blinding was not clearly reported for short-term outcomes but it is unlikely as the treatment regimens were different so there is a high risk of performance and detection bias. Selective reporting of outcomes was unclear and could not be judged.

[2] Statistical heterogeneity is present (I squared = 85%). The studies were similar but doses are not reported except for Phenobarbitone in Finnegan 1984), so the heterogeneity is unexplained. This was downgraded for unexplained inconsistency.

[3] The sample size is small and the event rate is low and the confidence interval is wide.

[4] No method of random generation was reported in the Madden 1977 RCT and allocation concealment was unlikely. There is a high risk of selection bias. Blinding was not reported performance and detection bias may be present. The study accounted for incomplete outcomes so attrition bias is a low risk.

[5] Not applicable as only one trial.

[6] The sample size is very small, the event rate is very low and the confidence interval is very wide.

[7] This meta-analysis combines a quasi-RCT (Khoo 1995) and a RCT (Jackson 2004). In Khoo 1995 there is a high risk of selection bias as random generation (use of last number of the participant's hospital number) and allocation concealment were judged to be inadequate. Blinding was not performed for treatment and not reported for assessment so performance and detection bias may be present. Jackson 2004 was well-conducted and at low risk of selection, performance and detection bias. However, the GRADE assessment is done according to the lower quality of evidence so the analysis is downgraded for bias.

[8] Statistical heterogeneity is not present and there did not appear to be unexplained clinical heterogeneity.

[9] There is statistical heterogeneity (I squared = 67%). The studies were similar but doses are not reported so the heterogeneity is unexplained. This was downgraded for unexplained inconsistency.

[10] Although the confidence interval is narrow, it was downgraded for imprecision due to the small sample size and low event rate.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD OPIOIDS AND SUPPORTIVE THERAPY VS SUPPORTIVE THERAPY BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opiates and supportive therapy	Supportive therapy	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: Finnegan score)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	7/46 (15.2%)	4/34 (11.8%)	RR 1.29 (0.41 to 4.07)	34 more per 1000 (from 69 fewer to 361 more)	⊕◯◯◯ VERY LOW	CRITICAL
Seizures – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Total length of hospital stay (measured with: Days in hospital; better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[4]	none	46	34	—	MD 15 higher (8.86 to 21.14 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight (better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[5]	none	44	28	—	MD 2.8 lower (5.33 to 0.27 lower)	⊕◯◯◯ VERY LOW	

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opiates and supportive therapy	Supportive therapy	Relative (95% CI)	Absolute		
Duration of treatment for NAS (measured with: Days; better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[4]	none	46	34	—	MD 12.5 higher (7.52 to 17.48 higher)	⊕◯◯◯ VERY LOW	CRITICAL

[1] This is reported as a quasi-randomized trial which allocated participants to groups using the last number of the participant's hospital number. Both random generation and allocation concealment were judged to be inadequate and there is thus a high risk of selection bias. There was no blinding of providers or parents so performance bias may be present. Blinding was unreported for short-term outcomes and the risk of detection bias is unclear. Long-term outcomes were not measured.
[2] Not applicable as results are from one study only.
[3] The sample size is small and the event rate is extremely low so imprecision is highly likely in the results.
[4] The sample size is small and the confidence interval is very wide.
[5] The sample size is small and the confidence interval is wide.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD OPIOIDS VS PHENOBARBITONE BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opiates	Phenobarbitone	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: See footnote [1])												
4	randomized trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	30/137 (21.9%)	46/165 (27.9%)	RR 0.76 (0.51 to 1.11)	67 fewer per 1000 (from 137 fewer to 31 more)	⊕⊕◯◯ LOW	CRITICAL
Seizures												
1	randomized trials	serious[5]	no serious inconsistency[6]	no serious indirectness	serious[7]	none	0/49 (0%)	7/62 (11.3%)	RR 0.08 (0 to 1.44)	104 fewer per 1000 (from 113 fewer to 50 more)	⊕⊕◯◯ LOW	CRITICAL
Total length of hospital stay (measured with: Days in hospital; better indicated by lower values)												
2	observational studies	serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	63	43	—	MD 2.54 lower (7.06 lower to 1.98 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight (better indicated by lower values)												
1	observational studies	serious[10]	no serious inconsistency	no serious indirectness	serious[11]	none	44	27	—	MD 1.4 lower (3.47 lower to 0.67 higher)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Opiates	Phenobarbitone	Relative (95% CI)	Absolute		
Duration of treatment for NAS (measured with: Days; better indicated by lower values)												
2	observational studies	serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	63	43	—	MD 3.73 lower (7.75 lower to 0.29 higher)	⊕◯◯◯ VERY LOW	CRITICAL

[1] Treatment failure defined by review as failure to reduce a standardised score of NAS from a clinically significant level to a clinically 'safe' level defined by author of the trial, or the use of additional pharmacological treatments for control of NAS.
[2] The meta-analysis combines results from two randomized controlled trials (Jackson 2004 and Madden 1977) and two quasi-randomized trials (Finnegan 1984 and Khoo 1995). Random generation and allocation concealment were lacking in three of the four studies and there is thus a risk of selection bias. Blinding of participants and providers was only performed in one study so performance and measurement bias may be present in the other studies. In Jackson 2004, infants randomly allocated to phenobarbitone tended to have been exposed to benzodiazepines and other classes of drugs compared with those randomized to morphine.
[3] Statistical heterogeneity was not present (I squared = 0%). Some clinical heterogeneity may be present as drug types and doses differed but it was not downgraded for unexplained inconsistency. The opiates and dosages used in the four studies were: Finnegan 1984 - Paregoric, dose not reported; Jackson 2004 - Morphine 50 microg/kg/dose four times a day with no titration; Khoo 1995 - Morphine 0.5mg/kg/day in 4 - 6 divided doses, titrated up to maximum 0.9mg/kg/day; Madden 1977 - Methadone 0.25mg 6 hourly increased every 6 hours to maximum 0.5mg 6 hourly
[4] The combined sample size is 302. The event rate is very low. Although the confidence interval is narrow, according to GRADE criteria for dichotomous data, event rates less than 300 are downgraded for imprecision.
[5] This RCT (Kandall 1983) was judged to be at unclear risk of selection bias as no method of random generation was reported. The randomized groups were very imbalanced (49 vs 62), increasing the likelihood of selection bias. Detection and performance bias may be present as no blinding was reported. Attrition was not reported and the risk of selective reporting was unclear.
[6] Not applicable as results are from one trial only.
[7] The sample size is small, the event rate very low (zero events in the opioid group) and the confidence interval is wide.
[8] The two studies (Khoo 1995 and Madden 1977) included in this meta-analysis are quasi-randomized trials. There is a high risk of selection bias as random generation and allocation concealment were inadequate. Blinding was not reported and there is thus an unclear risk of detection and performance bias. Both studies accounted for incomplete outcome data and attrition bias is thus a low risk. Selective reporting bias was unclear.
[9] The sample size is small and the confidence interval is very wide.
[10] This quasi-RCT (Khoo 1995) is at high risk of selection bias as random generation (use of last number of the participant's hospital number) and allocation concealment were judged to be inadequate. Blinding was not reported and performance and detection bias may be present.
[11] The sample size is small and the confidence interval is wide.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD OPIOID VS DIAZEPAM BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	opioid	Diazepam	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: See footnote [1])												
2	randomized trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	9/50 (18%)	14/36 (38.9%)	RR 0.43 (0.23 to 0.8)	222 fewer per 1000 (from 78 fewer to 299 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Seizures – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Total length of hospital stay (measured with: Days in hospital; better indicated by lower values)												
1	randomized trials	serious[5]	no serious inconsistency[6]	no serious indirectness	very serious[7]	none	17	16	—	MD 2.33 higher (1.79 lower to 6.45 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Duration of treatment for NAS (measured with: Days; better indicated by lower values)												
1	randomized trials	serious[5]	no serious inconsistency[6]	no serious indirectness	very serious[7]	none	17	16	—	MD 1.56 higher (1.59 lower to 4.71 higher)	⊕◯◯◯ VERY LOW	CRITICAL

[1] Treatment failure defined by review as failure to reduce a standardised score of NAS from a clinically significant level to a clinically 'safe' level defined by author of the trial, or the use of additional pharmacological treatments for control of NAS.
[2] The risk of selection bias is high for the quasi-trial (Finnegan 1988) as random generation and allocation concealment were judged as inadequate. No method was reported in the Madden 1977 RCT. Blinding was lacking or unclear and performance and detection bias may be present. Both studies accounted for incomplete outcomes so attrition bias is a low risk.
[3] The meta-analysis reported here was conducted using a fixed effects model and a RR = 0.43 (95%CI: 0.23, 0.80) with Finnegan 1984 showing a statistically significant benefit of opiates over diazepam and Madden 1977 showing a benefit of diazepam over opiates. Clinical heterogeneity may explain this result as Finnegan compared Paregoric with diazepam and Madden compared methadone with diazepam. In this situation when heterogeneity is present, a random effects model is more appropriate. This would change the RR = 0.55 (95% CI: 0.10, 2.89) and is no longer statistically significant. The relatively large difference in results following sensitivity analyses reduces the robustness of the results. The assessment is downgraded for unexplained inconsistency.
[4] The sample size is very small with very few events.
[5] This RCT (Madden 1977) was judged to be at unclear risk of selection bias as no random generation or allocation concealment was reported. Blinding was not reported for the trial so performance and detection bias may be present. Incomplete outcome data was addressed so attrition bias was minimal.
[6] Not applicable as only one study included.
[7] The sample size is very small and the confidence interval is wide.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD SUBLINGUAL BUPRENORPHINE VS NEONATAL OPIUM SOLUTION BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual Buprenorphine	Neonatal Opium Solution	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: Need for adjunctive treatment)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	4/13 (30.8%)	1/13 (7.7%)	RR 4 (0.51 to 31.13)	231 more per 1000 (from 38 fewer to 1000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Seizure												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	1/13 (7.7%)	0/13 (0%)	RR 3 (0.13 to 67.51)	—	⊕◯◯◯ VERY LOW	CRITICAL
Total length of hospital stay (measured with: Days in hospital; better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	12	13	—	MD 11 lower (21.69 to 0.31 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual Buprenorphine	Neonatal Opium Solution	Relative (95% CI)	Absolute		
Duration of treatment for NAS (better indicated by lower values)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	12	13	—	MD 10 lower (20.69 lower to 0.69 higher)	⨁◯◯◯ VERY LOW	CRITICAL

[1] This RCT (Kraft 2009) was judged to be at low risk of selection bias. Random generation and allocation concealment were adequate as the sequence was generated centrally by the Hospital Investigational Drug Service. The study was not blinded and detection and performance bias may be present. All outcomes were accounted for and attrition bias was judged to be low. Selective outcome reporting was not present.
[2] Not applicable as only one study.
[3] The sample size is very small with very few events and the confidence interval is very wide.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD MORPHINE VS TINCTURE OF OPIUM (TO) BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Tincture of Opium (TO)	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (measured with: Mean Finnegan score: proxy measure for treatment failure; Better indicated by lower values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency[2]	serious[3]	very serious[4]	none	17	16	—	Area under the curve 0 higher (0 to 0 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Seizure – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Total length of hospital stay (measured with: Days in hospital; better indicated by lower values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness	very serious[4]	none	17	16	—	MD 0 higher (0 to 0 higher)	⊕⊕◯◯ LOW	CRITICAL
Infant weight gain (better indicated by higher values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	17	16	—	MD 0 higher (0 to 0 higher)	⊕⊕◯◯ LOW	CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Duration of treatment for NAS (measured with: Skewed data; better indicated by lower values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0	—	—	MD 0 higher (0 to 0 higher)	⊕⊕◯◯ LOW	CRITICAL

[1] This RCT (Langefeld 2005) was well-conducted with adequate random generation and allocation concealment, blinding (solutions identical in appearance and flasks were only identified with a number and name of the newborn) and no attrition nor selection reporting.
[2] Not applicable as only one study included.
[3] The report did not provide details of treatment failure, but reported mean maximum Finnegan score values for each group: Morphine: 15.4g and Tincture: 15.5g. No SD reported.
[4] The mean and ranges were reported, not standard deviations or a confidence interval of the difference. Based on the sample size being very small and the wide ranges, the results are judged to be very imprecise.
[5] The sample size is very small. As no variance estimates are reported for means, it is not possible to calculate the mean difference nor the variance. The mean weight gain per day is reported for each group, but not for the mean difference between the groups. However, a 95% confidence interval for the mean difference in weight gain per day between the groups (15.9; -4.1g) is reported.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD SPECIFIC OPIOID VS SPECIFIC SEDATIVE BE USED TO REDUCE TREATMENT FAILURE IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Specific opioid	Specific sedative	Relative (95% CI)	Absolute	Quality	Importance
Treatment failure – paregoric versus phenobarbitone												
2	observational studies	very serious[1]	serious[2]	no serious indirectness	serious[1,3]	none	10/55 (18.2%)	39/123 (31.7%)	RR 0.55 (0.3 to 1.01)	143 fewer per 1000 (from 222 fewer to 3 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment failure – methadone versus phenobarbitone												
1	randomized trials	serious[4]	no serious inconsistency[5]	no serious indirectness	very serious[6]	none	1/18 (5.6%)	1/16 (6.3%)	RR 0.89 (0.06 to 13.08)	7 fewer per 1000 (from 59 fewer to 755 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment failure – morphine versus phenobarbitone												
2	randomized trials	serious[7]	no serious inconsistency[8]	no serious indirectness	serious[3]	none	21/87 (24.1%)	25/62 (40.3%)	RR 0.63 (0.39 to 1)	149 fewer per 1000 (from 246 fewer to 0 more)	⊕⊕◯◯ LOW	CRITICAL
Treatment failure – paregoric versus diazepam												
2	randomized trials	very serious[1]	serious[9]	no serious indirectness	serious[10]	none	10/55 (18.2%)	24/30 (80%)	RR 0.24 (0.14 to 0.43)	608 fewer per 1000 (from 456 fewer to 688 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment failure – methadone versus diazepam												
1	randomized trials	serious[4]	no serious inconsistency[5]	no serious indirectness	very serious[6]	none	1/18 (5.6%)	0/16 (0%)	RR 2.68 (0.12 to 61.58)	—	⊕◯◯◯ VERY LOW	CRITICAL

[1] This meta-analysis combined two quasi-trials (Finnegan 1984 and Kaltenbach 1986). It was unclear whether some of the infants reported in the study were also included in Finnegan 1984, and there is a risk of double-counting the participants. The studies allocated groups from envelopes designated according to the first letter of the last name. Allocation concealment was judged to be inadequate and selection bias may is a high risk. Blinding was not clearly reported for short-term outcomes but it is unlikely as the treatment regimens were different so there is a high risk of performance and detection bias. Selective reporting of outcomes was unclear and could not be judged.

