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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	7
OBJECTIVES	8
METHODS	8
RESULTS	13
Figure 1.	14
Figure 2.	16
Figure 3.	17
Figure 4.	19
Figure 5.	20
ADDITIONAL SUMMARY OF FINDINGS	21
DISCUSSION	24
AUTHORS' CONCLUSIONS	25
ACKNOWLEDGEMENTS	26
REFERENCES	26
CHARACTERISTICS OF STUDIES	28
DATA AND ANALYSES	35
WHAT'S NEW	35
HISTORY	35
CONTRIBUTIONS OF AUTHORS	36
DECLARATIONS OF INTEREST	36
SOURCES OF SUPPORT	36
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	36
INDEX TERMS	36

[Intervention Review]

Antidepressants for preventing postnatal depression

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ABSTRACT

Background

Depression is common in the postnatal period and can lead to adverse effects on the infant and wider family, in addition to the morbidity for the mother. It is not clear whether antidepressants are effective for the prevention of postnatal depression and little is known about possible adverse effects for the mother and infant, particularly during breastfeeding. This is an update of a Cochrane Review last published in 2005.

Objectives

To assess the effectiveness of antidepressant medication for the prevention of postnatal depression, in comparison with any other treatment, placebo or standard care.

Search methods

We searched the Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR - both Studies and References), CENTRAL (Wiley), MEDLINE (OVID), Embase (OVID), PsycINFO (OVID), on 13 February 2018. We also searched the World Health Organization (WHO) trials portal (ICTRP) and ClinicalTrials.gov on 13 February 2018 to identify any additional unpublished or ongoing studies.

Selection criteria

Randomised controlled trials (RCTs) of initiation of antidepressants (alone or in combination with another treatment), compared with any other treatment, placebo or standard care for the prevention of postnatal depression among women who were either pregnant or had given birth in the previous six weeks and were not currently depressed at baseline.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We requested missing information from investigators wherever possible and sought data to allow intention-to-treat analyses.

Antidepressants for preventing postnatal depression (Review)

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1

Main results

Two trials including a total of 81 participants fulfilled the inclusion criteria for this review. All participants in both studies had a history of postnatal depression and were not taking antidepressant medication at baseline. Both trials were conducted by the same research group. Risk of bias was low or unclear in most domains for both studies. We were unable to perform a meta-analysis due to the small number of studies.

One study compared nortriptyline with placebo and did not find any evidence that nortriptyline was effective in preventing postnatal depression. In this study, 23% (6/26) of women who took nortriptyline and 24% (6/25) of women who took placebo experienced postnatal depression (RR 0.96, 95% CI 0.36 to 2.59, very low quality evidence) in the first 17 weeks postpartum. One woman taking nortriptyline developed mania; and one side effect, constipation, was more common among women taking nortriptyline than those taking placebo.

The second study compared sertraline with placebo. In this study, 7% (1/14) of women who took sertraline developed postnatal depression in the first 17 weeks postpartum compared with 50% (4/8) of women who took placebo. It is uncertain whether sertraline reduces the risk of postnatal depression (RR 0.14, 95% CI 0.02 to 1.07, very low quality evidence). One woman taking sertraline had a hypomanic episode. Two side effects (dizziness and drowsiness) were more common among women taking sertraline than women taking placebo.

Conclusions are limited by the small number of studies, small sample sizes and incomplete outcome data due to study drop-out which may have led to bias in the results. We have assessed the certainty of the evidence as very low, based on the GRADE system. No

data were available on secondary outcomes of interest including child development, the mother–infant relationship, breastfeeding, maternal daily functioning, family relationships or maternal satisfaction.

Authors' conclusions

Due to the limitations of the current evidence base, such as the low statistical power of the included studies, it is not possible to draw any clear conclusions about the effectiveness of antidepressants for the prevention of postnatal depression. It is striking that no new eligible trials have been completed in the period of over a decade since the last published version of this review. Larger trials are needed which include comparisons of antidepressant drugs with other prophylactic treatments (e.g. psychological interventions), and examine adverse effects for the fetus or infant. Future reviews in this area may benefit from broadening their focus to examine the effectiveness of antidepressants for the prevention of perinatal (i.e. antenatal or postnatal) depression, which could include studies comparing antidepressant discontinuation with continuation for the prevention of relapse of depression during pregnancy and the postnatal period.

PLAIN LANGUAGE SUMMARY

Antidepressant medication for preventing postnatal depression

Review question

We examined the evidence to see whether antidepressants can prevent women from experiencing depression in the postnatal period, when compared with any other treatment, sham treatment (placebo), or standard clinical care. The studies we identified included only women who had previously experienced postnatal depression, and had a higher risk of experiencing postnatal depression again.

Background

Postnatal depression is a common condition. Approximately 10 to 15 of every 100 women experience elevated symptoms of depression in the period after giving birth, and 5 in every 100 women will experience a depressive disorder. Symptoms of depression include low mood, loss of pleasure, and feelings of guilt or worthlessness. Postnatal depression has an impact on the mother, and may have a negative impact on the well-being of the infant and wider family.

Women with a history of depression - and particularly women who have previously experienced postnatal depression - have a higher risk of postnatal depression. Pregnant women who are not depressed, but are at high risk of developing postnatal depression, may want to consider taking measures to try to prevent depression developing in the postnatal period.

We examined whether taking antidepressants during pregnancy or after giving birth can prevent women from developing postnatal depression.

Study characteristics

We identified two small, relevant trials. All the women in these trials had a history of postnatal depression, but were not depressed or using antidepressants at the beginning of the studies. Both studies compared antidepressant medicine with placebo. Women started taking the medicine or placebo on the first day after giving birth.

In the larger study (56 women), the antidepressant given to women was nortriptyline, which is a tricyclic antidepressant. In the other study (25 women), the antidepressant used was sertraline which is a selective serotonin reuptake inhibitor (SSRI); these types of antidepressants work in different ways. The women and the researchers assessing the outcomes in both studies did not know which women were taking antidepressants and which placebo (i.e. both studies were 'double-blind'). Both studies were funded by the National Institute of Mental Health (NIMH), a US government organisation.

