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[Intervention Review]

Pharmacologic Interventions for Pregnant Women Enrolled in Alcohol Treatment

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ABSTRACT

Background

Excessive alcohol use during pregnancy has been associated with adverse maternal and neonatal effects. It is therefore important to develop and evaluate effective interventions during this important time in a woman's life. To our knowledge there have been no systematic reviews of randomised control trials (RCT) in this population.

Objectives

To evaluate the effectiveness of pharmacologic interventions in pregnant women enrolled in alcohol treatment programs for improving birth and neonatal outcomes, maternal abstinence and treatment retention.

Search methods

We searched the Cochrane Drugs and Alcohol Group's Trial register (August 2008); MEDLINE (1.1950 to 6.2008); EMBASE (1.1974 - 8.2008); CINAHL (1.1982-6.2008); PsycInfo (1.1806-6.2008), and reference lists of articles.

Selection criteria

We sought to include randomised or quasi-randomised studies comparing any pharmacologic intervention versus other pharmacologic treatment alone or in association with psychosocial treatment, placebo, non-intervention or psychosocial intervention.

Data collection and analysis

Two review authors independently assessed trials for inclusion in the review. Included studies were to be assessed using standardized data extraction and quality assessment forms. No suitable trials were identified.

Main results

The search strategy identified 793 citations. Twenty-three citations were deemed relevant for full text review; an additional ten articles were retrieved through hand searching references, for a total of thirty-three articles. Following full text review no articles met the inclusion criteria. Data extraction and assessment of methodological quality were therefore not possible.

Authors' conclusions

The review question remains unanswered as there were no randomised control trials found relevant to the topic. There is a need for high quality research to determine the effectiveness of pharmacologic interventions in pregnant women enrolled in alcohol treatment program.

PLAIN LANGUAGE SUMMARY

Pharmacologic interventions for pregnant women enrolled in alcohol treatment programs

Drinking alcohol during pregnancy is common. Yet no safe level of alcohol consumption is known, with no conclusive evidence on any adverse effects on the unborn child with low levels of alcohol. During pregnancy, more than two units per day or more than four units per drinking session may increase the risk of miscarriage, reduce growth, and impair mental development of the baby. Foetal alcohol syndrome is evident as neurological abnormalities, mental retardation, varying degrees of psychosocial and behavioural problems and characteristic facial dysmorphism that are apparent in adolescents and adults. In some populations alcohol use during pregnancy leads to increased child abuse and neglect or compromised mother-infant attachment and responsiveness. Mothers who consume alcohol are more likely to have post-natal depression and are less likely to attend health facilities for education and medical treatment.

Specific interventions need to be put in place to assist pregnant and postpartum women who have alcohol problems. Medicines are given to assist with alcohol treatment by lessening the effects during detoxification. These include benzodiazepines, phenothiazines and chlormethiazone, used to reduce anxiety and insomnia. Anti-depressants may also be given after withdrawal. Disulfiram, naltrexone and acamprosate are used in more severe cases to decrease cravings for alcohol and maintain abstinence. The review authors could not identify any randomised controlled trials (RCTs) evaluating the effectiveness of pharmacologic interventions to improve maternal, birth, and infant outcomes in pregnant women enrolled in alcohol treatment programs.

The main reason for study exclusion was study design; we found trials without a control group or focusing only on outcomes for the newborn baby such as birth weight, length or head circumference. Given the stigma attached to alcohol use in pregnancy, recruitment for outcomes trials is likely to remain difficult, which adversely affects generalizability. Clearly the availability of quality evidence would assist with ante-partum decision making by both the physician and mother.

BACKGROUND

There are ten countries which have recommendations on alcohol use in pregnancy, all stating that women should avoid alcohol while pregnant. Such recommendations of complete abstinence are contrary to the fact that the consumption of alcohol during pregnancy is common (Doggett 2005). In the United States (US), 11.8% of pregnant women reported recent use of alcohol (NSDUH 2006; NSDUH 2007); whereas 75% of pregnant women in Australia reported some alcohol use in the prior twelve months (ONS 2006) and in the United Kingdom (UK), 61% of mothers continued to drink alcohol while they were pregnant (Taylor 2006). However, these figures are related to 'regular' use of alcohol and therefore are not necessarily at levels where there is evidence of associated harm. For example, the majority (71%) of those in the US who continued to drink consumed less than 1 unit of alcohol per week and only 3% had drunk more than 7 units a week (NSDUH 2006). Some countries including Australia, Spain, and the UK provide broader recommendations on alcohol use during pregnancy and state that if a woman decides to drink she should have no more one to two drinks a week and not binge drink (ICAP 2007).