[2] Statistical heterogeneity is present (I squared = 85%). The studies were similar but doses are not reported except for Phenobarbitone in Finnegan 1984), so the heterogeneity is unexplained. This was downgraded for unexplained inconsistency.

[3] The sample size is small and the event rate is low and the confidence interval is wide.

[4] No method of random generation was reported in the Madden 1977 RCT and allocation concealment was unlikely. There is a high risk of selection bias. Blinding was not reported performance and detection bias may be present. The study accounted for incomplete outcomes so attrition bias is a low risk.

[5] Not applicable as only one trial.

[6] The sample size is very small, the event rate is very low and the confidence interval is very wide.

[7] This meta-analysis combines a quasi-RCT (Khoo 1995) and a RCT (Jackson 2004). In Khoo 1995 there is a high risk of selection bias as random generation (use of last number of the participant's hospital number) and allocation concealment were judged to be inadequate. Blinding was not performed for treatment and not reported for assessment so performance and detection bias may be present. Jackson 2004 was well-conducted and at low risk of selection, performance and detection bias. However, the GRADE assessment is done according to the lower quality of evidence so the analysis is downgraded for bias.

[8] Statistical heterogeneity is not present and there did not appear to be unexplained clinical heterogeneity.

[9] There is statistical heterogeneity (I squared = 67%). The studies were similar but doses are not reported so the heterogeneity is unexplained. This was downgraded for unexplained inconsistency.

[10] Although the confidence interval is narrow, it was downgraded for imprecision due to the small sample size and low event rate.

PHENOBARBITONE COMPARED TO SUPPORTIVE CARE FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants
Settings: Hospital
Intervention: Phenobarbitone
Comparison: Supportive care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Supportive care	**Phenobarbitone**				
Death	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure Failure to settle measured with Finnegan score	**118 per 1000**	**321 per 1000** (111 to 934)	**RR 2.73** (0.94 to 7.94)	62 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	
Seizures	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment (days)		The mean duration of treatment (days) in the intervention groups was **17.9 higher** (11.98 to 23.82 higher)		62 (1 study)	⊕◯◯◯ VERY LOW[1,2,4]	
Total length of hospital stay Days in hospital		The mean total length of hospital stay in the intervention groups was **20.8 higher** (13.64 to 27.96 higher)		62 (1 study)	⊕◯◯◯ VERY LOW[1,2,4]	GRADE does not allow for upgrading for large effect sizes unless there are no threats to validity (not downgraded for any other reason).
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight		The mean days to regain birthweight in the intervention groups was **1.4 lower** (4.07 lower to 1.27 higher)		55 (1 study)	⊕◯◯◯ VERY LOW[1,2,5]	Measurements were available for 55 of the 62 study participants.
Duration of treatment for NAS	See comment	See comment	Not estimable	—	See comment	Not reported

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] This quasi-randomized trial (Khoo 1995) allocated participants to groups using the last number of the participant's hospital number. Both random generation and allocation concealment were judged to be inadequate and there is thus a high risk of selection bias. The group numbers are also not balanced (29 vs 36). There was no blinding of providers or parents so performance bias may be present. Blinding was unreported for short-term outcomes and the risk of detection bias is unclear.
[2] Not applicable as only one study is included.
[3] The sample size is very small and the event rate is very low so imprecision is likely in these results.
[4] The sample size is small and the confidence interval is wide. Notwithstanding the very large difference in means and the highly statistically significant finding, the lack of information about the primary outcome and power of the trial reduces our confidence in this estimate.
[5] The sample size is small. The primary outcome is not clearly defined and it is therefore not possible to determine the power of the study for this outcome: time to regain birthweight. In the light of this uncertainty, the GRADE criteria recommend that a sample size of less than 400 for continuous outcomes be downgraded for imprecision.

PHENOBARBITONE COMPARED TO DIAZEPAM FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants
Settings: Hospital
Intervention: Phenobarbitone
Comparison: Diazepam

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Diazepam	**Phenobarbitone**				
Death – not reported	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure	**389 per 1000**	**152 per 1000** (93 to 241)	**RR 0.39** (0.24 to 0.62)	139 (2 studies)	⊕◯◯◯ VERY LOW[1,2,3]	The meta-analysis included one quasi-trial (Finnegan 1984) and one RCT (Madden 1977). GRADE assessment was done within the RCT study design category.
Seizures	See comment	See comment	Not estimable	—	See comment	Not reported
Total length of hospital stay Days		The mean total length of hospital stay in the intervention groups was **3.07 higher** (2.02 lower to 8.16 higher)		31 (1 study)	⊕◯◯◯ VERY LOW[4,5,6]	Madden 1977 is an RCT and GRADE assessment was done within the RCT study design category.
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment for NAS Days		The mean duration of treatment for nas in the intervention groups was **4.3 higher** (0.73 lower to 9.33 higher)		31 (1 study)	⊕◯◯◯ VERY LOW[4,5,6]	Madden 1977 is an RCT and GRADE assessment was done within the RCT study design category.

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] The risk of selection bias is high for the quasi-trial (Finnegan 1984) as random generation and allocation concealment were judged as inadequate. No method was reported in the Madden 1977 RCT so risk is unclear. Blinding of clinical and research staff was not reported in Madden 1977 and was unlikely as the treatment regimens were different so performance bias may be present. In Finnegan 1984 the nurses were not blinded but the research staff were blinded for short-term outcome assessment. Detection bias may be present. Both studies accounted for incomplete outcomes so attrition bias is a low risk. The groups are unbalanced in Finnegan 1984 (87 vs 20) as the Diazepam group was found to have excessive complications at interim analysis and enrolment was stopped.

[2] The meta-analysis reported here was conducted using a fixed effects model and a RR = 0.39 (95%CI: 0.24, 0.62) with Finnegan 1984 showing a statistically significant benefit of phenobarbitone over diazepam and Madden 1977 showing a non-significant benefit of diazepam over phenobarbitone. In this situation when heterogeneity is present, a random effects model is more appropriate. This would change the RR = 0.60 (95% CI: 0.08, 4.56) and is no longer statistically significant. The relatively large difference in results following sensitivity analyses reduces the robustness of these results. The assessment is downgraded for unexplained inconsistency.

[3] The overall sample size is small and there are very few events.

[4] This RCT (Madden 1977) was judged to be at unclear risk of selection bias as no random generation or allocation concealment was reported. Blinding was not reported for the trial so performance and detection bias may be present. Incomplete outcome data was addressed so attrition bias was minimal.

[5] Not applicable as only one trial included.

[6] The sample size is very small and the confidence interval is very wide.

PHENOBARBITONE COMPARED TO CHLORPROMAZINE FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants
Settings: Hospital
Intervention: Phenobarbitone
Comparison: Chlorpromazine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chlorpromazine	**Phenobarbitone**				
Death – not reported	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure See comment	**316 per 1000**	**104 per 1000** (25 to 458)	**RR 0.33** (0.08 to 1.45)	38 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	Treatment failure was rated on a three point severity scale of tremor and irritability with failure being persistent symptoms > 4 days
Seizures	See comment	See comment	Not estimable	40 (1 study)	⊕◯◯◯ VERY LOW[1,2,4]	Zero events in both groups.
Total length of hospital stay	See comment	See comment	Not estimable	—	See comment	Not reported
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment for NAS	See comment	See comment	Not estimable	—	See comment	Not reported

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] In this RCT (Kahn 1969) the method of random generation was not reported and the risk of selection bias is unclear. The study was blinded for personnel and assessors so the risk of performance and detection bias is low. The risk of selective outcome reporting was unclear as the primary outcome was not explicitly stated and the trial pre-dates trial registration.
[2] Not applicable as only one trial included.
[3] The sample size is very small and the event rate low with a wide confidence interval.
[4] The sample size is very small and zero events.

PHENOBARBITONE TITRATION WITH LOADING DOSE COMPARED TO PHENOBARBITONE TITRATION ALONE FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants

Settings: Hospital

Intervention: Phenobarbitone titration with loading dose

Comparison: Phenobarbitone titration alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Phenobarbitone titration alone	**Phenobarbitone titration with loading dose**				
Treatment failure Need for a second drug	**500 per 1000**	**550 per 1000** (295 to 1000)	**RR 1.1** (0.59 to 2.07)	36 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	
Death	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Seizures	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Total length of hospital stay	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Duration of treatment for NAS	See comment	See comment	Not estimable	87 (1 study)	See comment	Finnegan 1984 (quasi-RCT) reported reduced time to symptom control in loading dose vs none (33 vs 64 hrs; p < 0.01). No other data reported. N = 87 (assumed)

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] The quasi-trial (Kaltenbach 1986) allocated groups from envelopes designated according to the first letter of the last name. Allocation concealment was judged to be inadequate and selection bias may be present. There was no blinding for short-term outcomes and there is a risk of performance and detection bias. Selective reporting of outcomes was unclear and could not be judged.
[2] Not applicable as only one trial included.
[3] The sample size is small, the event rate low and the confidence interval is wide.

SHORT COURSE PHENOBARBITONE COMPARED TO LONG COURSE PHENOBARBITONE FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants

Settings: Hospital

Intervention: Short course Phenobarbitone (8.4 mg/kg/day in four divided doses x 4 days, then stopped)

Comparison: Long course Phenobarbitone (8.4 mg/kg/day in four divided doses x 10 days, then reduced by 1/3rd every 2nd day)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long course Phenobarbitone (8.4 mg/kg/day in four divided doses x 10 days, then reduced by 1/3rd every 2nd day)	**Short course Phenobarbitone (8.4 mg/kg/day in four divided doses x 4 days, then stopped)**				
Death	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Treatment failure	**143 per 1000**	**83 per 1000** (6 to 1000)	**RR 0.58** (0.04 to 7.94)	19 (1 study)	⊕◯◯◯ VERY LOW[1,2,3]	
Seizures	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Total length of hospital stay	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison
Duration of treatment for NAS	See comment	See comment	Not estimable	—	See comment	Not reported for this comparison

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] In this RCT (Kahn 1969) the method of random generation was not reported and the risk of selection bias is unclear. The study was blinded for personnel and assessors so the risk of performance and detection bias is low. The risk of selective outcome reporting was unclear as the primary outcome was not explicitly stated and the trial pre-dates trial registration.
[2] Not applicable as only one trial is included.
[3] The sample size is very small, the number of events is is low and the confidence interval is very wide.

SHORT COURSE OF CHLORPROMAZINE COMPARED TO LONG COURSE OF CHLORPROMAZINE FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants

Settings: Hospital

Intervention: Short course of chlorpromazine (2.8 mg/kg/day in four divided doses x 4 days, then stopped)

Comparison: Long course of chlorpromazine (2.8 mg/kg/day in four divided doses x 10 days, then gradual reduction over six days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long course of chlorpromazine (2.8 mg/kg/day in four divided doses x 10 days, then gradual reduction over six days)	**Short course of chlorpromazine (2.8 mg/kg/day in four divided doses x 4 days, then stopped)**				
Death	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure Persistent symptoms > 4 days	**125 per 1000**	**455 per 1000** (65 to 1000)	**RR 3.64** (0.52 to 25.41)	19 (1 study)	⊕○○○ VERY LOW[1,2,3]	
Seizures	See comment	See comment	Not estimable	—	See comment	Not reported
Total length of hospital stay	See comment	See comment	Not estimable	—	See comment	Not reported
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment for NAS	See comment	See comment	Not estimable	—	See comment	Not reported

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] In this RCT (Kahn 1969) the method of random generation was not reported and the risk of selection bias is unclear. The study was blinded for personnel and assessors so the risk of performance and detection bias is low. The risk of selective outcome reporting was unclear as the primary outcome was not explicitly stated and the trial pre-dates trial registration

[2] Not applicable as only one trial is included.

[3] The sample size is very small, the number of events is low and the confidence interval is very wide.

PHENOBARBITONE AND OPIOID COMPARED TO OPIOID ALONE FOR OPIATE WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioid withdrawal in newborn infants
Settings: Hospital
Intervention: Phenobarbitone and opioid
Comparison: Opioid alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Opioid alone	Phenobarbitone and opioid				
Death	See comment	See comment	Not estimable	—	See comment	Not reported
Treatment failure Needing another drug	See comment	See comment	Not estimable	20 (1 study)	⊕○○○ VERY LOW[1,2,3]	There were no events in either group.
Seizures	See comment	See comment	Not estimable	20 (1 study)	⊕○○○ VERY LOW[1,3]	There were no events in either group.
Total length of hospital stay Days		The mean total length of hospital stay in the intervention groups was **41 lower** (59.85 to 22.15 lower)		20 (1 study)	⊕○○○ VERY LOW[1,4]	
Infant weight gain	See comment	See comment	Not estimable	—	See comment	Not reported
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment for NAS	See comment	See comment	Not estimable	—	See comment	Not reported

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] This study (Coyle 2002) is probably a quasi-randomized trial. Infants were matched on Finnegan scores but the method is incompletely described. If no match was possible, then infants were randomly assigned. Allocation concealment was judged to be inadequate. Selection bias is a high risk. Performance bias is a low risk as the trial was placebo-controlled and nurses were blinded to the treatment assignments. However, weekly phenobarbitone levels were reported to the physician so there is an unclear risk of detection bias as it is not certain if the physicians were also assessing the outcomes. Of note is that an earlier abstract reported 35 infants but the principal article only reports on 21 infants.

[2] Not applicable as only one study included.