Key results

There was no evidence that nortriptyline prevented postnatal depression. During the 17-week treatment period, 6 of the 26 women taking nortriptyline experienced postnatal depression compared with 6 of the 25 women taking placebo. One woman taking nortriptyline developed mania (a state of abnormally high arousal and energy level), and constipation was more common among women taking nortriptyline, but other unwanted, or harmful, effects did not differ between groups.

In the sertraline study, 1 of the 14 women taking sertraline developed postnatal depression compared with 4 of the 8 women taking placebo (during the 17-week treatment period). This study was very small, so we can't be sure whether the difference between sertraline and placebo is due to chance, or whether sertraline does prevent postnatal depression among women with a history of postnatal depression. One woman taking sertraline experienced a hypomanic episode (a state like mania but less severe); and dizziness and drowsiness were more common among women taking sertraline than women taking placebo.

Quality of the evidence

This evidence is current to February 2018.

We could only identify two relevant studies, which had small numbers of participants and inconsistent findings, and were conducted by the same research group. Therefore we consider the quality of evidence in this review to be very low. Further studies with larger samples are needed before we can know whether antidepressants can prevent postnatal depression.

It is worth noting that no new relevant trials have been completed in the 10 years since we last examined this evidence. It may be useful for future medical studies to investigate whether antidepressants can prevent depression during pregnancy as well as during the postnatal period; and whether women who continue to take antidepressants during pregnancy (compared with stopping medication) are less likely to have a relapse of depression at this time.

We also need studies which have longer follow-up periods; examine outcomes and side effects for both the mother and fetus or breastfeeding infant; and compare antidepressants with other preventative interventions (such as psychological therapies).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Nortriptyline for the prevention of postnatal depression						
Patient or population: women with a history of postnatal depression Intervention: nortriptyline Control: placebo						
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	Tricyclic antidepressants				
Postnatal depression (17 weeks)	240 per 1000 ¹	230 per 1000 (86 to 622)	RR 0.96 (0.36 to 2.59)	51 (1 study)	⊕○○○ very low ^{2,3}	
Adverse effects experienced by mother and/or foetus or nursing baby				51 (1 study)	⊕○○○ very low ^{2,3}	1 woman assigned to nortriptyline developed mania within the first week Constipation was reported more frequently in the nortriptyline than placebo group (78% among women taking nortriptyline and 22% among women taking placebo; Fischer's exact test P < 0.001) . This was the only side effect that was more common among women taking nortripty-

				line than placebo, but the other side effects assessed and the proportion of women experiencing these side effects was not reported
Acceptability of treatment (17 weeks)		51 (1 study)	⊕○○○ very low ^{2,3}	Acceptability of treatment was not assessed directly but 1 woman was lost to follow-up from the nortriptyline arm (and 1 women in the nortriptyline arm withdrew after developing mania in the first postpartum week) and 3 withdrew from the placebo arm (owing to side effects, personal reasons and pregnancy) 4 participants declined to take the study drug after randomisation
Overall maternal satisfaction (17 weeks)	No data available			
Improvement in the maternal relationship with the baby (17 weeks)	No data available			
Establishment or continuation of breastfeeding (17 weeks)	No data available			

*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%CI) 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.

¹Assumed risk calculated as the proportion of women on placebo with the outcome (postnatal depression) multiplied by 1000

²Downgraded due to high risk of bias in 1 domain (incomplete outcome data)

³Downgraded twice due to imprecision (only 1 small study available for this comparison)

BACKGROUND

Description of the condition

Many women experience depression after they give birth, which is known as postnatal or postpartum depression (O'Hara 1996; Howard 2014). Depressive episodes are characterised by a variety of symptoms, such as low mood, loss of enjoyment, feelings of guilt or worthlessness, loss of energy and possibly suicidal ideation. Standard diagnostic criteria for depression are used to diagnose depression in the postnatal period (e.g. the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or the Tenth Revision of the International Classification of Disease (ICD-10) (World Health Organization 2004; American Psychiatric Association 2013). As well as the impact on the mother, postnatal depression can have negative implications for the infant and the wider family (Cox 1982; Stein 2014). These outcomes may include adverse effects

on mother–infant attachment, and the emotional or behavioural development of the child (Stein 2014).

It is estimated that approximately 10% to 15% of women experience elevated symptoms of depression in the period after giving birth, and approximately 5% of women have an episode of major depression at this time (Howard 2014). Women who have had one or more previous episodes of depression are at increased risk of developing postnatal depression, and this is particularly the case for women with a previous episode of postnatal depression (Howard 2014). The period of time in which episodes of depression are classified as 'postnatal depression' varies between studies, but often refers to onset of depression in the first three months (e.g. Yonkers 2008) or six months (e.g. Sharp 2010) after delivery. However, it is important to remember that many women presenting with depression in the postnatal period may have developed depression before delivery, either before conception or during pregnancy (Wisner 2013).

Description of the intervention

Antidepressants are medications to treat the symptoms of depression, and meta-analyses have shown that their effectiveness increases with the severity of depression (Fournier 2010). In general, medication exposure in pregnancy should be minimised when possible, and non-pharmacological interventions can be effective for the prevention and treatment of mild to moderate depression (Dennis 2007; Morrell 2016). However, antidepressant medications are clinically indicated for women with more severe mental disorders during pregnancy or the postnatal period when there are substantial risks to the mother, the pregnancy, and the fetus or infant (Howard 2014). Current NICE guidelines recommend the use of antidepressants for the treatment of moderate to severe depression and also for the prevention of depressive episodes

in those with a high risk of relapse or a history of recurrent depression (NICE 2009). This review investigates the initiation of antidepressants during pregnancy or the early postpartum period for the prevention of postnatal depression. Antidepressants can be classified into the following types.