Even though there is no known safe level of alcohol consumption in pregnancy, there is no conclusive evidence that low level of alcohol consumption has any adverse effects to the unborn child (NICE 2008). However, excessive alcohol use (more than two units per day or more than four units per drinking session) during pregnancy has been associated with increased risk of miscarriage, a reduction in foetal growth and impaired neurodevelopment (AAP 2000; Taylor 2006).

Description of the condition

Along with the detrimental effects to both maternal and foetal health, innumerable costs are incurred to the economy from alcohol use. Alcohol misuse in the UK is estimated to cost in the region of £20 billion (Strategy Unit 2003). In developed countries, alcohol is the third leading cause of ill health after smoking and hypertension. Current estimates are that for every pound spent on effective substance use treatment, five pounds is saved in health and social care costs (Raistrick 2006).

Alcohol use during pregnancy is associated with a wide range of adverse effects. Alcohol is associated with a continuum of birth damage (Barrison 1985) including a combination of developmental delay, growth retardation, neurological abnormalities and characteristic facial dysmorphism referred to as the Foetal Alcohol Syndrome (FAS). Although FAS is the most commonly recognised cause of mental retardation, adolescents and adults with FAS have varying degrees of psychosocial and behavioural problems (Weintraub 1998). Less severe effects of alcohol use during pregnancy include mild to moderate mental and physical growth retardation, referred to as Foetal Alcohol Effects (FAE) (Sanchez 1979). Furthermore as many as 5% of all congenital anomalies have been attributed to prenatal alcohol exposure (Pietrantonio 1991). Children of women who consume alcohol can also be at risk of reduced developmental goal attainment as a result of either a direct effect of the exposure or from the associated lifestyle factors connected to alcohol use (Belcher 1999; Eriksson 2000; Faden 2000; Frank 2001; Jacobson 2002; Singer 2002). Increased child abuse and neglect have been documented in some populations as a result of alcohol use during pregnancy (Bessinger 1999; Nair 1997) along with child deaths (Jaudes

1997). Furthermore mother-infant attachment and responsiveness is compromised by alcohol use during pregnancy, along with post-natal depression and possible domestic violence within the household. Finally mothers who consume alcohol are less likely to attend health facilities for education and medical treatment (Doggett 2005).

Description of the intervention

There are many pharmacologic treatments available to assist with alcohol treatment. These drugs are given to both lessen the effects during the withdrawal period and to help maintain abstinence.

They are most commonly used in more severe cases of alcoholism.

Drugs given during detoxification include Benzodiazepines (BZs), phenothiazines and chlormethiazone among others (Mann 1996).

These drugs protect against the medical morbidity and mortality associated with withdrawal. Benzodiazepines in particular protect against seizures which are caused by autonomic instability secondary to withdrawal. In addition these medicines suppress the patient's anxiety and insomnia and increase the chances of completing detoxification.

In addition to the drugs listed above, anti-depressants have also been used in the post-withdrawal phase. However only three drugs have been approved by the United States Federal Drug Administration (FDA) for the treatment of alcohol dependence and abuse following detoxification; disulfiram, naltrexone and acamprosate (FDA 2007, Jaffe 1992). Each drug uses a different mechanism of action to influence alcohol abstinence. Disulfiram works by causing an adverse reaction with the consumption of alcohol; naltrexone attenuates the "high" of alcohol consumption; and acamprosate decreases the cravings for alcohol in abstinent alcohol dependent persons (Mann 1996, Kenna, 2004, Kenna 2004a). Naltrexone and acamprosate have been shown to be effective in reducing the frequency of drinking days and increasing the time to relapse and time to first drink (Garbutt 1999, Kranzler 2001). Although disulfiram is the oldest of the medications, trials have shown inconclusive results on the drug's overall effectiveness.

It does appear to be useful in delaying time to first drink from fear of the reaction (Garbutt 1999) but not necessarily effective in long term abstinence from alcohol (Kranzler 2001). Although much of the published literature includes both males and females there is little specific evidence for the effectiveness of any of these treatments in pregnancy. Each of these drugs holds a class C pregnancy category in the US which means that there is evidence of adverse effects in animal studies but no adequate or well-controlled human studies (FDA 2007). In Australia they hold either a B2 or B3 category which means that "the drugs have been taken by a small number of pregnant women with no increase in the frequency of malformation or harmful effects to the foetus and studies in animals have shown evidence of harmful effects but the correlation to humans is uncertain (TGA 2007, FDA 2007)". In short, the effectiveness of these drugs in pregnancy has not been fully ascertained. Due to the short duration of pregnancy and the importance of this time period, it may be especially important to find treatments that work effectively, even for short periods of time.