[3] The sample size is small. Although a sample size calculation was done a priori the outcome used in the formula is reduction in hospital days. This calculation found that 48 patients were required. However, the trial was stopped early on the basis of significance but no details are provided if formal stopping rules were applied to determine the significance level. A systematic review of RCTs stopped early for benefit found that such RCTs were found to overestimate treatment effects. When trials with events fewer than the median number (n=66) were compared with those with event numbers above the median, the odds ratio for a magnitude of effect greater than the median was 28 (95% CI 11–73) (Montori VM, Devereaux PJ and Adhikari NK et al.. Randomized trials stopped early for benefit: a systematic review. JAMA 2005;294:2203-09.)

[4] The sample size is small and the confidence interval is wide. Although a sample size calculation was done a priori for this outcome: reduction in hospital days. This calculation found that 48 patients were required. However, the trial was stopped early on the basis of significance but no details are provided if formal stopping rules were applied to determine the significance level. A systematic review of RCTs stopped early for benefit found that such RCTs were found to overestimate treatment effects. When trials with events fewer than the median number (n=66) were compared with those with event numbers above the median, the odds ratio for a magnitude of effect greater than the median was 28 (95% CI 11-73) (Montori VM, Devereaux PJ and Adhikari NK et al.. Randomized trials stopped early for benefit: a systematic review. JAMA 2005;294:2203-09.)

CLONIDINE AND OPIOID COMPARED TO OPIOID ALONE FOR OPIOID WITHDRAWAL IN NEWBORN INFANTS

Patient or population: Opioidwithdrawal in newborn infants
Settings: Hospital
Intervention: Clonidine and opioid
Comparison: Opioid alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Opioid alone	**Clonidine and opioid**				
Death	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 7** (0.37 to 131.28)	80 (1 study)	⊕⊕◯◯ LOW[1,2]	All deaths (n = 3) were in the Clonidine and Opioid group. Death occurred after discharge and cessation of clonidine. Causes: myocarditis, SIDS, homicide.
Treatment failure Required >= 0.9ml of diluted Tincture of Opium every 3 hours	**125 per 1000**	**11 per 1000** (1 to 199)	**RR 0.09** (0.01 to 1.59)	80 (1 study)	⊕⊕◯◯ LOW[1,3]	All infants with treatment failure were (n = 5) in the Opioid alone group.
Seizures	**75 per 1000**	**10 per 1000** (1 to 201)	**RR 0.14** (0.01 to 2.68)	80 (1 study)	⊕⊕◯◯ LOW[1,4]	All seizures (n = 3) were in the Opioid alone group.
Total length of hospital stay	See comment	See comment	Not estimable	—	See comment	Not reported
Infant maximum weight loss – % of birthweight[5]		The mean infant maximum weight loss in the intervention groups was **0.88 lower** (2.33 lower to 0.57 higher)		80 (1 study)	⊕⊕◯◯ LOW[4]	
Days to regain birthweight	See comment	See comment	Not estimable	—	See comment	Not reported
Duration of treatment for NAS		Medians reported		80 (1 study)	⊕⊕◯◯ LOW[1,4]	Median duration was 11 days (95% CI: 8–15) vs 15 days (95% CI: 13–17) in the Clonidine and opioid group vs the opioid alone respectively.

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further 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 very 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] This placebo-controlled RCT (Agthe 2009) was well-conducted and judged to be at low risk of selection, performance and detection bias. The infants in the Clonidine and Tincture of Opium group had statistically significantly lower mean birthweights. 61% of infants were also exposed to cocaine in utero and 6 of 80 infants had positive benzodiazepine urine screens.
[2] The event rates are very low and the confidence interval is very wide.
[3] The event rate is very low and the confidence interval is wide.
[4] The sample size is small and according to GRADE criteria for rating continuous data, a sample size of less than 400 indicates imprecision and should be downgraded.
[5] Inverse measure for infant weight gain (proxy outcome)

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD PHENOBARBITONE VS SUPPORTIVE CARE BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbitone	Supportive care	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: Failure to settle measured with Finnegan score)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	9/28 (32.1%)	4/34 (11.8%)	RR 2.73 (0.94 to 7.94)	204 more per 1000 (from 7 fewer to 816 more)	⊕◯◯◯ VERY LOW	CRITICAL
Seizure – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Duration of treatment (days) (better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[4]	none	28	34	—	MD 17.9 higher (11.98 to 23.82 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Total length of hospital stay (measured with: Days in hospital; better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[4]	none	28	34	—	MD 20.8 higher (13.64 to 27.96 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight (better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[5]	none	27	28	—	MD 1.4 lower (4.07 lower to 1.27 higher)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbitone	Supportive care	Relative (95% CI)	Absolute		
Duration of treatment for NAS – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL

[1] This quasi-randomized trial (Khoo 1995) allocated participants to groups using the last number of the participant's hospital number. Both random generation and allocation concealment were judged to be inadequate and there is thus a high risk of selection bias. The group numbers are also not balanced (29 vs 36). There was no blinding of providers or parents so performance bias may be present. Blinding was unreported for short-term outcomes and the risk of detection bias is unclear.

[2] Not applicable as only one study is included.

[3] The sample size is very small and the event rate is very low so imprecision is likely in these results.

[4] The sample size is small and the confidence interval is wide. Notwithstanding the very large difference in means and the highly statistically significant finding, the lack of information about the primary outcome and power of the trial reduces our confidence in this estimate.

[5] The sample size is small. The primary outcome is not clearly defined and it is therefore not possible to determine the power of the study for this outcome: time to regain birthweight. In the light of this uncertainty, the GRADE criteria recommend that a sample size of less than 400 for continuous outcomes be downgraded for imprecision.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD PHENOBARBITONE VS DIAZEPAM BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbitone	Diazepam	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure												
2	randomized trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	21/103 (20.4%)	14/36 (38.9%)	RR 0.39 (0.24 to 0.62)	237 fewer per 1000 (from 148 fewer to 296 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Seizure – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Total length of hospital stay (measured with: Days; better indicated by lower values)												
1	randomized trials	serious[4]	no serious inconsistency[5]	no serious indirectness	very serious[6]	none	15	16	—	MD 3.07 higher (2.02 lower to 8.16 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Infant weight gain – not reported												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[4]	none	28	34	—	MD 20.8 higher (13.64 to 27.96 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Duration of treatment for NAS (measured with: Days; better indicated by lower values)												
1	randomized trials	serious[4]	no serious inconsistency[5]	no serious indirectness	very serious[6]	none	15	16	—	MD 4.3 higher (0.73 lower to 9.33 higher)	⊕◯◯◯ VERY LOW	CRITICAL

[1] The risk of selection bias is high for the quasi-trial (Finnegan 1984) as random generation and allocation concealment were judged as inadequate. No method was reported in the Madden 1977 RCT so risk is unclear. Blinding of clinical and research staff was not reported in Madden 1977 and was unlikely as the treatment regimens were different so performance bias may be present. In Finnegan 1984 the nurses were not blinded but the research staff were blinded for short-term outcome assessment. Detection bias may be present. Both studies accounted for incomplete outcomes so attrition bias is a low risk. The groups are unbalanced in Finnegan 1984 (87 vs 20) as the Diazepam group was found to have excessive complications at interim analysis and enrolment was stopped.

[2] The meta-analysis reported here was conducted using a fixed effects model and a RR = 0.39 (95%CI: 0.24, 0.62) with Finnegan 1984 showing a statistically significant benefit of phenobarbitone over diazepam and Madden 1977 showing a non-significant benefit of diazepam over phenobarbitone. In this situation when heterogeneity is present, a random effects model is more appropriate. This would change the RR = 0.60 (95% CI: 0.08, 4.56) and is no longer statistically significant. The relatively large difference in results following sensitivity analyses reduces the robustness of these results. The assessment is downgraded for unexplained inconsistency.

[3] The overall sample size is small and there are very few events.

[4] This RCT (Madden 1977) was judged to be at unclear risk of selection bias as no random generation or allocation concealment was reported. Blinding was not reported for the trial so performance and detection bias may be present. Incomplete outcome data was addressed so attrition bias was minimal.

[5] Not applicable as only one trial included.

[6] The sample size is very small and the confidence interval is very wide.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD PHENOBARBITONE VS CHLORPROMAZINE BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbitone	Chlorpromazine	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: See comment)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	2/19 (10.5%)	6/19 (31.6%)	RR 0.33 (0.08 to 1.45)	212 fewer per 1000 (from 291 fewer to 142 more)	⊕◯◯◯ VERY LOW	
Seizures												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[4]	none	0/19 (0%)	0/21 (0%)	not pooled	not pooled	⊕◯◯◯ VERY LOW	
Total length of hospital stay – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Duration of treatment for NAS – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL

[1] In this RCT (Kahn 1969) the method of random generation was not reported and the risk of selection bias is unclear. The study was blinded for personnel and assessors so the risk of performance and detection bias is low. The risk of selective outcome reporting was unclear as the primary outcome was not explicitly stated and the trial pre-dates trial registration.
[2] Not applicable as only one trial included.
[3] The sample size is very small and the event rate low with a wide confidence interval.
[4] The sample size is very small and zero events.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD PHENOBARBITONE TITRATION WITH LOADING DOSE VS PHENOBARBITONE TITRATION ALONE BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbitone titration with loading dose	Phenobarbitone titration alone	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: Need for a second drug)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	11/20 (55%)	8/16 (50%)	RR 1.1 (0.59 to 2.07)	50 more per 1000 (from 205 fewer to 535 more)	⊕◯◯◯ VERY LOW	CRITICAL
Seizures – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Total length of hospital stay – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Duration of treatment for NAS												
1	randomized trials					none	N = 87 assumed		Finnegan 1984 (quasi-RCT) reported reduced time to symptom control in loading dose vs none (33 vs 64 hrs; $p < 0.01$). No other data			CRITICAL

1 The quasi-trial (Kaltenbach 1986) allocated groups from envelopes designated according to the first letter of the last name. Allocation concealment was judged to be inadequate and selection bias may be present. There was no blinding for short-term outcomes and there is a risk of performance and detection bias. Selective reporting of outcomes was unclear and could not be judged.
2 Not applicable as only one trial included.
3 The sample size is small, the event rate low and the confidence interval is wide.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole

Date: 2013-01-16

Question: SHOULD SHORT COURSE PHENOBARBITONE (8.4 MG/KG/DAY IN FOUR DIVIDED DOSES X 4 DAYS, THEN STOPPED) VS LONG COURSE PHENOBARBITONE (8.4 MG/KG/DAY IN FOUR DIVIDED DOSES X 10 DAYS, THEN REDUCED BY 1/3RD EVERY 2ND DAY) BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?

Settings: Hospital

Bibliography: Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course Phenobarbitone (8.4 mg/kg/day in four divided doses x 4 days, then stopped)	Long course Phenobarbitone (8.4 mg/kg/day in four divided doses x 10 days, then reduced by 1/3rd every 2nd day)	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	1/12 (8.3%)	1/7 (14.3%)	RR 0.58 (0.04 to 7.94)	60 fewer per 1000 (from 137 fewer to 991 more)	⊕◯◯◯ VERY LOW	
Seizures – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Total length of hospital stay – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Duration of treatment for NAS – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL

[1] In this RCT (Kahn 1969) the method of random generation was not reported and the risk of selection bias is unclear. The study was blinded for personnel and assessors so the risk of performance and detection bias is low. The risk of selective outcome reporting was unclear as the primary outcome was not explicitly stated and the trial pre-dates trial registration.

[2] Not applicable as only one trial is included.

[3] The sample size is very small, the number of events is is low and the confidence interval is very wide.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole

Date: 2013-01-16

Question: SHOULD SHORT COURSE OF CHLORPROMAZINE (2.8 MG/KG/DAY IN FOUR DIVIDED DOSES X 4 DAYS, THEN STOPPED) VS LONG COURSE OF CHLORPROMAZINE (2.8 MG/KG/DAY IN FOUR DIVIDED DOSES X 10 DAYS, THEN GRADUAL REDUCTION OVER SIX DAYS) BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?

Settings: Hospital

Bibliography: Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course of chlorpromazine (2.8 mg/kg/day in four divided doses x 4 days, then stopped)	Long course of chlorpromazine (2.8 mg/kg/day in four divided doses x 10 days, then gradual reduction over six days)	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: Persistent symptoms > 4 days)												
1	randomized trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	5/11 (45.5%)	1/8 (12.5%)	RR 3.64 (0.52 to 25.41)	330 more per 1000 (from 60 fewer to 1000 more)	⊕◯◯◯ VERY LOW	
Seizures – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Total length of hospital stay – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Duration of treatment for NAS – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL

[1] In this RCT (Kahn 1969) the method of random generation was not reported and the risk of selection bias is unclear. The study was blinded for personnel and assessors so the risk of performance and detection bias is low. The risk of selective outcome reporting was unclear as the primary outcome was not explicitly stated and the trial pre-dates trial registration

[2] Not applicable as only one trial is included.

[3] The sample size is very small, the number of events is low and the confidence interval is very wide.

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD PHENOBARBITONE AND OPIOID VS OPIOID ALONE BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbitone and opioid	Opioid alone	Relative (95% CI)	Absolute	Quality	Importance
Death – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Treatment failure (assessed with: Needing another drug)												
1	observational studies	serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	0/10 (0%)	0/10 (0%)	—	—	⊕◯◯◯ VERY LOW	CRITICAL
Seizures												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/10 (0%)	0/10 (0%)	—	—	⊕◯◯◯ VERY LOW	CRITICAL
Total length of hospital stay (measured with: Days; better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	10	10	—	MD 41 lower (59.85 to 22.15 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Infant weight gain – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbitone and opioid	Opioid alone	Relative (95% CI)	Absolute		
Duration of treatment for NAS – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL

[1] This study (Coyle 2002) is probably a quasi-randomized trial. Infants were matched on Finnegan scores but the method is incompletely described. If no match was possible, then infants were randomly assigned. Allocation concealment was judged to be inadequate. Selection bias is a high risk. Performance bias is a low risk as the trial was placebo-controlled and nurses were blinded to the treatment assignments. However, weekly phenobarbitone levels were reported to the physician so there is an unclear risk of detection bias as it is not certain if the physicians were also assessing the outcomes. Of note is that an earlier abstract reported 35 infants but the principal article only reports on 21 infants.

[2] Not applicable as only one study included.