- Selective serotonin reuptake inhibitors (SSRIs): e.g. fluoxetine, paroxetine, sertraline, citalopram
- Tricyclic antidepressants (TCAs): e.g. amitriptyline, nortriptyline, doxepin
- Heterocyclic antidepressants: e.g. mianserin
- Monoamine oxidase inhibitors (MAOIs): e.g. phenelzine, brofaromine
- Noradrenaline re-uptake inhibitors (NARIs): e.g. reboxetine
- Noradrenaline-dopamine re-uptake inhibitors (NDRIs): e.g. bupropion
- Serotonin-noradrenaline re-uptake inhibitors (SNRIs): e.g. venlafaxine, duloxetine
- Noradrenergic and specific serotonergic antidepressants (NASSAs): e.g. mirtazapine
- Serotonin antagonist and re-uptake inhibitors (SARIs): e.g. trazodone
- Other unclassified antidepressants: e.g. vilazodone

The fetus and the infant may be affected by exposure to psychotropic drugs across the placenta or through breastfeeding, although exposure to antidepressants in breastfed infants is five to ten times lower than exposure in utero (Howard 2014). Breastfeeding women have been advised to avoid doxepin (a TCA) as its main metabolite has been found in breast milk in higher concentrations than other antidepressants (Eberhard-Gran 2006). More broadly, there are limited data on the safety of antidepressants during breastfeeding (particularly for longer-term child outcomes) but the findings to date suggest that the benefits of taking antidepressants may outweigh the risks in breastfeeding women who need

treatment for depression (Howard 2014). The risk–benefit ratio is less clear for women offered antidepressants as a preventative intervention in the postpartum period, but it is important to note that the women who are offered antidepressants as a preventative intervention at this time often have a history of severe episodes of postnatal depression and are therefore at higher risk of experiencing another episode of postnatal depression.

How the intervention might work

The function of antidepressants is not fully understood. There is evidence from studies of both patients and healthy controls that antidepressants affect activity in areas of the medial prefrontal cortex and limbic system that are associated with emotion processing (e.g. the anterior cingulate, amygdala and thalamus), leading to increased activity in response to positive emotions and decreased activity in response to negative emotions (see systematic review and meta-analysis by Ma 2014). Most antidepressants appear to

inhibit uptake of monoamine neurotransmitters (e.g. serotonin or noradrenaline (norepinephrine)) into neurons, which increases the concentrations of these neurotransmitters at synapses (Berton 2006). The majority of evidence on the effects of antidepressants comes from treatment studies, but there is also evidence that antidepressants can reduce the risk of relapse of depression compared with placebo (Geddes 2003). Women at higher risk of postnatal depression (such as those with a history of postnatal depression) may be more likely to benefit from preventative interventions and also more motivated to accept them. This is particularly relevant when considering antidepressant prevention of postnatal depression, given the possible adverse effects of antidepressant use on the breastfeeding infant (or on the fetus, if started during pregnancy).

Why it is important to do this review

This is an update of a Cochrane Review published in 2005, and previously assessed as up to date in 2007. Research into postnatal depression is important due to its high prevalence and potential negative impact on both the mother and child, as well as other family members (Cox 1982; Stein 2014). Antidepressants have been shown to be more effective than placebo in treating postnatal depression (Molyneux 2014); but it is also important to consider the prevention of postnatal depression, particularly for high-risk women. Other interventions have been found to be effective for preventing postnatal depression, for example psychological and psychosocial interventions (Morrell 2016). However, these psychological interventions are not always available and some women may be recommended antidepressants as a preventative intervention, particularly those with a history of severe postnatal depression and those who have previously responded well to antidepressants. It is therefore important to determine whether antidepressants are effective for the prevention of postnatal depression. It is also important to examine antidepressant prevention of postnatal depression owing to the additional issues around the safety for the fetus (if preventative interventions begin during pregnancy) or the breastfeeding infant.

OBJECTIVES

To assess the effectiveness of antidepressant medication for the prevention of postnatal depression, in comparison with any other treatment, placebo or standard care.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials (RCTs), including cluster and cross-over trials.

Types of participants

Participant characteristics

Women who are pregnant or have given birth in the last six weeks, who are not depressed at the start of the trial.

Diagnosis

Women must not be depressed at the beginning of eligible trials, as the focus of the review is the prevention of depression in the postnatal period. Trials may include women with a history of depression or postnatal depression only, or offer the intervention to all at-risk women during pregnancy or the early postpartum period.

Co-morbidities

We placed no restrictions on studies involving participants with co-morbid medical or psychological disease or disorders, provided the co-morbidities were not the primary focus of the study.

Setting

We placed no restrictions on the setting of the studies.

Types of interventions

Experimental intervention

Any antidepressant medication at any dose, alone or in combination with another treatment, initiated in at least one arm of a trial. For the purposes of this review antidepressant medications were classified as follows.

- Selective serotonin reuptake inhibitors (SSRIs): e.g. fluoxetine, paroxetine, sertraline, citalopram
- Tricyclic antidepressants (TCAs): e.g. amitriptyline, nortriptyline, doxepin
- Heterocyclic antidepressants: e.g. mianserin
- Monoamine oxidase inhibitors (MAOIs): e.g. phenelzine, brofaromine
- Noradrenaline re-uptake inhibitors (NARIs): e.g. reboxetine
- Noradrenaline-dopamine re-uptake inhibitors (NDRIs): e.g. bupropion
- Serotonin-noradrenaline re-uptake inhibitors (SNRIs): e.g. venlafaxine, duloxetine
- Noradrenergic and specific serotonergic antidepressants (NASSAs): e.g. mirtazapine

- Serotonin antagonist and re-uptake inhibitors (SARIs): e.g. trazodone
- Other unclassified antidepressants: e.g. vilazodone

Comparator intervention

Placebo, standard clinical care, or any other treatment, such as psychological interventions (e.g. CBT) or psychosocial interventions (e.g. peer support).