How the intervention might work

Specific interventions need to be put in place to assist pregnant women and postpartum women who have alcohol problems. Interventions should be aimed at harmful alcohol use, pregnancy care, health surveillance and promotion, counselling, social

support, education, facilitation of mother-infant interaction and promotion of parenting (Doggett 2005). Such interventions should facilitate earlier and more intensive pregnancy care, improve pregnancy and neonatal outcomes, reduce alcohol use, aid in mother-infant interaction and improve the home environment. Ideally these interventions would improve longer-term outcomes such as reducing child neglect, reducing mother-infant separation, improving neurodevelopment outcomes, increasing successful schooling performance and decreasing problems in adolescence and young adulthood (Olds 2002).

Why it is important to do this review

Effective interventions are needed and need to be evaluated among pregnant women in alcohol treatment in order to reduce the number of infant born with foetal alcohol syndrome. A systematic review is necessary in this area as, to our knowledge, there are none to date. There is a parallel Cochrane review on Psychosocial interventions for women enrolled in alcohol treatment during pregnancy (Lui 2008) but none on pharmacological therapies.

OBJECTIVES

This review examined the effectiveness of pharmacologic treatments in pregnant women enrolled in alcohol treatment programmes when compared to other pharmacologic treatments, placebo, non-intervention, psychosocial interventions.

METHODS

Criteria for considering studies for this review

Types of studies

We sought to review all randomised controlled trials (RCTs) or quasi random methods of participant allocation.

Types of participants

Trials that enrolled pregnant or postpartum women in alcohol treatment programmes were to be included in this review. No minimum level of alcohol use was required for inclusion, so long as the authors stated the women were receiving alcohol treatment. Studies were excluded if the participants were illicit drug (i.e. cannabis, heroin, cocaine, amphetamine etc) users and were treated for their illicit substance use disorders. Studies that did not report participants' alcohol use were not included.

Types of interventions

Experimental intervention:

This review sought to include any pharmacologic treatments used for the treatment of alcohol dependence. In order to be eligible, a study must include at least one group where only a pharmacologic treatment was given.

Control Intervention:

This review compared the experimental intervention to: other pharmacologic treatment alone or in association with psychosocial treatment, placebo, non-intervention, psychosocial intervention alone

Types of outcome measures

Each trial must, at minimum, must report at least birth, abstinence and retention outcomes

Primary outcomes

Birth outcomes:

1. birth weight.
2. gestational age at birth.
3. placental abruption.
4. foetal alcohol syndrome (FAS).
5. admission to and length of time spent in hospital (i.e. neonatal intensive care unit [NICU]).

Secondary outcomes

Abstinence outcomes:

1. alcohol abuse measured by: maternal toxicology, maternal self-report, newborn toxicology and any biological markers provided in the original studies.

Retention outcomes

1. treatment attendance as measured by the proportion or count of treatment visits attended.
2. treatment attendance as measured by the proportion or count of individuals who complete treatment.
3. prenatal care attendance as measured by the proportion or count of prenatal visit attended.

Search methods for identification of studies

We undertook both electronic and manual searches to identify the studies of review.

Electronic searches

We searched the following databases:

1. Cochrane Drug and Alcohol Group trials register (August 2008)
2. MEDLINE (1950 to August 2008)
3. EMBASE (1974 to August 2008)
4. CINAHL (1982 to August 2008)
5. PsycINFO (1806 to August 2008)

Search strategies for each database can be found in the appendices (Appendix 1, Appendix 2, Appendix 3, Appendix 4). Each search was based on the MEDLINE search strategy (Host: Dialog DataStar) developed in conjunction with a librarian (Leeds Partnership Foundation Trust). We did not apply any language restriction to the review.

Searching other resources

We searched:

1. the reference lists of all relevant papers to identify further studies.
2. some of the main electronic sources of ongoing trials (Current controlled trials meta register of controlled trials (mRCT); clinicaltrials.gov; The International Federation of

Pharmaceutical Manufacturers & Associations (IFPMA) Clinical trials portal: www.ifpma.org/clinicaltrials.html).

3. conference proceedings likely to contain trials relevant to the review. We contact investigators seeking information about unpublished or incomplete trials.

All searches included non-English language literature and studies with English abstracts were assessed for inclusion. When considered likely to meet inclusion criteria, studies were translated.

Data collection and analysis

Selection of studies

Two reviewers read all titles and/or abstracts resulting from the search process and eliminated any irrelevant studies. We obtained full copies of all the potentially relevant studies. Two reviewers acting independently classified these as included, excluded or unclear. Decisions were based upon inclusion criteria outlined in the protocol. Differences in opinion were resolved through consensus or referral to a third reviewer.

Data extraction and management

Data was to be extracted by two reviewers independently using a data-extraction form that will be developed to assess the following data: study location, methods, participant details, type of intervention, and outcomes.