[3] The sample size is small. Although a sample size calculation was done a priori the outcome used in the formula is reduction in hospital days. This calculation found that 48 patients were required. However, the trial was stopped early on the basis of significance but no details are provided if formal stopping rules were applied to determine the significance level. A systematic review of RCTs stopped early for benefit found that such RCTs were found to overestimate treatment effects. When trials with events fewer than the median number (n=66) were compared with those with event numbers above the median, the odds ratio for a magnitude of effect greater than the median was 28 (95% CI 11–73) (Montori VM, Devereaux PJ and Adhikari NK et al.. Randomized trials stopped early for benefit: a systematic review. JAMA 2005;294:2203-09.)

4 The sample size is small and the confidence interval is wide. Although a sample size calculation was done a priori for this outcome: reduction in hospital days. This calculation found that 48 patients were required. However, the trial was stopped early on the basis of significance but no details are provided if formal stopping rules were applied to determine the significance level. A systematic review of RCTs stopped early for benefit found that such RCTs were found to overestimate treatment effects. When trials with events fewer than the median number (n=66) were compared with those with event numbers above the median, the odds ratio for a magnitude of effect greater than the median was 28 (95% CI 11-73) (Montori VM, Devereaux PJ and Adhikari NK et al.. Randomized trials stopped early for benefit: a systematic review. JAMA 2005;294:2203-09.)

Author(s): David A Osborn, Heather E Jeffery, Michael J Cole
Date: 2013-01-16
Question: SHOULD CLONIDINE AND OPIOID VS OPIOID ALONE BE USED IN OPIOID WITHDRAWAL IN NEWBORN INFANTS?
Settings: Hospital
Bibliography: Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database of Systematic Reviews

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine and opioid	Opioid alone	Relative (95% CI)	Absolute	Quality	Importance
Death												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/40 (7.5%)	0/40 (0%)	RR 7 (0.37 to 131.28)	—	⊕⊕◯◯ LOW	CRITICAL
Treatment failure (assessed with: Required >= 0.9ml of diluted Tincture of Opium every 3 hours)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/40 (0%)	5/40 (12.5%)	RR 0.09 (0.01 to 1.59)	114 fewer per 1000 (from 124 fewer to 74 more)	⊕⊕◯◯ LOW	CRITICAL
Seizures												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/40 (0%)	3/40 (7.5%)	RR 0.14 (0.01 to 2.68)	65 fewer per 1000 (from 74 fewer to 126 more)	⊕⊕◯◯ LOW	CRITICAL
Total length of hospital stay – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL
Infant maximum weight loss (measured with: % of birthweight[5]; better indicated by lower values)												
1	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	40	40	—	MD 0.88 lower (2.33 lower to 0.57 higher)	⊕⊕◯◯ LOW	CRITICAL
Days to regain birthweight – not reported												
0	—	—	—	—	—	none	—	—	—	—		CRITICAL

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine and opioid	Opioid alone	Relative (95% CI)	Absolute	Quality	Importance
Duration of treatment for NAS (better indicated by lower values)												
1	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	40	40	—	—	⨁⨁◯◯ LOW	CRITICAL

[1] This placebo-controlled RCT (Agthe 2009) was well-conducted and judged to be at low risk of selection, performance and detection bias. The infants in the Clonidine and Tincture of Opium group had statistically significantly lower mean birthweights. 61% of infants were also exposed to cocaine in utero and 6 of 80 infants had positive benzodiazepine urine screens.
[2] The event rates are very low and the confidence interval is very wide.
[3] The event rate is very low and the confidence interval is wide.
[4] The sample size is small and according to GRADE criteria for rating continuous data, a sample size of less than 400 indicates imprecision and should be downgraded.
[5] Inverse measure for infant weight gain (proxy outcome)

ANNEX 2: SYSTEMATIC REVIEW METHODOLOGY

Methods

Criteria for considering studies for this review

Types of studies

1. Randomized controlled trials
2. Systematic reviews and/or meta-analyses categorized as:
   a. Cochrane reviews from any year
   b. Non-Cochrane systematic review conducted between 2008 and 2013
   c. Non-Cochrane systematic reviews conducted prior to 2008

We determined ***a priori*** that systematic reviews conducted prior to 2008 would require extensive updating and we therefore chose to focus on evaluating Cochrane reviews regardless of year and non-Cochrane reviews published since 2008.

Types of participants

Varied according to each evidence question (see Annex 1)

Types of interventions

Intervention

As defined by each evidence question

Comparison

As defined by each evidence question

Types of outcome measures

Maternal outcomes:

1. Withdrawal
2. Substance use
3. Retention in substance use treatment (if necessary, we used retention in the trial as a proxy measure)
4. Termination of maternal rights (e.g. baby taken into care)

Fetal/Infant outcomes:

1. Birthweight
2. Spontaneous abortion
3. Termination
4. Foetal death
5. Intra-uterine growth retardation (IUGR)
6. Gestational age at delivery
7. Premature delivery (before 37 weeks)
8. Neonatal Abstinence Syndrome (NAS)(drug-specific)
9. Neonatal death
10. Sudden Infant Death Syndrome
11. Birth defects
12. Head circumference at birth
13. Length at birth
14. Custody of infant

Summary of findings table

We used the GRADE approach to interpret findings (Schünemann 2008) and used the GRADE profiler to import data from Review Manager (RevMan) to create 'Summary of findings' (SOF) tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient-care and decision making.
The outcomes were rated independently by nine members of the Pregnancy and Substance Use Guidelines Committee. We selected seven patient-centred outcomes for each evidence question for inclusion in the SOF tables on the basis of these ratings.

Search methods for identification of studies

The search was conducted by using a search strategy developed in consultation with the WHO Pregnancy and Substance Use Guidelines Technical Team. The search was iterative and the strategy was refined to ensure that it had maximum sensitivity to identify all relevant RCTs.

Electronic searches

We developed the search strategy with the assistance of the World Health Organization Information Specialist. We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant randomized controlled trials, systematic reviews and meta-analyses regardless of language or publication status (published, unpublished, in press, and in progress).

We combined the RCT strategy developed by The Cochrane Collaboration and detailed in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) with the PUBMED strategy for Systematic Reviews together with database-specific terms for pregnancy, lactation and the postpartum period. This was combined with database-specific terms for substance use, abuse and dependence. We did not limit the search to specific substances or interventions as the search was intentionally general to be applicable to all evidence questions to be addressed during the guideline process.

The search was iterative and a number of trial searches were run first to ensure maximal sensitivity.

We searched the following databases:

1. Journal databases

- Medline via Pubmed – see search strategy conducted on 9 June 2013 below
- EmBase – see search strategy conducted on 10 June 2013 below
- PsychInfo – see search strategy conducted on 10 June 2013 below
- CINAHL – see search strategy conducted on 10 June 2013 below
- Cochrane Central Register of Controlled Trials (CENTRAL) – see search strategy conducted on 13 June 2013 below

Searching other resources

We checked the reference lists of all studies identified by the above methods and examined any systematic reviews, meta-analyses, or guidelines we identified during the search process for references.

We were in close contact with individual researchers working in the field, and policymakers based in inter-governmental organizations including WHO and UNODC.

Data collection and analysis

Selection of studies

Two review authors (NS for all; NC for records from 2012 and an intern for records pre-2012) inspected all citations from the electronic search and identified relevant abstracts of trials and systematic reviews for inclusion criteria. The full text articles were obtained for all potentially relevant studies and NS assessed each of these for eligibility. This process was duplicated by NC and two interns.

Where there were uncertainties or disagreements, or where disputes could not be resolved, these studies remained in awaiting assessment or ongoing studies and the authors were contacted for clarification. NS and NC made final decisions regarding inclusion.

Data extraction and management

1. Extraction

NS extracted data from included studies. NC checked each data entry. We resolved disputes by discussion. If it was not possible to extract data or if further information was needed, we attempted to contact the authors. We extracted data presented only in tables and figures whenever possible, and when further information was necessary, we contacted authors of studies in order to obtain missing data or for clarification of methods.

2. Management

2.1 Forms

We extracted data onto standardized, simple forms, including:

- Administrative details: Trial or study identification number; author(s); published or unpublished; year of publication; number of studies included in paper; year in which study was conducted; details of other relevant papers cited;
- Details of the study: Study design; type, duration and completeness of follow-up; country and location of study (e.g. higher-income vs. lower-income country); informed consent and ethics approval;
- Details of participants: Setting, numbers, relevant baseline characteristics including age;
- Details of intervention: Type of intervention, timing and duration of intervention, additional co-interventions;
- Details of comparison: Type and comparison, timing and duration of comparative intervention;
- Details of outcomes: Maternal and infant outcomes;
- Details of the analysis: For RCTs, details of the type of analysis (intention-to-treat or per protocol).

2.2 Scale-derived data

We included continuous data from rating scales only if:

- the psychometric properties of the measuring instrument have been described in a peer-reviewed journal; and
- the measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally the measuring instrument should either be i) a self-report or ii) completed by an independent rater or relative (not the therapist). We realize that this is not often reported clearly and noted this to assist in the Risk of Bias assessment.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult to measure conditions such as substance dependence. We decided to primarily use endpoint data, and only use change data if the former were not available. We combined endpoint and change data in the analysis as we used mean differences (MD) rather than standardized mean differences throughout (Higgins 2011, Chapter 9.4.5.2).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aimed to apply the following standards to all data before inclusion:

- standard deviations and means are reported in the paper or obtainable from the authors;
- when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996).

Endpoint scores on scales often have a finite start and end point and these rules can be applied. We entered skewed endpoint data from studies of fewer than 200 participants as other data within Data and analyses rather

than into a statistical analysis. Skewed data pose less of a problem when looking at means if the sample size is large; we entered such endpoint data into syntheses.

When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. For these cases, we entered skewed change data into analyses regardless of size of study.

2.5 Common measure

To facilitate comparison between trials, we intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for the treatment intervention. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not improved') we reported data where the left of the line indicates an unfavourable outcome. This was noted in the relevant graphs.

Assessment of risk of bias in included studies

NS worked independently by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

Full details of the Risk of Bias tool can be viewed in the table below.

Item	Low risk	High risk	Unclear risk
Sequence generation	Investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelope shuffling	Investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number	Insufficient information to permit judgment of the sequence generation process
Allocation concealment	Participants and the investigators enrolling participants cannot foresee assignment, e.g. central allocation; or sequentially numbered, opaque, sealed envelopes	Participants and investigators enrolling participants can foresee upcoming assignment, e.g. an open random allocation schedule (e.g. a list of random numbers); or envelopes were unsealed or non¬opaque or not sequentially numbered	Insufficient information to permit judgment of the allocation concealment or the method not described
Blinding	Blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias.	No blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding	Insufficient information to permit judgment of adequacy or otherwise of the blinding
Incomplete outcome data	No missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups	Reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data	Insufficient reporting of attrition or exclusions

Item	Low risk	High risk	Unclear risk
Selective reporting	A protocol is available which clearly states the primary outcome as the same as in the final trial report	The primary outcome differs between the protocol and final trial report	No trial protocol is available or there is insufficient reporting to determine if selective reporting is present

Where inadequate details of randomization and other characteristics of trials were provided, we contacted authors of the studies in order to obtain additional information.

We have noted the level of risk of bias in the text of the review.

Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI).

2. Continuous data

For continuous outcomes we estimated mean difference (MD) between groups. We would prefer not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity were used, we presumed there was a small difference in measurement, and we would have calculated effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomization' (such as randomization by clinician or practice), but analysis and pooling of clustered data poses problems. Authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997).

Where study authors were unable to provide the information needed to correct for flawed analysis of cluster randomized trials, the data was analysed as a non cluster RCT but with downgrading of the certainty of effect in the GRADE table.

2. Cross-over trials

None of the present included studies employed a cross-over trial design.

3. Studies with multiple treatment groups

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up data must lose credibility. We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we would not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss is less than 50%, we would address this within the Summary of Findings table(s) by down-rating quality. Finally, we would also downgrade quality within the Summary of Findings table(s) should loss be 25-50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0 and 50% and where these data are not clearly described, we presented data on a 'once-randomized-always-analysed' basis (an intention to treat analysis). Those leaving the study early were assumed to have the same rates of negative outcome as those who completed in that particular arm of the trial. We undertook a sensitivity analysis testing how prone the primary

outcomes are to change when data only from people who complete the study to that point were compared to the intention to treat analysis using the above assumptions.

3. Continuous Data

3.1 Attrition

In the case where attrition for a continuous outcome is between 0 and 50%, and data only from people who complete the study to that point are reported, we reproduced these.

3.2 Standard deviations

If standard deviations are not reported, we first tried to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error and confidence intervals available for group means, and either 'p' value or 't' value available for differences in mean, we can calculate them according to the rules described in the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011): when only the standard error (SE) is reported, standard deviations (SDs) are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the Cochrane Handbook for Systemic reviews of Interventions (Higgins 2011) present detailed formula for estimating SDs from p-values, t or F values, confidence intervals, ranges or other statistics.

3.3 Last observation carried forward

We anticipated that in some studies the method of last observation carried forward (LOCF) would be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results (Leucht 2007). Therefore, where LOCF data have been used in the trial, if less than 50% of the data have been assumed, we would present and use these data and indicate that they are the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We inspected all studies for clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arose, we fully discussed these.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We inspected all studies for clearly outlying methods which we had not predicted would arise. When such methodological outliers arose, we fully discussed these.

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i) magnitude and direction of effects and ii) strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic was interpreted as evidence of substantial levels of heterogeneity (Higgins 2011). When substantial levels of heterogeneity were found in the primary outcome, we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the Handbook (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not plan to use funnel plots for outcomes where there were 10 or fewer studies, or where

all studies were of similar sizes. As no meta-analyses of more than five studies were undertaken, we did not conduct funnel plot analysis.

Data synthesis

Where RCTs are found to be methodologically or clinically comparable, we pooled trial results in a meta-analysis. Where we found the presence of statistical heterogeneity we combined the data using the random effects model.

For meta-analysis of RCTs, we combined the results and the relative risk and the 95% confidence intervals for dichotomous data. For continuous data, we combined the mean differences to calculate a weighted mean difference and standard deviation.