Types of outcome measures

We included studies that meet the above inclusion criteria regardless of whether they report on the following outcomes.

Primary outcomes

1. Onset of postnatal depression. Depression was defined as measured in each trial using any of the following: clinical diagnostic interview; standard observer-rated depression symptom scales based on a recognised diagnostic scheme (e.g. the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or the International Classification of Disease (ICD-10); other standardised criteria (e.g. the Research Diagnostic Criteria (RDC) (Spitzer 1978)); or screening instruments (e.g. the Edinburgh Postnatal Depression Scale (EPDS) (Cox 1987)). Studies examining onset of depression up to six months postpartum were eligible. Time to onset was reported if examined in individual studies.
2. Adverse events experienced by the mother, or the fetus/breastfed infant, or both.

Secondary outcomes

3. Acceptability of treatment assessed directly through questionnaires for trial participants or indirectly through drop-out rates.
4. Cognitive and emotional development of the infant (e.g. assessment of the mental and psychomotor development of infants using the Mental Development Index (MDI) and Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development (Bayley 2006); parental report of child development using the Parent Report of Children's Abilities-Revised (PARCA-R) (Johnson 2008).
5. Overall maternal satisfaction (e.g. self-reported general satisfaction, satisfaction with self/baby/partner using the Mackay Childbirth Satisfaction Rating Scale (Goodman 2004); self-reported beliefs, values and perceived skills regarding motherhood using the Parenting Sense of Competence Scale (Gidaud-Wallston 1978).
6. Improvement in the maternal relationship with the baby (e.g. improved mother–infant interactions measured using the CARE-Index (Crittenden 1988).
7. Improvement in the mother's ability to carry out daily activities and social functioning (e.g. improved score on the Global Assessment of Functioning Scale (Endicott 1976); increased social network, measured using the Social Network Index (Cohen 1997).

8. The establishment or continuation of breastfeeding (e.g. rates of establishment, continuation or discontinuation).
9. Prevention of neglect or abuse of the baby (e.g. using the Parent-Report Multidimensional Neglectful Behavior Scale (Kaufman Kantor 2004).
10. The effect on marital and family relationships (e.g. using the Quality of Marriage Index (Norton 1983).

Timing of outcome assessment

- Zero to eight weeks: immediate effects.
- Nine to 16 weeks: short-term effects.
- 17 to 24 weeks: intermediate effects.
- More than 24 weeks: long-term effects.

Hierarchy of outcome measures

If multiple measures had been used for one of these outcomes, we intended to select measures which have been validated among women with postnatal depression above measures which have been validated in other populations. If possible, we intended to report one outcome from each of the above time periods.

Search methods for identification of studies

Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

The Cochrane Common Mental Disorders Group (CCMD) maintains two archived clinical trials registers at its editorial base in York, UK: a references register and a studies-based register. The CCMDCTR-References Register contains over 40,000 reports of RCTs in depression, anxiety and neurosis. Approximately 50% of these references have been tagged to individual, coded trials. The coded trials are held in the CCMDCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual, using a controlled vocabulary; (please contact the CCMD Information Specialists for further details). Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950 to 2016), Embase (1974 to 2016) and PsycINFO (1967 to 2016); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from international trial registers via the World Health Organization's trials portal (the International Clinical Trials Registry Platform (ICTRP)), pharmaceutical companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's generic search strategies (used to identify RCTs) can be found on the Group's website. The Group's Spe-

cialised Register had fallen out of date with the Editorial Group's move from Bristol to York in the summer of 2016.

Electronic searches

1. CCMDCTR

We conducted an update search of the CCMDCTR-Studies and References registers on 13 February 2018 using the terms listed in Appendix 1.

2. International trial registries

We also searched the WHO trials portal (ICTRP) and Clinical-Trials.gov on 13 February 2018 to identify any additional unpublished or ongoing studies using the following terms.

ICTRP: *depress* and prevent* and postpartum or depress* and prevent* and postnatal*

or depress and prophyla* and postpartum or depress* and prophyla* and postnatal*

CT.gov: *(prevention or prevent or prophylaxis) and (depression or depressive) and (postnatal or post-natal or postpartum or post-partum)*
Records were filtered (for pharmacological interventions) using Excel.

3. Web of Science (citation search)

A cited reference search of the Web of Science was also conducted (4 May 2016), for reports citing the first version of this review, a companion publication published in PLOS Medicine (Howard 2006) and all of the included studies to date.

Earlier searches conducted for the first version of this review (to June 2007) can be found in Appendix 2.

4. In keeping with MECIR conduct standard c37, a final pre-publication search was conducted on 13 February 2018 on the following databases (2016 to date).

- Cochrane Common Mental Disorders Specialised Register;
- Ovid MEDLINE;
- Ovid Embase;
- Ovid PsycINFO;
- CENTRAL;
- Trial Registries.

This was necessary as the Group's Specialised Register had fallen out of date with the Editorial Group's move from Bristol to York in the summer of 2016. The details of this search can be found in Appendix 3

Searching other resources

Grey literature

We did not search grey literature for this update of the review as relevant unpublished studies should be identified through searches of clinical trials registries.

Reference lists

We checked reference lists and conducted forward citation tracking for all included studies to identify additional studies missed from the original electronic searches (for example unpublished or in-press citations).

Correspondence

We contacted trialists for information on unpublished or ongoing studies, or to request additional trial data when required.

Data collection and analysis

Selection of studies

Titles and abstracts of studies identified in the above search were examined by two review authors (LT and EM) independently. We removed duplicate records; and obtained the full-text article for any publication which was potentially relevant. LT and EM then independently assessed full-text articles to examine whether they fulfilled the inclusion criteria. Where the authors disagreed, the matter was discussed until agreement was reached; or we sought guidance and arbitration from a third review author (LH) when necessary.