Assessment of risk of bias in included studies

The reviewers were to assess the methodological quality of included studies as per Cochrane Handbook for Systematic Reviews for Interventions (Higgins 2008). Appraisal of the included studies was carried out independently by two reviewers. Any differences were to be negotiated by a third reviewer to reach consensus. We evaluated the included studies as follow:

A. Sequence generation was to be assessed for all outcomes. Studies were considered at low risk of bias if they provided a clear method of generating an allocation sequence to produce comparable groups, i.e. random number table, computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice. Studies were considered at high risk of bias if they used some systematic, non-random approach, i.e. date of birth, date of admission, clinic record number, by clinician.

B. Allocation concealment was to be assessed for all outcomes. Studies were considered at low risk of bias if they provided adequate allocation concealment, i.e. central allocation including telephone, web-based, and pharmacy-controlled, randomization; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes. Studies were determined at high risk of bias if they had inadequate allocation concealment, i.e. using an open random allocation schedule such as a list of random numbers; assignment envelopes were used without appropriate safeguards e.g. if envelopes were unsealed or non-opaque or not sequentially numbered; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

C. Blinding of participants, personnel, and outcome assessor was to be considered separately for objective outcomes (discontinuation rates) and subjective outcomes (global state, craving, and

withdrawal symptoms). For discontinuation rates, we judged that lack of blinding was unlikely to influence data collection.

D. Incomplete outcome data were to be considered for all outcomes except for discontinuation rates. It was assessed for results at the end of the study period. Studies were considered at low risk of bias if they adequately addressed missing data.

E. Selective outcome reporting was to be considered for all outcomes except for discontinuation rates.

Studies were to be judged to have unclear risk of bias if there was insufficient information to permit judgment of 'low' or 'high' risk of bias for each of the domains.

Measures of treatment effect

Dichotomous outcomes were to be analysed calculating the Relative risk (RR) for each trial with the uncertainty in each result being expressed by their confidence intervals. Continuous outcomes were to be analysed by calculating the WMD (weighted mean difference) with 95%CI.

Unit of analysis issues

Although none was available we had not planned to use data presented as number of positive urine tests over total number of tests in the experimental and control group as a measure of alcohol use. This is because using tests instead of the participants as the unit of analysis violates the hypothesis of independence among observations. As multiple urine tests would likely have been done in an individual patient, a urine test would not have been an appropriate unit of analysis.

Dealing with missing data

In this study population it is plausible to assume there would have been missing information for participants for different study points. Therefore a sensitivity analysis would have been performed. We were not going to exclude studies based on missing data for study subjects, as retention was one of the outcomes of interest for this review.

Assessment of heterogeneity

Due to the nature of the studies in this review, it was anticipated that there would be some degree of heterogeneity in the study interventions, outcome measures reported and methodological quality. Therefore pooling of the results may not have always been appropriate. We planned to use a p-value of the chi-square test less than 0.05 in the assessment of heterogeneity.

Assessment of reporting biases

Funnel plots were to be used to assess the potential for bias related to both trial size and negative versus positive outcomes, evidence of publication bias

Data synthesis

We planned to perform meta-analysis and narrative review where appropriate for each of the nominated outcomes. Where possible, we planned to pool results of similar studies. The RR or the WMD from the individual trials were to be combined through meta-analysis using a fixed effect model unless there was significant heterogeneity, in which case a random effect model was to be used.

A p-value of the chi-square test less than 0.05 was to indicate a significant heterogeneity.

The RevMan 5 software package was to be used to perform the meta-analysis for continuous and dichotomous outcome measures.

Sensitivity analysis

The methodological assessments was not used as inclusion criteria for the review, but was to be described and discussed. Sensitivity analysis was to be used to assess the methodological quality of the results

RESULTS

Description of studies

Results of the search

The search strategy identified 793 citations. Twenty-three citations were deemed relevant for full text review, an additional ten articles were retrieved through hand searching references, for a total of thirty-three articles. Following full text review no articles met the inclusion criteria. Data extraction and assessment of methodological quality were therefore not possible.

Included studies

We found no studies which met our inclusion criteria for this review.

Excluded studies

Thirty-one of the retrieved for full text review were excluded because they were not the correct study design. A majority of the articles we found described cohorts, case series or case reports concerning the effects of drinking or pharmacologic interventions on the foetus. Many articles did not provide a control group with which to compare the results. Other articles were excluded because they were review articles. The references of these articles were searched for potentially relevant articles. Some of these reviews explained the limitations in implementing drug trials in pregnant women. See [Characteristics of excluded studies](#)

Risk of bias in included studies

Not applicable as no articles no articles met the inclusion criteria for this study.

Effects of interventions

Not applicable as no articles no articles met the inclusion criteria for this study.