Subgroup analysis and investigation of heterogeneity

We will explore heterogeneity by conducting sub-group analyses between:

1. Type of substance dependence
2. Setting of treatment (e.g. inpatient versus outpatient)

Main results

Results of the search

The number of records retrieved from each database can be seen in the table below:

Database	Number of records
PUBMED	1479
EMBASE	3614
PsychInfo	512
CINAHL	754
CENTRAL	84
Total	**6443**

After electronic and manual deduplication using ENDNOTE software, we screened 5632 records of which 172 were identified as potentially eligible RCTs and 73 systematic reviews and the full texts for these were obtained – see Figure 1.

FIGURE 1: FLOW DIAGRAM OF LITERATURE SEARCH

TABLE OF EVIDENCE QUESTIONS (PICO) BY NUMBER OF ARTICLES IDENTIFIED AND NUMBER OF RCTS

PICO	Intervention	Articles	RCTs
1	Screening and brief intervention	17	10
2	Psychosocial interventions	30	15
3	Detoxification	0	0
4	Dependence management	36	4
5	Lactation	0	0
6	Management of infant withdrawal	5	4
	Unclassified	5	
Total		93	33

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PUBMED search strategy			
Search	**Add to builder**	**Query**	**Items found**
#9	Add	Search (#5) AND #8	1476
#8	Add	Search (#6) OR #7	1242301
#7	Add	Search (((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR (systematic review [tiab] AND review [pt]) OR consensus development conference [pt] OR practice guideline [pt] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR drug class reviews [ti]) OR (clinical guideline [tw] AND management [tw])OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [tiab] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook))))	212906
#6	Add	Search (((clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR "clinical trials as topic"[mesh: noexp] OR randomly [tiab] OR trial [tiab]) NOT (animals [mh] NOT humans [mh])))	1081782
#5	Add	Search (#3) AND #4	18324
#4	Add	Search (((pregnant women[mh] OR pregnancy[mh] OR pregnant[tiab] OR pregnancy[tiab] OR antenatal[tiab] OR ante-natal[tiab] OR prenatal[tiab] OR breast feeding[mh] OR breast feed*[tiab] OR breastfeed*[tiab] OR postnatal[tiab] OR post-natal[tiab] OR postpartum[tiab] OR postpartum period[mh] OR lactat*[tiab] OR maternal exposure[mh] OR maternal exposure*[tiab])))	942452
#3	Add	Search (#1) OR #2	350542
#2	Add	Search (((substance-related disorders[mh] OR prescription drug misuse[mh] OR street drugs[mh] OR street drugs[tiab] OR recreational drugs[tiab] OR illicit drugs[tiab] OR cocaine[tiab] OR designer drugs[mh] OR designer drugs[tiab] OR cannabis[mh] OR cannabis[tiab] OR marijuana*[tiab] OR hashish[tiab] OR bhang*[tiab] OR ganja*[tiab] OR hemp[tiab] OR heroin[mh] OR heroin[tiab] OR amphetamine[mh] OR amphetamine*[tiab] OR (drug[tiab] OR benzodiazepine [tiab] OR opioids[tiab] OR prescription[tiab] OR barbiturate[tiab] OR tramadol[tiab] OR oxycodone[tiab] OR substance[tiab]) AND (misuse[tiab] OR use[tiab] OR abuse[tiab] OR abuses[tiab] OR dependence[tiab] OR dependency[tiab] OR addiction[tiab] OR habituation[tiab] OR disorder*[tiab] OR consumption[tiab]))))	168206
#1	Add	Search (((alcohol drinking[mh] OR alcoholism[mh] OR alcohol-related disorders[mh] OR fetal alcohol syndrome[mh] OR alcohol[tiab])))	227539

EmBase search strategy		
#	**Searches**	**Results**
1	'drinking behavior'/exp OR 'drinking behaviour':ti,ab OR 'alcohol abstinence'/exp OR 'alcoholism'/exp OR 'alcohol':ti,ab OR alcoholic:ti,ab OR alcoholism:ti,ab OR 'fetal alcohol syndrome'/exp	306,329
2	'addiction'/exp OR 'substance-related disorders' OR 'substance-related disorder' OR 'chemical dependence' OR 'addictive behavior' OR 'addictive behaviour' OR 'addictive behaviors' OR 'addictive behaviours' OR 'drug misuse'/exp OR 'drug misuse' OR 'street drug'/exp OR 'street drugs' OR 'recreational drugs' OR 'recreational drug' OR 'illicit drugs' OR 'illicit drug' OR cocaine OR 'cannabis'/exp OR cannabis:ti,ab OR 'cannabis smoking'/exp OR marijuana*:ti,ab OR hashish:ti,ab OR bhang:ti,ab OR ' C indica':ti,ab OR cannador*:ti,ab OR charas*:ti,ab OR ganja*:ti,ab OR ganjah*:ti,ab OR hemp*:ti,ab OR marihuana*:ti,ab OR heroin OR 'amphetamine'/exp OR amphetamine OR 'actedron' OR ' actemin' OR ' adderall' OR ' adderall ir' OR ' adderall xr' OR ' adipan' OR ' aktedrin' OR ' aktedron' OR ' alentol' OR ' allodene' OR ' alpha amphetamine' OR ' alpha methylphenethylamine' OR ' alpha methylphenylethylamine' OR ' amfetamine' OR ' amphamed' OR ' amphamine' OR ' amphetaime' OR ' amphetamin' OR ' amphetamine base phosphate' OR ' amphetamine base sulfate' OR ' amphetamine detection' OR ' amphetamine hydrochloride' OR ' amphetamine intoxication' OR ' amphetamine metabolism' OR ' amphetamine phosphate' OR ' amphetamine resin complex' OR ' amphetamine sulfate' OR ' amphetamine toxicity' OR ' amphetaminyl' OR ' amphethamine' OR ' amphezamin' OR ' anara' OR ' astedin' OR ' badrin' OR ' benzafinyl' OR ' benzebar' OR ' benzedrine' OR ' benzolone' OR ' benzpropamin' OR ' benzpropamine' OR ' beta aminopropylbenzene' OR ' beta phenyl isopropylamine' OR ' beta phenylisopropylamine' OR ' betafen' OR ' bluzedrin' OR ' centramina' OR ' centramine' OR ' d l amphetamine' OR ' delta amphetamine' OR ' desoxynorephedrin' OR ' dextro levo 2 methylphenethylamine' OR ' dextro levo 2 methylphenetylamine' OR ' dextro levo alpha methylphenethylamine' OR ' dextro levo amphetamine' OR ' dextrolevo amphetamine' OR ' diethamine' OR ' diethanine' OR ' dipan' OR ' elastonin' OR ' elastonon' OR ' euphobine' OR ' euphodine' OR ' euphodyn' OR ' fabedrine' OR ' fenara' OR ' fenedrin' OR ' ibiozedrine' OR ' isoamin' OR ' isoamine' OR ' isoamyn' OR ' isoamyne' OR ' isomyn' OR ' l amphetamine' OR ' levamfetamine' OR ' levamphetamine' OR ' levedrine' OR ' levo amphetamine' OR ' levo amphetamine sulphate' OR ' levoamphetamine' OR ' linampheta' OR ' mecodrin' OR ' mimetina' OR ' monetamin' OR ' monophos' OR ' noclon' OR ' norephedrane' OR ' norphedrane' OR ' novydrine' OR ' obesin andromacro' OR ' obetrol' OR ' oktedrin' OR ' oraldrina' OR ' ortedrine' OR ' percomon' OR ' pharmamedrine' OR ' pharmedrine' OR ' phenamin' OR ' phenedrine' OR ' phenoprominum' OR ' phenpromin' OR ' phenyl isopropylamine' OR ' phenylaminopropane' OR ' profamina' OR ' profetamine' OR ' propisamine' OR ' psychedrin' OR ' psychedrine' OR ' psychoton' OR ' racemic desoxy nor ephedrine' OR ' racemic desoxy norephedrine' OR ' racephen' OR ' raphetamine' OR ' rhinalator' OR ' sedolin' OR ' simpamina' OR ' simpamine' OR ' simpatedrin' OR ' simpatedrine' OR ' stimulan' OR ' sympametin' OR ' sympamine' OR ' sympatedrine' OR ' theptine' OR ' vapedrine' OR ' zedrin' OR ' zedrine' OR (Drug:ti,ab OR 'sedative agent'/exp OR benzodiazepine OR 'opiate'/exp OR opioids OR 'tramadol'/exp OR 'adamon' OR ' amanda' OR ' analab' OR ' analdol' OR ' andalpha' OR ' bellatram' OR ' biodalgic' OR ' calmador' OR ' calmol' OR ' cg 315e' OR ' cg315e' OR ' contramal' OR ' contramal lp' OR ' dolana' OR ' dolika' OR ' dolmal' OR ' dolotral' OR ' dolzam' OR ' dromadol' OR ' e 381' OR ' e 382' OR ' e381' OR ' e382' OR ' eufindol' OR ' exopen' OR ' katrasic' OR ' kontram xl' OR ' kontram xl sr' OR ' mabron' OR ' melanate' OR ' mosepan' OR ' newdorphin' OR ' nobligan' OR ' nonalges' OR ' o.p. pain' OR ' omnidol' OR ' pengesic' OR ' penimadol' OR ' prontofort' OR ' radol' OR ' rofy' OR ' ryzolt' OR ' sefmal' OR ' sensitram' OR ' takadol' OR ' tamolan' OR ' tandol' OR ' tarol' OR ' topalgic' OR ' trabar' OR ' trabilan' OR ' trabilin' OR ' tradol' OR ' tradol-puren' OR ' tradolan' OR ' tradonal' OR ' tralic' OR ' tramada' OR ' tramadex' OR ' tramadol hydrochloride' OR ' tramadolium chloride' OR ' tramagetic' OR ' tramagit' OR ' tramahexal' OR ' tramake' OR ' tramal' OR ' tramal sr' OR ' tramazac' OR ' tramed' OR ' tramol' OR ' tramundin' OR ' tramundin retard' OR ' trans 2 [(dimethylamino) methyl] 1 (3 methoxyphenyl) cyclohexanol' OR ' trans 2 [(dimethylamino) methyl] 1 (meta methoxyphenyl) cyclohexanol hydrochloride' OR ' trans 2 dimethylaminomethyl 1 (3 methoxyphenyl) cyclohexanol' OR ' trasedal' OR ' trasik' OR ' trd-contin' OR ' trexol' OR ' tridol' OR ' trodon' OR ' trondon' OR ' u 26225a' OR ' u26225a' OR ' ultram' OR ' ultram er' OR ' unitral' OR ' urgendol' OR ' zamadol' OR ' zamudol' OR ' zodol' OR ' zumatran' OR ' zydol' OR ' zytram bd' OR ' zytram xl sr' OR 'oxycodone'/exp OR 'bionine' OR ' bionone' OR ' bolodorm' OR ' broncodal' OR ' bucodal' OR ' cafacodal' OR ' cardanon' OR ' codenon' OR ' codix 5' OR ' col 003' OR ' col003' OR ' dihydrohydroxycodeinone' OR ' dihydrohydroxydodeinone' OR ' dihydrone' OR ' dinarkon' OR ' endone' OR ' eubine'	418,269

EmBase search strategy		
#	**Searches**	**Results**
	OR ‘ eucodal’ OR ‘ eucodale’ OR ‘ eucodalum’ OR ‘ eudin’ OR ‘ eukdin’ OR ‘ eukodal’ OR ‘ eumorphal’ OR ‘ eurodamine’ OR ‘ eutagen’ OR ‘ hydrocodal’ OR ‘ hydroxycodeinoma’ OR ‘ ludonal’ OR ‘ m-oxy’ OR ‘ medicodal’ OR ‘ narcobasina’ OR ‘ narcobasine’ OR ‘ narcosin’ OR ‘ nargenol’ OR ‘ narodal’ OR ‘ nsc 19043’ OR ‘ nucodan’ OR ‘ opton’ OR ‘ ossicodone’ OR ‘ oxanest’ OR ‘ oxecta’ OR ‘ oxicone’ OR ‘ oxicontin’ OR ‘ oxiconum’ OR ‘ oxikon’ OR ‘ oxy ir’ OR ‘ oxycod’ OR ‘ oxycodeinonhydrochloride’ OR ‘ oxycodone hydrochloride’ OR ‘ oxycodonhydrochlorid’ OR ‘ oxycodyl’ OR ‘ oxycone’ OR ‘ oxycontin’ OR ‘ oxycontin cr’ OR ‘ oxycontin lp’ OR ‘ oxydose’ OR ‘ oxyfast’ OR ‘ oxygesic’ OR ‘ oxyir’ OR ‘ oxykon’ OR ‘ oxynorm’ OR ‘ pancodine’ OR ‘ pavinal’ OR ‘ percolone’ OR ‘ pronarcin’ OR ‘ remoxy’ OR ‘ roxicodone’ OR ‘ roxycodone’ OR ‘ sinthiodal’ OR ‘ stupenal’ OR ‘ supeudol’ OR ‘ tebodal’ OR ‘ tekodin’ OR ‘ thecodin’ OR ‘substance’:ti,ab) AND (misuse:ti,ab OR use:ti,ab OR abuse:ti,ab OR dependence:ti,ab OR dependency:ti,ab OR addiction:ti,ab OR habituation:ti,ab OR disorder*:ti,ab OR consumption:ti,ab)	
3	#1 AND #2	650,852
4	'pregnant woman'/exp OR 'pregnancy'/exp OR 'child bearing':ti,ab OR 'childbearing':ti,ab OR pregnant:ti,ab OR pregnancy:ti,ab OR 'breast feeding education'/exp OR 'breastfed':ti,ab OR breastfeed*:ti,ab OR breast NEXT/2 feed* OR 'puerperium'/exp OR 'postpartum':ti,ab OR postpartum:ti,ab OR 'ante natal':ti,ab OR prenatal:ti,ab OR postnatal:ti,ab OR 'postnatal':ti,ab OR lactat*:ti,ab OR 'prenatal drug exposure'/exp OR 'maternal exposure':ti,ab	990,027
5	#3 AND #4	29,732
6	'Clinical trial'/exp OR 'Randomized controlled trial'/exp OR 'Randomization'/exp OR 'Single blind procedure'/exp OR 'Double blind procedure'/exp OR 'Crossover procedure'/exp OR 'Placebo'/exp OR 'Randomized controlled trials':ti,ab OR 'Randomized controlled trial':ti,ab OR 'Randomized controlled trials':ti,ab OR 'Randomized controlled trial':ti,ab OR rct:ti,ab OR 'Random allocation':ti,ab OR 'Randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEAR/2 random):ti,ab OR ('Single' NEAR/2 blind*):ti,ab OR ('double' NEAR/2 blind*):ti,ab OR ((treble or triple) NEAR/3 blind*):ti,ab OR Placebo*:ti,ab OR 'Prospective study'/exp	1,361,716
7	'systematic review'/exp OR 'systematic review (topic)'/exp OR 'review'/exp/mj OR 'medlars':ti,ab OR 'pubmed':ti,ab OR 'scisearch':ti,ab OR 'bibliographic database'/exp OR 'psychlit':ti,ab OR 'psyclit':ti,ab OR biosis:ti,ab OR ‘british nursing index’:ti,ab OR ‘cinahl’:ti,ab OR ‘cochrane library’:ti,ab OR ‘campbell library’:ti,ab OR ‘full text databases’:ti,ab OR ‘international pharmaceutical abstracts’:ti,ab OR toxlit:ti,ab OR 'electronic databases':ti,ab OR 'electronic database':ti,ab OR (hand NEAR/3 search*) OR (manual* NEAR/3 search*) OR (bibliographic NEAR/3 database*) OR (pooled NEAR/3 analys*) OR pooling OR peto OR sesimonian OR (fixed NEAR/3 effect) OR 'mantel haenszel':ti,ab OR 'meta analysis'/exp OR 'meta analysis' OR 'retracted article'/exp OR 'retracted article' OR (systematic* NEAR/3 review*) OR (systematic* NEAR/5 overview*) OR (quantitative* NEAR/3 review*) OR (quantitative* NEAR/3 overview*) OR (methodologic* NEAR/3 review*) OR (methodologic* NEAR/5 overview*) OR (integrative NEAR/3 review*) OR (research NEAR/3 integration) OR (quantitative* NEAR/3 synthesi*) OR (systematic* NEAR/3 search*) OR medline:ti,ab OR embase:ti,ab	256,647
8	#6 OR #7	1,525,780
9	#5 AND #8	3614