We collated multiple reports related to the same study so that data from each trial were included only once even if the trial, or aspects of it, had been reported in multiple published papers. When multiple reports of a single trial were identified, we included the report with the largest sample size. We recorded the selection process in detail and produced a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (LT and EM) independently extracted data from the trial reports. We developed a data extraction form and piloted it for this review. We requested missing information from investigators wherever possible; and we extracted the following study characteristics.

1. Methods: study design, study setting, number and location of study centres, study date and duration, details of blinding/allocation concealment.
2. Participants: total number of participants and number in each group, inclusion and exclusion criteria, key socio-demographic information (e.g. age), number of withdrawals.
3. Interventions: number of intervention groups, type of interventions and comparisons, duration of intervention and key details (e.g. dosage), details of any 'run-in' period.
4. Outcomes: primary and secondary outcomes specified and reported, time points reported, adverse events, and details of measures used to assess outcomes.

5. Analysis: statistical techniques used, subgroup analyses, number of participants included in each analysis, study results.

6. Notes: trial funding and conflicts of interest of trial authors. Where possible, we resolved any inconsistencies in the information extracted by discussion between review authors (LT and EM). When this was not possible, we sought further information from the trial investigator(s). One author (EM) entered data into Review Manager 5 software (RevMan 5); and all entries were checked by the other author (LT). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. LT spot-checked study characteristics for accuracy against the trial report.

Main comparisons

The main planned comparison was antidepressant medication versus placebo. We had also planned to compare antidepressants with standard clinical care and with psychological or psychosocial interventions but no included studies provided data for these comparisons. Comparisons are presented separately for individual antidepressants.

Assessment of risk of bias in included studies

Two review authors (LT and EM) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion, including a third review author (LH) when necessary. We assessed risk of bias in the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias (adherence to medication)

We judged each potential source of bias as high, low or unclear and provided a supporting quotation from the study report together with a justification for our judgment in the 'Risk of bias' table. We considered blinding separately for different key outcomes where necessary. We assessed selective outcome reporting by obtaining trial protocols (where possible) and comparing these with the final trial report. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

Measures of treatment effect

We presented the primary outcome (postnatal depression) using risk ratios (RR) for all studies. If the RR was not presented in the original trial report, we calculated it for this review. We summarised other outcomes using the data as quoted in the original

papers (e.g. odds ratio (OR), hazard ratio (HR), RR, mean difference (MD)). If there had been sufficient data for meta-analyses to be performed on any outcomes (i.e. three or more comparable studies), we would have calculated the RR for dichotomous outcomes, the HR for time-to-event outcomes, and the MD or standardised mean difference (SMD) for continuous outcomes.

Dichotomous data

We calculated the RR and its 95% confidence interval (CI) for dichotomous outcome data. It has been shown that RRs are more intuitive than ORs and that ORs tend to be interpreted as RRs by clinicians (Bland 2000). This misinterpretation then leads to an overestimation of the effect. If necessary for studies included in future updates of this review, we will attempt to convert continuous primary outcome measures to dichotomous data using cut-off points on rating scales to identify those who did and did not fulfil the criteria for depression.

Time-to-event data

We presented the HR and 95% CI for time-to-event outcome data, when applicable. In future updates of this review, if time-to-event data is given in an original paper but not presented as an HR then the HR will be estimated using the methods described by Tierney 2007. If there are sufficient studies presenting time-to-event data to conduct a meta-analysis in future updates of this review, we will pool data following the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Continuous data

We did not conduct any meta-analyses for this review. However, if a meta-analysis of continuous data is performed in future updates of the review, we will calculate the mean difference between groups (if studies used the same outcome measure) or the standardised mean difference (if studies used different measures to assess the same outcome). If future updates of this review include reports which present standard errors instead of standard deviations, we will convert these to standard deviations. If standard deviations are not reported and cannot be calculated from the available data, we will request the necessary data from trial authors. In the absence of data from authors, we will use the mean standard deviation from other comparable studies.

Unit of analysis issues

Cluster-randomised trials

Cluster RCTs must be analysed taking into account the clustered nature of the data. No cluster RCTs meeting inclusion criteria for this review were identified, but we will use the following methods

to address any cluster RCTs included in future updates of this review: we will extract the intra-cluster correlation coefficient (ICC) for each trial or request it from study authors if not reported. If the ICC cannot be obtained, estimates of the ICC from similar studies will be used to 'correct' for clustering, in line with guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The generic inverse variance method will be used to meta-analyse results from cluster RCTs (Higgins 2011).

Cross-over trials

The results of cross-over trials may be influenced by the carry-over effect, whereby a treatment in the first randomised treatment period of the trial has an effect which carries over to the second randomised treatment period. Cross-over trials are also not appropriate if the condition of interest is unstable (Elbourne 2002). Both of these issues apply to trials of postnatal depression prevention. We identified no cross-over trials for inclusion in this review, but if we identify any in future updates of the review we will include only data from the first randomised treatment period.

Studies with multiple treatment groups

Trials with more than two relevant treatment groups can lead to issues with pairwise meta-analysis. We identified no studies with more than two groups for inclusion in this review but if we identify any in future updates the following methods will be used, in line with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For dichotomous outcomes, we will combine the active treatment groups into a single arm for comparison against the control group; or we will split the control group equally for separate comparisons with the active treatment groups (based on sample size). For continuous outcomes, we will pool the means and standard deviation in each treatment group (as a function of the number of participants in each group) for comparison with the control group.

Dealing with missing data

We contacted study investigators to verify key study characteristics and obtain missing numerical outcome data where necessary. When possible, we presented data on a 'once randomised, always analyse' basis, assuming an intention-to-treat (ITT) analysis. When studies had not performed ITT analyses, we calculated the RR based on ITT assuming a negative outcome (i.e. onset of postnatal depression) for all women lost to follow-up. If this was done, a sensitivity analysis was also performed assuming a positive outcome (i.e. no postnatal depression) for all women lost to follow-up. We anticipated that some studies would have used the method of last observation carried forward (LOCF) to do an ITT analysis. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results: therefore we have indicated where we have reported LOCF data in

this review. We presented ITT analysis for all primary outcomes. Where ITT analyses were not available for secondary outcomes, we reported this in the relevant section of the results.