DISCUSSION

The main reason for study exclusion was study design, we found no randomised or quasi-randomised control trials focused on pregnant women in alcohol treatment. We found case series, case reports or cohorts among women who had either used alcohol or pharmacologic treatments for alcohol use during their pregnancy. Many of these studies did not have a control group nor did they assess the efficacy of treatment for maternal abstinence or harm reduction, rather they focused instead on foetal outcomes. For example, Flores-Huerta ([Flores-Huerta 1992](#)) assessed the effects on the newborn of ethanol consumption during the prenatal and postpartum periods using a prospective cohort of 94 women in

Mexico. The 32 alcohol consuming participants in this study reportedly drank between 5 and 10 units of alcohol, in the form of a cultural drink pulque, a day. While this study found no significant difference in terms of mean birth weight, length or head circumference between drinking and non drinking mothers it did find significantly more offspring of drinking mothers ranked below the third percentile in birth weight and head circumference. mothers ranked below the third percentile in birth weight and head circumference. A second excluded study, Laegreid and colleagues assessed the effects of benzodiazepine use in pregnancy on birth outcomes by comparing benzodiazepine exposed births to infants exposed to other psychotropic drugs and those without drug exposure. It is important to note that the drug treatment was for any psychological issues and not necessarily alcohol treatment. In fact pregnant women were excluded if they were currently abusing alcohol or other drugs in addition to the use of benzodiazepine. The benzodiazepine exposed infants were found to have significantly lower birth weight for gestational age, as well as greater impairment on neurologic and behavioural exams at birth than the non-exposed reference group ([Laegreid 1992a](#)). While these and other excluded studies may provide insight into the potential effects of alcohol use and pharmacologic interventions, they are not able to fully answer the research question of this review. Without an adequate control group or the ability to accurately control for potential confounders it is impossible to know if observed adverse events are attributable to the pharmacologic intervention, alcohol use or another unknown reason. We did not find any articles examining maternal abstinence outcomes with the use of pharmaceutical interventions.

As has been stated in other reviews of the subject ([Rayburn 2004](#), [Ryberg 2003](#), [Schottenfeld 1995](#)), given the rarity of outcomes it is difficult to adequately power studies to observe neonatal and development effects of pharmaceuticals in pregnant women.

Rather it may be more appropriate to place treatment outcome studies in the context of the maternal life course and child development.

The clinical and obstetrical care surrounding alcohol use in pregnancy is difficult and complex; each clinician must weigh the effects of a drug on the mother's health and substance use against the potential harmful effects on her foetus. Clearly the availability of quality evidence would assist with ante-partum decision making by both the physician and mother.

Summary of main results

This review assessed the effectiveness of pharmacologic interventions of pregnant women in alcohol treatment. After a comprehensive search of electronic databases and hand searching of all references we found no articles which met our inclusion criteria.

Overall completeness and applicability of evidence

Not applicable as no articles no articles met the inclusion criteria for this study

Quality of the evidence

Not applicable as no articles no articles met the inclusion criteria for this study.

AUTHORS' CONCLUSIONS

Implications for practice

As there were no RCTs found to answer this question we can make no evidence based recommendations for practice.

Implications for research

Our review has raised the question of whether randomised control trials are the most appropriate study design for use in the evaluation of ante-partum alcohol use. The size of the population necessary to power such a study, particularly in terms of assessing adverse neonatal outcomes would be extremely large. Also the long time course of follow-up needed to assess developmental outcomes is not amendable to a RCT design as it would be prohibitably expensive.

Furthermore as our prior review ([Terplan 2007](#)) noted, the population of pregnant women who participate in RCTs for drug and alcohol treatment is not representative of women who continue to use drugs and alcohol in pregnancy and who might

benefit from interventions. The women enrolled in the RCTs of psychosocial interventions for illicit drug use in pregnancy were overwhelmingly poor and socially marginalized. Given the stigma attached to drug and alcohol use in pregnancy, recruitment for outcomes trials is likely to remain difficult and adversely affect generalizability.

Quality epidemiologic outcome research is needed due to the magnitude of suffering alcohol use has on the public's health. As our review noted the poor quality of published observational trials, rather than pushing future research towards RCTs, we suggest that quality cohort studies with appropriate unexposed controls to assess potential confounders such as continued maternal alcohol use and socioeconomic variables would be more appropriate and cost effective.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bartu 2006	Substance treatment for illicit drugs, not alcohol.
Bergman 1992	Study design not randomised control trial.
Brewer 2008	Study design not randomised control trial.
Ferreira 2007	Study design not randomised control trial; not in alcohol treatment.
Flores-Huerta 1992	Study design not randomised control trial; not in alcohol treatment.
Fuller 2004	Study design not randomised control trial, opinion.
Heading 2008	Study design not randomised control trial, review article, not pregnant women.
Kanto 1982	Study design not randomised control trial, review article, participants not in alcohol treatment.
Laegreid 1992	Study design not randomised control trial, not in alcohol treatment.
Laegreid 1992a	Study design not randomised control trial, not in alcohol treatment.
Lewis 1979	Study design not randomised control trial, letter to the editor.
Lingford-Hughes 2004	Study design not randomised control trial, review, not stratified by pregnancy status.
Loebstein 1997	Study design not randomised control trial, participants not in alcohol treatment.
Maier 1997	Study design not randomised control trial, not in alcohol treatment.
Matalon 2002	Study design not randomised control trial, not in alcohol treatment.
Mattison 2006	Study design not randomised control trial, review article, participants not in alcohol treatment.
Mattson 2006	Study design not randomised control trial, not in alcohol treatment.
Noland 2003	Study design not randomised control trial, not in alcohol treatment.
Nora 1977	Study design not randomised control trial.
Ornoy 1998	Study design not randomised control trial.
Ostrea 2006	Study design not randomised control trial, not in alcohol treatment.
Ramkisson 2008	Study design not randomised control trial, not in alcohol treatment.