PsychInfo search strategy		
#	**Searches**	**Results**
1	(((DE "Alcohol Drinking Attitudes" OR DE "Alcohol Drinking Patterns" OR DE "Alcohol Abuse" OR DE "Alcohol Intoxication" OR DE "Social Drinking" OR DE "Alcohol Intoxication" OR DE "Acute Alcoholic Intoxication" OR DE "Chronic Alcoholic Intoxication" OR DE "Alcohol Rehabilitation" OR DE "Alcoholics Anonymous" OR DE "Detoxification" OR DE "Alcohol Withdrawal" OR DE "Alcoholic Beverages" OR DE "Beer" OR DE "Liquor" OR DE "Wine" OR DE "Alcoholism" OR DE "Alcoholic Psychosis" OR DE "Alcohols" OR DE "Ethanol" OR DE "Isoproterenol" OR DE "Methanol" OR DE "Methoxamine") AND (DE "Alcohol Withdrawal" OR DE "Alcoholism")) AND (DE "Fetal Alcohol Syndrome" OR DE "Prenatal Exposure")) OR (DE "Fetal Alcohol Syndrome") OR TI "alcohol drinking" OR TI alcoholism OR TI alcohol OR AB "alcohol drinking" OR AB alcoholism OR AB alcohol	83,667
2	(DE "Addiction" OR DE "Alcoholism" OR DE "Drug Addiction") AND (DE "Drug Abuse" OR DE "Drug Addiction" OR DE "Drug Dependency") OR TI "recreational drug*" OR TI "street drug*" OR TI "designer drug*" OR TI "illicit drug*" OR AB "recreational drug*" OR AB "street drug*" OR AB "designer drug*" OR AB "illicit drug*" OR DE "Heroin" OR DE "Heroin Addiction" OR DE "Cannabis" OR DE "Hashish" OR DE "Marijuana" OR DE "Amphetamine" OR DE "Dextroamphetamine" OR DE "Methamphetamine" OR 'addiction' OR 'substance-related disorders' OR 'substance-related disorder' OR 'chemical dependence' OR 'addictive behavior' OR 'addictive behaviour' OR 'addictive behaviors' OR 'addictive behaviours' OR 'drug misuse'/exp OR 'drug misuse' OR 'street drug' OR 'street drugs' OR 'recreational drugs' OR 'recreational drug' OR 'illicit drugs' OR 'illicit drug' OR cocaine OR 'cannabis' OR cannabis OR 'cannabis smoking' OR marijuana* OR hashish OR TI bhang OR ' C indica' OR cannador* OR charas* OR ganja* OR ganjah* OR hemp* OR marihuana* OR heroin OR 'amphetamine' OR amphetamine OR 'actedron' OR ' actemin' OR ' adderall' OR ' adderall ir' OR ' adderall xr' OR ' adipan' OR ' aktedrin' OR ' aktedron' OR ' alentol' OR ' allodene' OR ' alpha amphetamine' OR ' alpha methylphenethylamine' OR ' alpha methylphenylethylamine' OR ' amfetamine' OR ' amphamed' OR ' amphamine' OR ' amphetaime' OR ' amphetamin' OR ' amphetamine base phosphate' OR ' amphetamine base sulfate' OR ' amphetamine detection' OR ' amphetamine hydrochloride' OR ' amphetamine intoxication' OR ' amphetamine metabolism' OR ' amphetamine phosphate' OR ' amphetamine resin complex' OR ' amphetamine sulfate' OR ' amphetamine toxicity' OR ' amphetaminyl' OR ' amphethamine' OR ' amphezamin' OR ' anara' OR ' astedin' OR ' badrin' OR ' benzafinyl' OR ' benzebar' OR ' benzedrine' OR ' benzolone' OR ' benzpropamin' OR ' benzpropamine' OR ' beta aminopropylbenzene' OR ' beta phenyl isopropylamine' OR ' beta phenylisopropylamine' OR ' betafen' OR ' bluzedrin' OR ' centramina' OR ' centramine' OR ' d l amphetamine' OR ' delta amphetamine' OR ' desoxynorephedrin' OR ' dextro levo 2 methylphenethylamine' OR ' dextro levo 2 methylphenetylamine' OR ' dextro levo alpha methylphenethylamine' OR ' dextro levo amphetamine' OR ' dextrolevo amphetamine' OR ' diethamine' OR ' diethanine' OR ' dipan' OR ' elastonin' OR ' elastonon' OR ' euphobine' OR ' euphodine' OR ' euphodyn' OR ' fabedrine' OR ' fenara' OR ' fenedrin' OR ' ibiozedrine' OR ' isoamin' OR ' isoamine' OR ' isoamyn' OR ' isoamyne' OR ' isomyn' OR ' l amphetamine' OR ' levamfetamine' OR ' levamphetamine' OR ' levedrine' OR ' levo amphetamine' OR ' levo amphetamine sulphate' OR ' levoamphetamine' OR ' linampheta' OR ' mecodrin' OR ' mimetina' OR ' monetamin' OR ' monophos' OR ' noclon' OR ' norephedrane' OR ' norphedrane' OR ' novydrine' OR ' obesin andromacro' OR ' obetrol' OR ' oktedrin' OR ' oraldrina' OR ' ortedrine' OR ' percomon' OR ' pharmamedrine' OR ' pharmedrine' OR ' phenamin' OR ' phenedrine' OR ' phenoprominum' OR ' phenpromin' OR ' phenyl isopropylamine' OR ' phenylaminopropane' OR ' profamina' OR ' profetamine' OR ' propisamine' OR ' psychedrin' OR ' psychedrine' OR ' psychoton' OR ' racemic desoxy nor ephedrine' OR ' racemic desoxy norephedrine' OR ' racephen' OR ' raphetamine' OR ' rhinalator' OR ' sedolin' OR ' simpamina' OR ' simpamine' OR ' simpatedrin' OR ' simpatedrine' OR ' stimulan' OR ' sympametin' OR ' sympamine' OR ' sympatedrine' OR ' theptine' OR ' vapedrine' OR ' zedrin' OR ' zedrine' OR (TI Drugs OR AB Drugs OR benzodiazepine OR 'opiate' OR opioids OR 'tramadol' OR 'adamon' OR ' amanda' OR ' analab' OR ' analdol' OR ' andalpha' OR ' bellatram' OR ' biodalgic' OR ' calmador' OR ' calmol' OR ' cg 315e' OR ' cg315e' OR ' contramal' OR ' contramal lp' OR ' dolana' OR ' dolika' OR ' dolmal' OR ' dolotral' OR ' dolzam' OR ' dromadol' OR ' e 381' OR ' e 382' OR ' e381' OR ' e382' OR ' eufindol' OR ' exopen' OR ' katrasic' OR ' kontram xl' OR ' kontram xl sr' OR ' mabron' OR ' melanate' OR ' mosepan' OR ' newdorphin' OR ' nobligan' OR ' nonalges' OR ' o.p. pain' OR ' omnidol' OR ' pengesic' OR ' penimadol' OR ' prontofort' OR ' radol' OR ' rofy' OR ' ryzolt' OR ' sefmal' OR ' sensitram' OR ' takadol' OR ' tamolan' OR ' tandol' OR ' tarol' OR ' topalgic' OR ' trabar' OR ' trabilan' OR ' trabilin' OR ' tradol' OR ' tradol-puren' OR ' tradolan' OR ' tradonal' OR ' tralic' OR ' tramada' OR ' tramadex' OR	170,118

PsychInfo search strategy		
#	**Searches**	**Results**
	‘ tramadol hydrochloride’ OR ‘ tramadolium chloride’ OR ‘ tramagetic’ OR ‘ tramagit’ OR ‘ tramahexal’ OR ‘ tramake’ OR ‘ tramal’ OR ‘ tramal sr’ OR ‘ tramazac’ OR ‘ tramed’ OR ‘ tramol’ OR ‘ tramundin’ OR ‘ tramundin retard’ OR ‘ trasedal’ OR ‘ trasik’ OR ‘ trd-contin’ OR ‘ trexol’ OR ‘ tridol’ OR ‘ trodon’ OR ‘ trondon’ OR ‘ u 26225a’ OR ‘ u26225a’ OR ‘ ultram’ OR ‘ ultram er’ OR ‘ unitral’ OR ‘ urgendol’ OR ‘ zamadol’ OR ‘ zamudol’ OR ‘ zodol’ OR ‘ zumatran’ OR ‘ zydol’ OR ‘ zytram bd’ OR ‘ zytram xl sr’ OR 'oxycodone' OR ‘bionine’ OR ‘ bionone’ OR ‘ bolodorm’ OR ‘ broncodal’ OR ‘ bucodal’ OR ‘ cafacodal’ OR ‘ cardanon’ OR ‘ codenon’ OR ‘ codix 5’ OR ‘ col 003’ OR ‘ col003’ OR ‘ dihydrohydroxycodeinone’ OR ‘ dihydrohydroxydodeinone’ OR ‘ dihydrone’ OR ‘ dinarkon’ OR ‘ endone’ OR ‘ eubine’ OR ‘ eucodal’ OR ‘ eucodale’ OR ‘ eucodalum’ OR ‘ eudin’ OR ‘ eukdin’ OR ‘ eukodal’ OR ‘ eumorphal’ OR ‘ eurodamine’ OR ‘ eutagen’ OR ‘ hydrocodal’ OR ‘ hydroxycodeinoma’ OR ‘ ludonal’ OR ‘ m-oxy’ OR ‘ medicodal’ OR ‘ narcobasina’ OR ‘ narcobasine’ OR ‘ narcosin’ OR ‘ nargenol’ OR ‘ narodal’ OR ‘ nsc 19043’ OR ‘ nucodan’ OR ‘ opton’ OR ‘ ossicodone’ OR ‘ oxanest’ OR ‘ oxecta’ OR ‘ oxicone’ OR ‘ oxicontin’ OR ‘ oxiconum’ OR ‘ oxikon’ OR ‘ oxy ir’ OR ‘ oxycod’ OR ‘ oxycodeinonhydrochloride’ OR ‘ oxycodone hydrochloride’ OR ‘ oxycodonhydrochlorid’ OR ‘ oxycodyl’ OR ‘ oxycone’ OR ‘ oxycontin’ OR ‘ oxycontin cr’ OR ‘ oxycontin lp’ OR ‘ oxydose’ OR ‘ oxyfast’ OR ‘ oxygesic’ OR ‘ oxyir’ OR ‘ oxykon’ OR ‘ oxynorm’ OR ‘ pancodine’ OR ‘ pavinal’ OR ‘ percolone’ OR ‘ pronarcin’ OR ‘ remoxy’ OR ‘ roxicodone’ OR ‘ roxycodone’ OR ‘ sinthiodal’ OR ‘ stupenal’ OR ‘ supeudol’ OR ‘ tebodal’ OR ‘ tekodin’ OR ‘ thecodin’ OR ‘substance’:ti,ab) AND (TI misuse OR AB misuse OR TI use OR AB use OR TI abuse OR AB abuse OR TI dependence OR AB dependence OR TI dependency OR AB dependency OR TI addiction OR AB addiction OR TI habituation OR AB habituation OR TI disorder* OR AB disorder* OR TI consumption OR AB consumption)	
3	#1 AND #2	207,330
4	DE "Pregnancy" OR DE "Adolescent Pregnancy" OR DE "Pregnancy Outcomes" OR DE "Birth" OR DE "Induced Abortion" OR DE "Premature Birth" OR DE "Spontaneous Abortion" OR DE "Prenatal Care" OR DE "Childbirth Training" OR DE "Prenatal Development" OR DE "Prenatal Developmental Stages" OR DE "Prenatal Developmental Stages" OR DE "Embryo" OR DE "Fetus" OR DE "Prenatal Exposure" OR TI Pregnancy OR AB Pregnancy OR TI pregnant OR AB Pregnant OR DE "Postnatal Period" OR DE "Perinatal Period" OR DE "Prenatal Care" OR DE "Prenatal Development" OR DE "Prenatal Developmental Stages" OR DE "Prenatal Exposure" OR DE "Prenatal Care" OR DE "Childbirth Training" OR DE "Prenatal Development" OR DE "Prenatal Developmental Stages" OR DE "Prenatal Developmental Stages" OR DE "Prenatal Exposure" OR TI postpartum OR AB postpartum OR TI postnatal OR AB Postnatal OR TI perinatal OR AB perinatal OR TI postpartum OR AB postpartum OR "maternal exposure" OR TI lactat* OR AB lactat*	63,174
5	#3 AND #4	7,796
6	(((DE "Placebo") OR (DE "Clinical Trials")) OR (DE "Evidence Based Practice" OR DE "Treatment Effectiveness Evaluation")) OR (DE "Random Sampling") OR TX allocat* random* OR TX placebo* OR TX random* allocate* OR TX randomi* control* trial* OR TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*)) OR TX clinic* n1 trial*	92,996
7	(MH "Meta Analysis") OR "meta analysis" OR (MH "Literature Review+") OR "literature review" OR (MH "Systematic Review") OR "meta analys*" OR metaanalys* OR (Systematic AND (review OR overview)) OR TI medlars OR AB medlars OR TI pubmed OR AB pubmed OR TI scisearch OR AB scisearch OR TI “british nursing index” OR AB “british nursing index” OR “Cochrane library” OR “Campbell library” OR “full text databases “ OR “electronic databases” OR handsearching OR systematic n3 literature OR systematic review* OR meta-analy* OR metaanaly* OR "research synthesis" OR embase OR medline OR psyclit OR pubmed OR scopus OR "sociological abstracts" OR "web of science" OR "systematic review" or "meta analysis"	66,904
8	#6 OR #7	152,807
9	#5 AND #8	512