Assessment of heterogeneity

There were insufficient studies to conduct a meta-analysis. However, if future updates of this review include sufficient comparable studies to conduct a meta-analysis, we will assess statistical heterogeneity visually by studying the degree of overlap of the confidence intervals for individual studies in a forest plot. We will also conduct more formal assessments of heterogeneity using a Chi² test with the P value set at 0.1 (taking into account the fact that this test has low statistical power when there are few studies). We will use the I² statistic, and will interpret its results based on the following overlapping bands, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: represents considerable heterogeneity

Assessment of reporting biases

There were insufficient studies to conduct a meta-analysis. However, if a future update of this review includes a meta-analysis pooling data from 10 or more studies, we will generate a funnel plot and visually inspect it for asymmetry, which can indicate publication bias. We will also consider other possible causes of funnel plot asymmetry (e.g. poor methodological quality of small studies).

Data synthesis

We identified insufficient studies in this review to conduct a meta-analysis. However, if a future update of this review includes three or more studies using the same class of antidepressants and the same comparison group (e.g. placebo), we will perform a meta-analysis. Due to the anticipation of clinical heterogeneity between studies, for example in the participant groups included, we will conduct a random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

We were unable to include sufficient studies in this review to conduct subgroup analyses or further investigations of heterogeneity. However, if we identify sufficient data in future updates of this review we will conduct the following subgroup analyses to investigate heterogeneity between trials and assess the effectiveness of the intervention in the following groups.

1. Studies in which women started antidepressants during pregnancy versus studies in which women started antidepressants in the postpartum period, to examine whether the timing of antidepressant use influences its effectiveness in preventing postnatal depression.

2. Studies in which all women had a history of postnatal depression versus studies in which women had a history of non-postnatal depression, to examine whether this influences the effectiveness of antidepressant prevention of postnatal depression.

Sensitivity analysis

We were unable to include sufficient studies in this review to conduct sensitivity analyses. However, if future updates of this review include sufficient data, we will conduct a priori sensitivity analyses to examine the robustness of pooled estimates to decisions made in the methods of this systematic review. We will assess the effects of excluding studies with the following characteristics.

1. Study quality: excluding studies that had a high risk of bias in any domain.
2. Blinding: excluding antidepressant versus placebo trials that were unblinded.
3. Attrition: excluding studies with more than 20% drop-out.
4. Validation: excluding outcomes based on non-validated assessments.

We also planned additional sensitivity analyses to examine missing data (described in [Dealing with missing data](#)). If studies have not performed ITT analyses, we will calculate the RR assuming a negative outcome (i.e. onset of postnatal depression) for all women lost to follow-up and a sensitivity analysis assuming a positive outcome (i.e. no postnatal depression) for all women lost to follow-up.

'Summary of findings' tables

We have produced 'Summary of findings' tables for the key findings of the review for all main comparisons in the time frame of intermediate effects (12 to 24 weeks) ([Summary of findings for the main comparison](#); [Summary of findings 2](#)). The tables present findings for primary and secondary outcomes (see [Types of outcome measures](#)) including the standardised effect size estimates (with 95% confidence intervals), number of studies and participants, and the quality of evidence based on standards of the

GRADE working group (see [Balslem 2011](#)). The secondary outcomes included in the 'Summary of findings' tables are: acceptability of treatment, overall maternal satisfaction, improvement in the maternal relationship with the baby, and establishment or continuation of breastfeeding.