Study	Reason for exclusion
Rayburn 2004	Study design not randomised control trial, review article.
Reitnauer 1997	Study design not randomised control trial.
Rosenberg 1983	Study design not randomised control trial.
Ryberg 2003	Study design not randomised control trial, review article.
Scanlon 1975	Study design not randomised control trial, letter to the editor.
Schottenfeld 1995	Study design not randomised control trial, review.
Stuppaeck 1992	Population not pregnant women.
Vocci 1995	Study design not randomised control trial, review.
Vocci 2005	Study design not randomised control trial, not in pregnancy.
Wozniak 2006	Study design not randomised control trial, not in alcohol treatment.
Wright 2001	Study design not randomised control trial, review article.

APPENDICES

Appendix 1. MEDLINE search strategy

- SUBSTANCE?RELATED?DISORDERS.DE.
- ((DRUG OR SUBSTANCE) ADJ (ADDICT\$3 OR ABUS\$3 OR DEPENDEN\$4)).TI,AB.
- (INTOXICAT\$3 OR ABSTINEN\$2 OR WITHDRAW\$3).TI,AB.
- (EXCESSIVE\$2 ADJ USE\$3).TI,AB.(USE\$3 ADJ DISORDER\$2).TI,AB.
- (DRINKING ADJ BEHAVI\$3).TI,AB.
- DRINKING?BEHAVIOR.DE.
- ALCOHOL\$3.TI,AB.
- ALCOHOLISM.W..DE. OR ALCOHOL?DRINKING.DE. OR ALCOHOLISM.W..DE.
- 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
- PSYCHOPHARMACOLOGY.W..DE.
- PHARMACOLOGY.W..DE.
- PHARMACOLOG\$4.TI,AB.
- PHARMACOTHERAP\$3.TI,AB.
- BENZODIAZEPINES#.W..DE.
- BENZODIAZEPINE.TI,AB.
- ANTI ?ANXIETY?AGENTS#.DE.
- ANXIOLYTIC.TI,AB.
- HYPNOTICS AND SEDATIVES#.DE.
- ANTIDEPRESSIVE?AGENTS#.DE. OR ANTIDEPRESSIVE?AGENTS SECOND?GENERATION#.DE. OR ANTIDEPRESSIVE?AGENTS?TRICYCLIC#.DE.
- ANTIDEPRESS\$4.TI,AB.
- ANTICONVULSANTS#.W..DE.
- SEROTONIN?UPTAKE?INHIBITORS#.DE.
- ADRENERGIC?BETA?ANTAGONISTS#.DE.

24.ADRENERGIC?BETA?AGONISTS#.DE.
 25.DISULFIRAM#.W..DE.
 26.DISULFIRAM.TI,AB.
 27.ACAMPROSATE.TI,AB.
 28.NARCOTIC?ANTAGONISTS#.DE.
 29.NALTREXONE.TI,AB.
 30.PHENOTHIAZINES#.W..DE.
 31.PHENOTHIAZINES.TI,AB.
 32.CHLORMETHIAZONE.TI,AB.
 33.MONOAMINE?OXIDASE?INHIBITORS.DE.
 34.(MONOAMINE ADJ OXIDASE ADJ INHIBITOR).TI,AB.
 35.10/34 OR
 36.PREGNANCY#.W..DE.
 37.PREGNAN\$5.TI,AB.
 38.PREGNANCY?COMPLICATIONS.DE.
 39.(PREGNANCY ADJ COMPLICATIONS).TI,AB.
 40.INFANT?NEWBORN.DE.
 41.POSTPARTUM?PERIOD#.DE.
 42.PRENATAL?DIAGNOSIS#.DE.
 43. FETUS#.W..DE.
 44.36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43
 45.PT=RANDOMIZED-CONTROLLED TRIAL
 46.PT=CONTROLLED-CLINICALTRIAL
 47. RANDOMIZED.TI,AB.
 48.PLACEBO.TI,AB.
 49.RANDOMLY.TI,AB.
 50.GROUPS.TI,AB.
 51.TRIAL.TI,AB.
 52.45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51
 53.52 AND HUMAN=YES
 54.9 AND 35 AND 44 AND 53