CINAHL search strategy		
#	Searches	Results
1	"alcohol drinking" OR (MH "Drinking Behavior+") OR (MH "Alcohol Rehabilitation Programs+") OR (MH "Alcohol Withdrawal Syndrome+") OR (MH "Alcohol-Induced Disorders, Nervous System+") OR (MH "Alcohol-Related Disorders") OR (MH "Substance Abuse+") OR (MH "Alcohol Abuse Control (Saba CCC)") OR (MH "Alcohol Abuse (Saba CCC)") OR (MH "Alcohol Deterrents+") OR (MH "Alcoholism") OR (MH "Substance Use Treatment: Alcohol Withdrawal (Iowa NIC)") OR (MH "Alcoholics") OR (MH "Fetal Alcohol Syndrome") OR (MH "Substance Abuse Detection") OR TI "alcohol drinking" OR TI alcoholism OR TI alcohol OR AB "alcohol drinking" OR AB alcoholism OR AB alcohol	65,704
2	(MH "Addictions Nursing") OR (MH "Infant, Drug-Exposed") OR (MH "Substance Addiction Consequences (Iowa NOC)") OR (MH "Analgesics, Opioid+") OR (MH "Substance Dependence+") OR (MH "Street Drugs") OR "illicit drugs" OR (MH "Substance Abuse Detection") OR (MH "Substance Abusers") OR (MH "Drug Abuse (Saba CCC)") OR (MH "Drug Abuse Control (Saba CCC)") OR (MH "Designer Drugs") OR (MH "Cannabis") OR (MH "Cocaine+") OR "cocaine" OR (MH "Heroin") OR (MH "Amphetamine") OR (MH "Albuterol") OR 'addiction' OR 'substance-related disorders' OR 'substance-related disorder' OR 'chemical dependence' OR 'addictive behavior' OR 'addictive behaviour' OR 'addictive behaviors' OR 'addictive behaviours' OR 'drug misuse'/exp OR 'drug misuse' OR 'street drug' OR 'street drugs' OR 'recreational drugs' OR 'recreational drug' OR 'illicit drugs' OR 'illicit drug' OR cocaine OR 'cannabis' OR cannabis OR 'cannabis smoking' OR marijuana* OR hashish OR TI bhang OR ' C indica' OR cannador* OR charas* OR ganja* OR ganjah* OR hemp* OR marihuana* OR heroin OR 'amphetamine' OR amphetamine OR 'actedron' OR ' actemin' OR ' adderall' OR ' adderall ir' OR ' adderall xr' OR ' adipan' OR ' aktedrin' OR ' aktedron' OR ' alentol' OR ' allodene' OR ' alpha amphetamine' OR ' alpha methylphenethylamine' OR ' alpha methylphenylethylamine' OR ' amfetamine' OR ' amphamed' OR ' amphamine' OR ' amphetaime' OR ' amphetamin' OR ' amphetamine base phosphate' OR ' amphetamine base sulfate' OR ' amphetamine detection' OR ' amphetamine hydrochloride' OR ' amphetamine intoxication' OR ' amphetamine metabolism' OR ' amphetamine phosphate' OR ' amphetamine resin complex' OR ' amphetamine sulfate' OR ' amphetamine toxicity' OR ' amphetaminyl' OR ' amphethamine' OR ' amphezamin' OR ' anara' OR ' astedin' OR ' badrin' OR ' benzafinyl' OR ' benzebar' OR ' benzedrine' OR ' benzolone' OR ' benzpropamin' OR ' benzpropamine' OR ' beta aminopropylbenzene' OR ' beta phenyl isopropylamine' OR ' beta phenylisopropylamine' OR ' betafen' OR ' bluzedrin' OR ' centramina' OR ' centramine' OR ' d l amphetamine' OR ' delta amphetamine' OR ' desoxynorephedrin' OR ' dextro levo 2 methylphenethylamine' OR ' dextro levo 2 methylphenetylamine' OR ' dextro levo alpha methylphenethylamine' OR ' dextro levo amphetamine' OR ' dextrolevo amphetamine' OR ' diethamine' OR ' diethanine' OR ' dipan' OR ' elastonin' OR ' elastonon' OR ' euphobine' OR ' euphodine' OR ' euphodyn' OR ' fabedrine' OR ' fenara' OR ' fenedrin' OR ' ibiozedrine' OR ' isoamin' OR ' isoamine' OR ' isoamyn' OR ' isoamyne' OR ' isomyn' OR ' l amphetamine' OR ' levamfetamine' OR ' levamphetamine' OR ' levedrine' OR ' levo amphetamine' OR ' levo amphetamine sulphate' OR ' levoamphetamine' OR ' linampheta' OR ' mecodrin' OR ' mimetina' OR ' monetamin' OR ' monophos' OR ' noclon' OR ' norephedrane' OR ' norphedrane' OR ' novydrine' OR ' obesin andromacro' OR ' obetrol' OR ' oktedrin' OR ' oraldrina' OR ' ortedrine' OR ' percomon' OR ' pharmamedrine' OR ' pharmedrine' OR ' phenamin' OR ' phenedrine' OR ' phenoprominum' OR ' phenpromin' OR ' phenyl isopropylamine' OR ' phenylaminopropane' OR ' profamina' OR ' profetamine' OR ' propisamine' OR ' psychedrin' OR ' psychedrine' OR ' psychoton' OR ' racemic desoxy nor ephedrine' OR ' racemic desoxy norephedrine' OR ' racephen' OR ' raphetamine' OR ' rhinalator' OR ' sedolin' OR ' simpamina' OR ' simpamine' OR ' simpatedrin' OR ' simpatedrine' OR ' stimulan' OR ' sympametin' OR ' sympamine' OR ' sympatedrine' OR ' theptine' OR ' vapedrine' OR ' zedrin' OR ' zedrine' OR (TI Drugs OR AB Drugs OR benzodiazepine OR 'opiate' OR opioids OR 'tramadol' OR 'adamon' OR ' amanda' OR ' analab' OR ' analdol' OR ' andalpha' OR ' bellatram' OR ' biodalgic' OR ' calmador' OR ' calmol' OR ' cg 315e' OR ' cg315e' OR ' contramal' OR ' contramal lp' OR ' dolana' OR ' dolika' OR ' dolmal' OR ' dolotral' OR ' dolzam' OR ' dromadol' OR ' e 381' OR ' e 382' OR ' e381' OR ' e382' OR ' eufindol' OR ' exopen' OR ' katrasic' OR ' kontram xl' OR ' kontram xl sr' OR ' mabron' OR ' melanate' OR ' mosepan' OR ' newdorphin' OR ' nobligan' OR ' nonalges' OR ' o.p. pain' OR ' omnidol' OR ' pengesic' OR ' penimadol' OR ' prontofort' OR ' radol' OR ' rofy' OR ' ryzolt' OR ' sefmal' OR ' sensitram' OR ' takadol' OR ' tamolan' OR ' tandol' OR ' tarol' OR ' topalgic' OR ' trabar' OR ' trabilan' OR ' trabilin' OR ' tradol' OR ' tradol-puren' OR ' tradolan' OR ' tradonal' OR ' tralic' OR ' tramada' OR ' tramadex' OR ' tramadol hydrochloride' OR ' tramadolium chloride' OR ' tramagetic' OR ' tramagit' OR	105,036

CINAHL search strategy		
#	**Searches**	**Results**
	' tramahexal' OR ' tramake' OR ' tramal' OR ' tramal sr' OR ' tramazac' OR ' tramed' OR ' tramol' OR ' tramundin' OR ' tramundin retard' OR ' trasedal' OR ' trasik' OR ' trd-contin' OR ' trexol' OR ' tridol' OR ' trodon' OR ' trondon' OR ' u 26225a' OR ' u26225a' OR ' ultram' OR ' ultram er' OR ' unitral' OR ' urgendol' OR ' zamadol' OR ' zamudol' OR ' zodol' OR ' zumatran' OR ' zydol' OR ' zytram bd' OR ' zytram xl sr' OR 'oxycodone' OR 'bionine' OR ' bionone' OR ' bolodorm' OR ' broncodal' OR ' bucodal' OR ' cafacodal' OR ' cardanon' OR ' codenon' OR ' codix 5' OR ' col 003' OR ' col003' OR ' dihydrohydroxycodeinone' OR ' dihydrohydroxydodeinone' OR ' dihydrone' OR ' dinarkon' OR ' endone' OR ' eubine' OR ' eucodal' OR ' eucodale' OR ' eucodalum' OR ' eudin' OR ' eukdin' OR ' eukodal' OR ' eumorphal' OR ' eurodamine' OR ' eutagen' OR ' hydrocodal' OR ' hydroxycodeinoma' OR ' ludonal' OR ' m-oxy' OR ' medicodal' OR ' narcobasina' OR ' narcobasine' OR ' narcosin' OR ' nargenol' OR ' narodal' OR ' nsc 19043' OR ' nucodan' OR ' opton' OR ' ossicodone' OR ' oxanest' OR ' oxecta' OR ' oxicone' OR ' oxicontin' OR ' oxiconum' OR ' oxikon' OR ' oxy ir' OR ' oxycod' OR ' oxycodeinonhydrochloride' OR ' oxycodone hydrochloride' OR ' oxycodonhydrochlorid' OR ' oxycodyl' OR ' oxycone' OR ' oxycontin' OR ' oxycontin cr' OR ' oxycontin lp' OR ' oxydose' OR ' oxyfast' OR ' oxygesic' OR ' oxyir' OR ' oxykon' OR ' oxynorm' OR ' pancodine' OR ' pavinal' OR ' percolone' OR ' pronarcin' OR ' remoxy' OR ' roxicodone' OR ' roxycodone' OR ' sinthiodal' OR ' stupenal' OR ' supeudol' OR ' tebodal' OR ' tekodin' OR ' thecodin' OR 'substance':ti,ab) AND (TI misuse OR AB misuse OR TI use OR AB use OR TI abuse OR AB abuse OR TI dependence OR AB dependence OR TI dependency OR AB dependency OR TI addiction OR AB addiction OR TI habituation OR AB habituation OR TI disorder* OR AB disorder* OR TI consumption OR AB consumption)	
3	#1 AND #2	105,036
4	(MH "Expectant Mothers") OR "pregnant women" OR "pregnant woman" OR (MH "Pregnancy+") OR (MH "Pregnancy in Adolescence+") OR (MH "Attitude to Pregnancy") OR (MH "Prenatal Exposure Delayed Effects") OR (MH "Pregnancy, Unwanted") OR (MH "Pregnancy, Unplanned") OR (MH "Pregnancy Trimesters") OR (MH "Pregnancy, Multiple") OR (MH "Breast Feeding+") OR (MH "Knowledge: Breastfeeding (Iowa NOC)") OR (MH "Breastfeeding Impairment (Saba CCC)") OR (MH "Attitude to Breast Feeding") OR (MH "Breast Feeding Promotion") OR (MH "Perinatal Care") OR (MH "Postnatal Care+") OR (MH "Intrapartum Care+") OR (MH "Prenatal Care") OR (MH "Prepregnancy Care") OR (MH "Postpartum Care (Saba CCC)") OR (MH "Postpartum (Omaha)") OR (MH "Maternal Exposure") OR "maternal exposure" OR (MH "Maternal Behavior") OR (MH "Maternal Attitudes") OR (MH "Postexposure Follow-Up") OR (MH "Substance Abuse, Perinatal")	131,778
5	#3 AND #4	5,985
6	TX allocat* random* OR (MH "Quantitative Studies") OR (MH "Placebos") OR TX placebo* OR TX random* allocate* OR (MH "Random Assignment") OR TX randomi* control* trial* OR TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*)) OR TX clinic* n1 trial* OR PT Clinical trial OR (MH "Clinical trial+")	70,555
7	(MH "Meta Analysis") OR "meta analysis" OR (MH "Literature Review+") OR "literature review" OR (MH "Systematic Review") OR "meta analys*" OR metaanalys* OR (Systematic AND (review OR overview)) OR TI medlars OR AB medlars OR TI pubmed OR AB pubmed OR TI scisearch OR AB scisearch OR TI psychlit OR AB psychlit OR TI psycINFO OR AB psycINFO OR TI "british nursing index" OR AB "british nursing index" OR "Cochrane library" OR "Campbell library" OR "full text databases " OR "electronic databases" OR handsearching	211,972
8	#6 OR #7	211,972
9	#5 AND #8	754