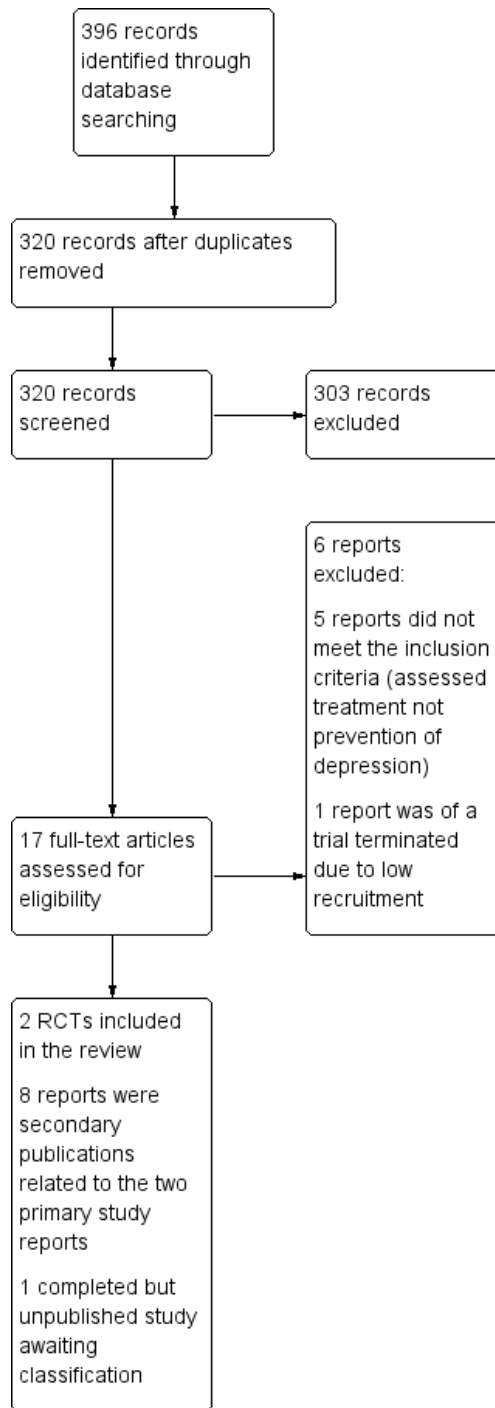
RESULTS

Description of studies

Results of the search

The searches were carried out to 13 February 2018. They identified 396 references, of which 320 remained after de-duplication. Two review authors (LT and EM) independently screened the titles and abstracts of these records and excluded 303 which did not meet the inclusion criteria. We retrieved and inspected the full-text papers (or trial protocols) for the remaining 17 study reports. We excluded a total of six of these for not meeting our inclusion criteria: one because the trial terminated due to low recruitment ([NCT02235064](#)); and the remaining five reports (four studies) as these assessed treatment rather than prevention of postnatal depression or continuation with discontinuation of antidepressants during pregnancy for the prevention of perinatal (i.e. antenatal or postnatal) depression rather than examining initiation of antidepressants for the prevention of postnatal depression. There are two primary study reports with an additional eight secondary publications for the two trials which meet the inclusion criteria and are included in the review. In addition, there is one completed but unpublished study ([NCT00276900](#)) (see Characteristics of studies awaiting classification). We contacted the trial investigator for additional information but unfortunately it was not possible for her to respond to our request due to the period of time that has elapsed since the included trials were conducted. The study selection process is detailed in our PRISMA flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.



Included studies

We included two studies in this review ([Wisner 2001](#) and [Wisner 2004](#)), with characteristics as follows (see also [Characteristics of included studies](#)).

Design

Both studies were double-blind, randomised controlled trials comparing an antidepressant medication with a placebo. We found no eligible cluster-randomised or cross-over trials.

Sample sizes

[Wisner 2001](#) had a sample size of 56 participants at baseline, of whom 51 were included in their analyses (26 participants taking nortriptyline and 25 participants taking placebo). [Wisner 2004](#) had a sample size of 25 women at baseline with 22 included in the analyses (14 women in the sertraline arm and 8 in the placebo arm, recruited in a 2:1 intervention to placebo ratio). In both studies, women were excluded from the analyses if they refused to take the study drug after randomisation. Three women randomised to sertraline who never took the medication were excluded from [Wisner 2004](#), and four women were excluded from [Wisner 2001](#) for refusing to take the study drug (treatment allocation unknown). [Wisner 2001](#) also excluded one participant (randomised to nortriptyline) who developed mania in the first week postpartum from the analyses.

Setting

Both studies recruited pregnant women (up to 35 weeks' gestation) who were not depressed in the index pregnancy; and both began medication in the immediate postpartum period. In both trials, the first dose of the antidepressant or placebo medication was provided for women in the hospital following delivery. For both studies, participants had to be aged 21 to 45 years, and not be depressed in the index pregnancy but have at least one previous episode of postnatal depression within five years prior to enrolment. [Wisner 2001](#) stated that to be considered to be postnatal depression, symptom onset must have been within three months of a live birth. Both studies excluded women with previous episodes of psychosis and bipolar disorder, other current Axis I diagnoses (except for generalised anxiety and panic disorder) and antisocial or borderline personality disorders. Women receiving psychotherapy or who used psychotropic medications after the first trimester of the index pregnancy were also excluded from both studies. [Wisner 2004](#) also excluded women with an incomplete blood count or abnormal results from thyroid tests.

Interventions

[Wisner 2001](#) examined nortriptyline (a tricyclic antidepressant) and [Wisner 2004](#) examined sertraline (a selective serotonin reuptake inhibitor (SSRI)). In both studies the antidepressant was taken as soon as possible after delivery, ideally within 24 hours.

In [Wisner 2001](#), the dose of nortriptyline was increased from 20 mg/day to 70 mg/day over the first week. A dose of 75 mg/day was then maintained to day 21, after which the dose was calculated individually for each participant, based on their serum level measured on day 14. The dose was then adjusted over time based on further serum levels and side effects data, in order to maintain the nortriptyline serum level between 50 mg/day and 150 mg/mL with the optimum set at 80 mg/day to 120 mg/mL. The dose was then tapered through weeks 17 to 20 at a rate of 33% per week. Doses (three capsules of either nortriptyline or placebo) were taken once daily at bedtime.

In [Wisner 2004](#), the dose of sertraline was originally started at 50 mg/day. However, a dose reduction was recommended by the non-blind side effects monitoring team after the first two study participants withdrew after experiencing severe headaches. Therefore, for all remaining participants the dose began with 25 mg/day increased to 50 mg/day over the first four weeks of treatment and up to 75 mg/day over weeks 5 to 17. From week 17, the dose of sertraline was tapered and treatment was discontinued at week 20.

Outcome

Primary outcome assessment

In both studies, onset of postnatal depression was determined through screening with the Hamilton Rating Scale for Depression (HAM-D) followed by a diagnostic interview. In [Wisner 2001](#), the HAM-D was administered to all women weekly. If a participant scored 15 or more on the HAM-D they were evaluated a second time within seven days. If they scored 15 or more on the HAM-D again and met research diagnostic criteria for major depression on both occasions, the principal investigator and an independent board-certified psychiatrist evaluated the participant. Both psychiatrists were blinded to participant allocation (i.e. antidepressants or placebo). Women were classified as having depression if both psychiatrists reached a diagnosis of major depressive disorder.

A similar but simpler approach was used in [Wisner 2004](#). If a woman scored 15 or more on the HAM-D on two occasions, one week apart, she was assessed by a single psychiatrist who was associated with the study but blinded to participant allocation. In both studies, the treatment period lasted 17 weeks and primary outcomes were assessed at the end of the treatment period (i.e. 17 weeks post randomisation), prior to the medication being tapered.

Both studies assessed symptoms of mania weekly and assessed side effects with the Asberg Side Effects rating scale. Adverse events occurring during both studies were also reported.