Appendix 2. EMBASE search strategy

1. substance-related disorders/
2. ((drug or substance) adj (Addict\$ or abus\$ or dependen\$)).mp
3. (intoxicat\$ or abstinen\$ or withdrawal\$).mp.
4. (excessive\$ adj use\$).mp.
5. (use\$ adj disorder\$).mp.
6. (drinking adj behavi\$3).mp.
7. drinking [behavior.mp](#).
8. alcohol\$.mp.
9. alcoholism/
10. (alcohol adj abuse).mp
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. [psychopharmacology.mp](#).
13. [pharmacolog*.mp](#).
14. pharmacotherap\$3.mp.
15. benzodiazepine#.mP
16. [benzodiazepine.mp](#)
17. anti-anxiety agent\$.mp.
18. [anxiolytic.mp](#).
19. (hypnotics and sedative\$).mp.

20. antidepressive agent\$1.mp.
21. antidepressive agent\$1 second generation.mp.
22. antidepressive agent\$1 tricyclic.mp.
23. antidepress\$4.mp.
24. anticonvulsants.mp.
25. serotonin uptake inhibitors.mp.
26. adrenergic beta antagonists.mp.
27. adrenergic beta agonists/
28. disulfiram.mp.
29. disulfiram/
30. acamprosate.mp.
31. lithium.mp.
32. 12/31 OR
33. pregnancy/
34. pregnan\$5.mp.
35. pregnancy complications/
- 36.(pregnancy adj complications).mp.
- 37.infant newborn/
- 38.postpartum period/
- 39.prenatal diagnosis/
- 40.fetus.mp.
- 41.33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
- 42.randomised controlled trial.mp.
- 43.randomised controlled trial/
- 44.control trial.mp.
- 45.random allocation.mp.
- 46.double blind method.mp.
- 47.single blind method.mp.
- 48.clinical trial/
- 49.(clin\$ adj trial).mp.
- 50.clinical trial.mp.
- 51.((singl\$ or doubl\$ or trbl\$) adj (blind or mask\$)).mp.
- 52.plaCEBO/
- 53.placebo\$.mp.
- 54.randomis\$.mp.
- 55.research design.mp.
- 56.42/55 OR
- 57.11 and 32 and 41 and 56

Appendix 3. PsycInfo search strategy

1. Addiction#.W..DE. OR Alcoholism#.W.DE.
2. (drug OR substance).TI,AB. AND (addict\$4 OR abus\$3 OR dependen\$3 OR misuse\$3).TI,AB.
3. (overdos\$4 OR intoxicat\$4OR abstinen\$3 OR withdraw\$3OR relaps\$2).TI,AB.
4. (excessive\$2 ADJ use\$3).TI,AB.
5. (use\$4 ADJ disorder\$4).TI,AB.
6. Drinking?Behavior#.DE.
7. Alcoholism#.W.DE.
8. Alcohol?Abuse#.DE.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
- 10.Pregnancy#.W..DE.
- 11.pregnan\$5.TI,AB.
- 12.pregnan\$4 ADJ complication\$2

- 13.(Infant ADJ newborn).TI,AB.
- 14.Postpartum?Depression#.DE. OR Postpartum?Psychosis#.DE.
- 15.(postpartum ADJ period).TI,AB.
- 16.Prenatal?Diagnosis#.DE.
- 17.Fetus#.W..DE.
- 18.1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
- 19.Psychopharmacology#.W..DE.
- 20.Pharmacology#.W..DE.
- 21.pharmacolog\$4.TI,AB.
- 22.pharmacotherap\$3.TI,AB.
- 23.Benzodiazepines#.W..DE.
- 24.benzodiazepine\$2.TI,AB.
- 25.Tranquilizing?Drugs#.DE.
- 26.(anti-anxiety ADJagents).TI,AB.
- 27.(antianxiety ADJagents).TI,AB.
- 28.anxiolytic.TI,AB.
- 29.(hypnotics ADJ sedatives).TI,AB.
- 30.antidepress\$4.TI,AB.
- 31.anticonvulsants.TI,AB.
- 32.Serotonin#.W..DE. OR
- 33.Serotonin?Reuptake? Inhibitors#.DE.
- 34.Adrenergic?Blocking?Drugs#.DE. OR Adrenergic?Drugs#.DE.
- 35.disulfiram.TI,AB.
- 36.Disulfiram#.W..DE.
- 37.acamprosate.TI,AB.
- 38.Narcotic?Agonists#.DE. OR Narcotic?Antagonists#.DE. OR Narcotic?Drugs#.DE.
- 39.naltrexone.TI,AB.
- 40.phenothiazines.TI,AB.
- 41.chlormethiazone.TI,AB.
- 42.Monoamine?Oxidase Inhibitors#.DE.
- 43.(monoamine ADJ oxidase ADJinhibitors).TI,AB.
- 44.19/43 OR
- 45.random\$9.TI,AB.
- 46.random\$9.TI,AB.
- 47.Placebo#.W..DE.
- 48.placebo.TI,AB.
- 49.Clinical?Trials#.DE.
- 50.(clinical ADJtrials).TI,AB
- 51.((singl\$6 OR doubl\$3 OR trebl\$3 OR tripl\$3) ADJ(blind\$2 OR mask\$3 OR stud\$4)).TI,AB.
- 52.45 or 46 or 47 or 48 or 49 or 50 or 51
- 53.27/50 OR
- 54.9 AND 18 AND 44 AND 53