CENTRAL search strategy		
ID	**Search**	**Hits**
#1	MeSH descriptor: [Alcohol Drinking] explode all trees	2140
#2	MeSH descriptor: [Alcohol-Related Disorders] explode all trees	3234
#3	MeSH descriptor: [Alcoholism] this term only	2215
#4	MeSH descriptor: [Fetal Alcohol Syndrome] explode all trees	33
#5	alcohol:ti,ab	8351
#6	#1 or #2 or #3 or #4 or #5	9549
#7	MeSH descriptor: [Substance-Related Disorders] explode all trees	10670
#8	MeSH descriptor: [Prescription Drug Misuse] explode all trees	7
#9	MeSH descriptor: [Street Drugs] explode all trees	203
#10	MeSH descriptor: [Designer Drugs] explode all trees	5
#11	MeSH descriptor: [Cannabis] explode all trees	247
#12	MeSH descriptor: [Heroin] explode all trees	240
#13	MeSH descriptor: [Amphetamines] explode all trees	1039
#14	street drugs:ti,ab or "recreational drugs":ti,ab or "illicit drugs":ti,ab or cocaine:ti,ab or designer drugs:ti,ab or cannabis:ti,ab or marijuana*:ti,ab or hashish:ti,ab or bhang*:ti,ab or ganja*:ti,ab or hemp:ti,ab or heroin:ti,ab or amphetamine*:ti,ab (Word variations have been searched)	4251
#15	(drug or benzodiazepine or opioids or prescription or barbiturate or tramadol or oxycodone or substance):ti,ab next/6 (misuse or use or abuse or abuses or dependence or dependency or addiction or habituation or disorder or consumption):ab,ti (Word variations have been searched)	9715
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	20886
#17	MeSH descriptor: [Pregnant Women] explode all trees	74
#18	MeSH descriptor: [Pregnancy] explode all trees	5318
#19	MeSH descriptor: [Breast Feeding] explode all trees	1154
#20	MeSH descriptor: [Postpartum Period] explode all trees	957
#21	MeSH descriptor: [Maternal Exposure] explode all trees	27
#22	pregnant:ti,ab or pregnancy:ti,ab or antenatal:ti,ab or ante-natal:ti,ab or prenatal:ti,ab or "breast feed*":ti,ab or breastfeed*:ti,ab or postnatal:ti,ab or post-natal:ti,ab or postpartum:ti,ab or lactat*:ti,ab or "maternal exposure*":ti,ab (Word variations have been searched)	22381
#23	#17 or #18 or #19 or #20 or #21 or #22	24867
#24	#6 and #16 and #23 in Trials	84

ANNEX 3: SCREENING INSTRUMENTS FOR SUBSTANCE USE IN PRENATAL OR PREGNANT WOMEN

Measure	Acronym	Substances screened	Number of items	Method of administration	Training in administration	Other considerations	Internal consistency reliability	Sensitivity	Specificity
♦Alcohol, Smoking, and Substance Involvement Screening Test (Version 3.0)[1]	ASSIST	Tobacco, Alcohol, and Substances	^8	Interviewer	Yes	‡		Alcohol: 67% Cannabis: 100%	Alcohol: 36% Cannabis: 20%
4P's Plus[2]	4Ps Plus	Alcohol and General Substance Use	4	Paper-and-pencil	No	Inpatient and Outpatient	.62	87%	76%
Hospital Screening Questionnaire[3]	HSQ	Tobacco, Alcohol, and Substances	18–40	Paper-and-pencil	No	Inpatient: Postpartum			
Pregnancy Information Program[4]	PIP	Tobacco, Alcohol, and Substances	~200	Computer	No	Prenatal Clinic and Ob/Gyn Offices			
Substance Use Risk Profile – Pregnancy[5]	SURP-P	Alcohol and Substances	3	Paper-and-pencil	No	Prenatal Clinic		†Low-risk: 80–100% High-risk: 48–100%	Low-risk: 61–64% High-risk: 84–86%
Alcohol Use Disorder Identification Test[6]	AUDIT	Alcohol	10	Paper-and-pencil and Interviewer	No	‡		*7–23%	*97–100%
Alcohol Use Disorder Identification Test – Consumption[7]	AUDIT-C	Alcohol	3	Paper-and-pencil and Interviewer	No	‡		*18–100%	*71–100%
CAGE[8,9]	CAGE	Alcohol	4	Paper-and-pencil	No	‡		*38–59%	*82–92%
NET[10]	NET	Alcohol	3	Paper-and-pencil	No	Inpatient and Outpatient		*24–71%	*86–99%
Short Michigan Alcohol Screening Test[11]	SMAST	Alcohol	13	Paper-and-pencil	No	‡		*11–15%	*96–98%
Ten Question Drinking History[12]	TQDH	Alcohol	10	Interviewer	Yes	Prenatal Clinic			
T-ACE[13]	T-ACE	Alcohol	4	Paper-and-pencil	No	Prenatal Clinic		*60–91%	*37–79%
TWEAK[14]	TWEAK	Alcohol	5	Paper-and-pencil	No	Prenatal Clinic		*59–92%	*64–92%

Notes: Sensitivities and Specificities are only provided for samples of prenatal or pregnant women. ♦The researchers report that "The role of the ASSIST V3.0 is uncertain for this population" [pregnant women] (Abstract). ^Questions 1-7 each ask about 10 classes of substances. ‡ Not initially developed and validated for prenatal or pregnant populations. *Sensitivities and Specificities vary depending on the cutpoint used to determine risk. †Alcohol, Cannabis, Cocaine, Sedatives, Opioids

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ANNEX 4: COMPOSITION OF GUIDELINE GROUPS

WHO Steering Group

Name	WHO Department
Avni Amin	Reproductive Health and Research
Lubna Bhatti	Tobacco Free Initiative
Nicolas Clark	Mental Health and Substance Abuse
Ahmet Metin Gulmezoglu	Reproductive Health and Research
Rajat Khosla	Gender Equity and Human Rights
Mathews Mathai	Maternal and Child Health
Mario Merialdi	Reproductive Health and Research
Vladimir Poznyak	Mental Health and Substance Abuse
Shekhar Saxena	Mental Health and Substance Abuse
Edouard Tursan d'Espaignet	Tobacco Free Initiative

Guideline Development Group

	F/M	AFFILIATION	ORIGIN (WHO REGION)		EXPERIENCE/KNOWLEDGE BASIS				
Name	**Gender**	**Current affiliation**	**Country of origin**	**WHO Region**	**Has expertise on substance use treatment**	**Has expertise on obstetric care**	**Has expertise on infants exposed to psychoactive substances**	**Has extensive low and middle income setting experience**	**Methodologist (systematic reviews)**
Sawitri **Assanangkornchai**	F	Prince of Songkla University	Thailand	SEARO	●			●	
Guilherme **Borges**	M	Instituto Nacional de Psiquiatria Ramon de la Fuente Muñiz	Mexico	AMRO	●			●	●
Grace **Chang**	F	Harvard Medical School	USA	AMRO	●	●	●		
Anju **Dhawan**	F	All India Institute of Medical Sciences (AIIMS)	India	SEARO	●	●		●	
Elizabeth **Elliott**	F	University of Sydney	Australia	WPRO	●		●	●	
Gabriele **Fischer**	F	Medical University of Vienna	Austria	EURO	●	●	●		
Erikson F. **Furtado**	M	University of Sao Paulo	Brazil	AMRO	●		●	●	●
Hendree **Jones**	F	Johns Hopkins School of Medicine University of North Carolina	USA	AMRO	●	●	●	●	
Fareed **Minhas**	M	Insitute of Psychiatry, Rawalpindi General Hospital	Pakistan	EMRO	●			●	
Katherine **Murphy**	F	University of Cape Town	South Africa	AFRO	●	●		●	
Alice **Ordean**	F	Toronto Centre for Substance Use in Pregnancy	Canada	AFRO	●	●	●	●	
Gabrielle **Welle-Strand**	F	Norwegian Directorate of Health	Norway	EURO	●	●	●		

External reviewers

Name	Gender	Affiliation	Country of residence	WHO Region
Steve Allsop	Male	Professor, Director National Drug Research Institute Curtin University	Australia	WPRO
Espen Ajo Arnevik	Male	Head of National resource centre for addiction treatment Oslo University	Norway	EURO
Matthew Chersich	Male	Associate Professor Centre for Health Policy, School of Public Health University of Witwatersrand	South Africa	AFRO
Andreea Creangea	Female	US Centers for Disease Control and Prevention, Atlanta	United States of America	AMRO
Marica Ferri	Female	Head of sector — Best practice, knowledge exchange and economic issues European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)	United States of America	AMRO
David A. Fiellin	Male	Professor of Medicine, Investigative Medicine and Public Health Yale University School of Medicine	Portugal	EURO
Louise Floyd	Female	US Centers for Disease Control and Prevention, Atlanta	United States of America	AMRO
Chris Howson	Male	March of Dimes	United States of America	AMRO
Irma Kirtadze	Female	Sr. Researcher Alternative Georgia Addiction Research Center Tbilisi	Georgia	EURO
Yukiko Kusano	Female	Consultant, Nursing & Health Policy International Council of Nurses, Geneva	Switzerland	EURO
Andre B. Lalonde	Male	Professor Of Obstetrics and Gynaecology, University of Ottawa, McGill	Canada	AMRO
Carla Marienfeld-Calderon	Female	Assistant Professor of Psychiatry, Yale University School of Medicine Course Director and Council Chair, Yale Global Mental Health Program, New Haven	United States of America	AMRO
Nester Moyo	Female	International Federation of Midwives	Kenya	AFRO
Michael Farrell	Male	Director National Drug and Alcohol Research Centre University of New South Wales	Australia	WPRO
Dzianis Padruchny	Male	Information and Training Centre of Belarusian Psychiatric Association	Belarus	EURO
Svetlana Popova	Female	Senior Scientist Social and Epidemiological Research, Centre for Addiction and Mental Health Assistant Professor, Epidemiology Division, Dalla Lana School of Public Health, University of Toronto	Canada	AMRO
Roland Simon	Male	Head of unit — Interventions, best practice and scientific partners European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)	Portugal	EURO
Anna Woods	Female	Senior Consultant Eastern DASSA 92 Osmond Tce Norwood SA	Australia	WPRO

ANNEX 5: DECLARATIONS OF INTEREST

Guidelines development group members

Name	Current affiliation	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
Sawitri **Assanangkornchai**	Prince of Songkla University	None	
Guilherme **Borges**	Instituto Nacional de Psiquiatria Ramon de la Fuente Muñiz	None	
Grace **Chang**	Harvard Medical School	None	
Anju **Dhawan**	All India Institute of Medical Sciences (AIIMS)	Yes: 1b,2a,2b	Funding from UNODC for a study on the effectiveness and feasibility of buprenorphine Funding from DFID (TAST) for supporting opioid maintenance treatment in Punjab Funding from UNDOC for a study on the effectiveness and feasibility of methadone Funding from Rusan Pharmaceuticals (manufacturer of methadone and buprenorphine) for a post-marketing study on methadone
Elizabeth **Elliott**	University of Sydney	None	
Gabriele **Fischer**	Medical University of Vienna	Yes: 2a	Approximately 5000 EUR per year from a combination of Mundipharma, Lannacher, and Reckitt Benckiser (pharmaceutical companies manufacturing morphine, psychiatric medications and buprenorphine respectively)
Erikson F. **Furtado**	University of Sao Paulo	Yes: 2a	Funding from research support from Brazilian National Council for Scientific and Technological Development
Hendree **Jones**	Johns Hopkins School of Medicine University of North Carolina	Yes: 2b	Travel costs and medication costs from Reckitt Benckiser (pharmaceutical company manufacturing buprenorphine) for conduct and reporting of the MOTHER study on buprenorphine in pregnancy
Fareed **Minhas**	Insitute of Psychiatry, Rawalpindi General Hospital	None	
Katherine **Murphy**	University of Cape Town	None	
Alice **Ordean**	Toronto Centre for Substance Use in Pregnancy	None	
Gabrielle **Welle-Strand**	Norwegian Directorate of Health	None	

Consultants supporting GDG

Nandi Siegfried: no interest declared
Margaret Harris: no interest declared

External reviewers

Name	Current affiliation	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
Steve Allsop	Professor, Director National Drug Research Institute Curtin University	None	
Espen Ajo Arnevik	Head of National Resource Centre for Addiction Treatment, Oslo University	None	
Matthew Chersich	Associate Professor Centre for Health Policy, School of Public Health University of Witwatersrand	None	
Andreea Creangea	US Centers for Disease Control and Prevention, Atlanta	None	
Michael Farrell	Director National Drug and Alcohol Research Centre University of New South Wales	None	
Marica Ferri	Head of sector — Best practice, knowledge exchange and economic issues European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)	None	
David A. Fiellin	Professor of Medicine, Investigative Medicine and Public Health Yale University School of Medicine	Yes: 1a	Honorarium from Pinney Associates for involvement in post-marketing surveillance of buprenorphine
Louise Floyd	US Centers for Disease Control and Prevention, Atlanta	None	
Chris Howson	March of Dimes	None	
Irma Kirtadze	Sr. Researcher Alternative Georgia Addiction Research Center Tbilisi	None	
Yukiko Kusano	Consultant, Nursing & Health Policy International Council of Nurses, Geneva	None	
Andre B. Lalonde	Professor Of Obstetrics and Gynaecology, University of Ottawa, McGill	None	
Carla Marienfeld-Calderon	Assistant Professor of Psychiatry, Yale University School of Medicine Course Director and Council Chair, Yale Global Mental Health Program, New Haven	None	
Nester Moyo	International Federation of Midwives	None	
Dzianis Padruchny	Information and Training Centre of Belarusian Psychiatric Association	None	
Svetlana Popova	Senior Scientist Social and Epidemiological Research, Centre for Addiction and Mental Health Assistant Professor, Epidemiology Division, Dalla Lana School of Public Health, University of Toronto	None	
Roland Simon	Head of unit — Interventions, best practice and scientific partners European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)	None	
Anna Woods	Senior Consultant Eastern DASSA 92 Osmond Tce Norwood SA	None	

The harmful use of alcohol and illicit drugs is the third leading risk factor for premature deaths and disabilities in the world. It is estimated that 2.5 million people worldwide died of alcohol-related causes in 2004, including 320 000 young people between 15 and 29 years of age.

EXIT THE MAZE OF
SUBSTANCE USE FOR
BETTER GLOBAL HEALTH

Contact

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