Appendix 4. CINAHL search strategy

1. Substance?Use?Disorders#.DE.
2. ((drug OR substance) ADJ (addict\$3 OR abus\$4 OR dependen\$3)).TI,AB.
3. (overdos\$3 OR intoxicat\$3 OR abstin\$3 OR withdrawal\$2 OR relaps\$2).TI,AB.
4. (excessive\$2 ADJ use\$3).TI,AB.
5. (use\$3 ADJ disorder\$2).TI,AB.
6. (drinking ADJ behavi\$5).TI,AB.
7. Drinking?Behavior#.DE.
8. alcohol\$4.TI,AB.

9. Alcoholism#.W..DE. Alcohol?Abuse.DE. OR Alcoholism.W..DE. OR Alcoholism.W..DE. OR Alcoholism.W..DE.
- 10.1/9 OR
- 11.Psychopharmacology#.W..DE.
- 12.Pharmacy and Pharmacology.DE. OR Pharmacy and Pharmacology.DE.
- 13.pharmacolog\$4.TI,AB.
- 14.pharmacotherap\$3.TI,AB.
- 15.Antianxiety?Agents Benzodiazepine#.DE.benzodiazepine.TI,AB.
- 16.Antianxiety?Agents#.DE.anxiolytic.TI,AB.
- 17.Hypnotics and Sedatives#.DE.
- 18.Antidepressive?Agents#.DE. OR Antidepressive?Agents Second-Generation#.DE. OR Antidepressive?Agents Tricyclic#.DE.
- 19.antidepress\$4.TI,AB.
- 20.Anticonvulsants#.W..DE.
- 21.Serotonin?Uptake Inhibitors#.DE.
- 22.Adrenergic?Beta Agonists#.DE.
- 23.Disulfiram.W..DE.disulfiram.TI,AB.
- 24.acamprosate.TI,AB.
- 25.Narcotic?Antagonists#.DE.
- 26.naltrexone.TI,AB.
- 27.Antipsychotic?Agents?Phenothiazine#.DE.
- 28.phenothiazines.TI,AB.
- 29.chloromethiazone.TI,AB.
- 30.Monoamine-Oxidase Inhibitors#.DE.
- 31.(monoamine ADJ oxidase ADJ inhibitor).TI,AB.
- 32.11/31
- 33.PREGNANCY#.W..DE.
- 34.PREGNAN\$4.TI,AB.
- 35.33 OR 34
- 36.(CLINIC\$2 ADJ TRIAL\$2).TI,AB.
- 37.DOUBLE?BLIND?STUDIES#.DE. OR SINGLE?BLIND?STUDIES#.DE. OR TRIPLE? BLIND STUDIES#.DE.
- 38.CLINICAL?TRIALS#.
- 39.RANDOM?ASSIGNMENT#.DE.
- 40.META?ANALYSIS#.DE.
- 41.ALLOCAT\$4.TI,AB.
- 42.CLIN\$4.TI,AB.
- 43.RANDOM\$4.TI,AB.
- 44.TRIAL\$4.TI,AB.
- 45.36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
- 46.10 and 32 and 33 and 45

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 3, 2009

Date	Event	Description
26 March 2009	New search has been performed	became a review

CONTRIBUTIONS OF AUTHORS

ES contributed to the conception, design and development of the protocol; identified, extracted and entered data, participated in the review and interpretation of the results and drafted and edited the manuscript.

SL contributed to the conception, design and development of the protocol and search strategy for the review, identified and extracted and entered data, interpreted the results and contributed to the revision of the manuscript.

MT contributed to the conception, design and development of the protocol, identified, extracted and entered data, participated in the review and interpretation of the results and to the drafting and revision of the manuscript.

DECLARATIONS OF INTEREST

The authors report no conflict of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methodological quality of included studies was updated from the protocol, according to the new recommendation reported in the Cochrane Handbook.

INDEX TERMS

Medical Subject Headings (MeSH)

Alcohol Drinking [*drug therapy]; Pregnancy Complications [*drug therapy]

MeSH check words

Female; Humans; Pregnancy