Secondary outcome assessment

There was no direct assessment of the acceptability of treatment in either study: we used the number of participants withdrawing from each treatment group as an indirect measure of acceptability. Neither Wisner 2001 nor Wisner 2004 provided information about the cognitive and emotional development of the infant, overall maternal satisfaction, maternal relationship with the infant, the mother's ability to carry out daily activities, breastfeeding, neglect or abuse of the infant or the effect on marital and family relationships.

Excluded studies

We excluded two records during full-text screening, as they evaluated the treatment rather than prevention of postnatal depression. For full details of these studies see [Characteristics of excluded studies](#).

New studies found at this update

No new studies have been included in the review in this update.

Studies awaiting classification

No studies are awaiting classification.

Ongoing studies

Two RCTs are currently ongoing. Both studies are investigating the use of sertraline to prevent postnatal depression compared with a placebo control. One study has completed recruitment, but results of the trial are not yet available (NCT00276900). The second RCT is currently recruiting (NCT02235064). Future updates of this review should consider these studies for inclusion. See [Characteristics of ongoing studies](#) for further details.

Risk of bias in included studies

The [Characteristics of included studies](#) section provides full details of risk of bias judgements for each study. Graphical representations of the overall risk of bias in included studies are presented in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

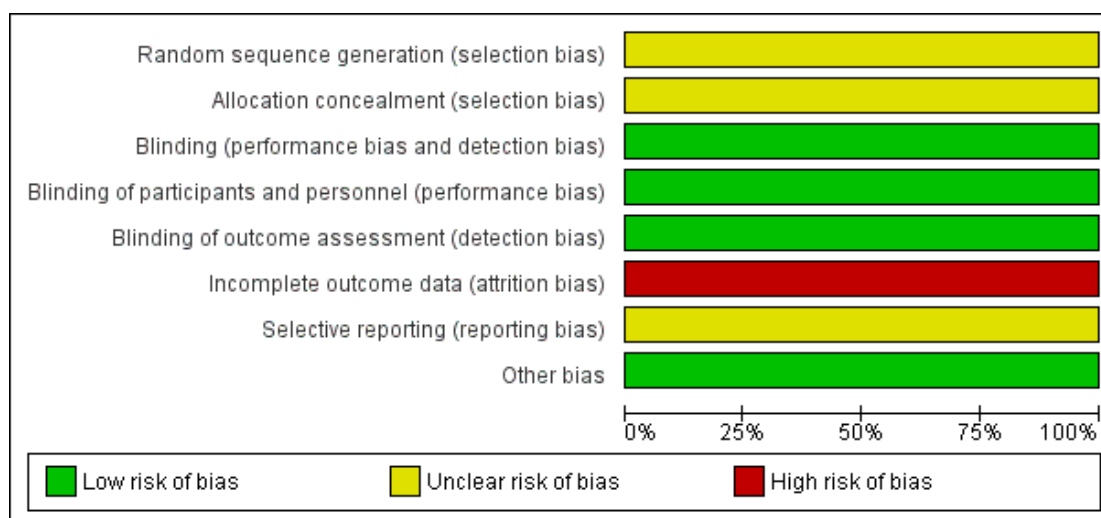


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection 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
Wisner 2001	?	?	+	+	+	-	?	+
Wisner 2004	?	?	+	+	+	-	?	+

Allocation

Random Sequence Generation

Neither study report gave details of the method of randomisation.

Allocation Concealment

Neither study provided information about allocation concealment.

Blinding

Blinding of participants and personnel

Both studies were conducted with a double-blind design (participants and study personnel were blinded to treatment allocation). Blinding was facilitated in both cases by providing placebo and antidepressant medication in identical forms. Blinded study staff were questioned to assess the integrity of blinding in both studies. In [Wisner 2001](#), staff did not successfully identify drug assignment more often than chance, other than the nurse monitoring

side effects. In [Wisner 2004](#), no staff or participants were more successful than chance at identifying allocation. Both studies were rated as low risk of bias for blinding of participants and personnel.

Blinding of outcome assessment

Both studies were rated as having low risk of bias for the blinding of outcome assessment, as mood symptom raters and the psychiatrists assessing outcomes were blind to participant group allocation. Outcome assessors were included in the assessment of blinding described above and did not successfully identify drug assignment more often than chance.

Incomplete outcome data

In [Wisner 2001](#), four participants declined to take the study drug after randomisation and one participant developed mania in the first week postpartum: none of these five were included in the analysis. This means that analyses were not performed on a 'once randomised, always analyse' basis. In addition, one other participant randomised to nortriptyline was lost to follow-up from the study and three participants withdrew from the placebo arm (due to side effects, personal reasons and pregnancy). These participants were included in the analyses (but censored at the week they withdrew from the study).

In [Wisner 2004](#), three participants assigned to sertraline who did not take any medication were not included in the analyses (also therefore not performed on a 'once randomised, always analyse' basis). Of those who took sertraline, two withdrew due to side effects and one due to an episode of hypomania, but these participants were included in the analyses. It is not explicitly stated how many participants withdrew from the placebo arm but it is recorded that there was no significant difference between groups for the number of participants withdrawing from the study. The risk of bias related to incomplete outcome data in both studies was therefore rated as high owing to the exclusion of participants from the analyses and relatively high proportions of drop-outs for the small sample sizes.

Selective reporting

Protocols were not available for either study. The risk of bias related to selective reporting was therefore unclear for both studies.

Other potential sources of bias

Both studies assessed adherence to medication with frequent serum level tests. In the [Wisner 2001](#) study, five participants randomised to nortriptyline were considered non-adherent (in addition to the four who withdrew without taking the study drug). Sensitivity analyses showed that excluding these non-adherent participants did not significantly alter the results. In the [Wisner 2004](#) study, serum levels indicated that all participants randomised to sertraline and included in the analyses were adherent. The risk of bias related to adherence to medication therefore appears to be low in both studies.

Effects of interventions

See: [Summary of findings for the main comparison Nortriptyline for the prevention of postnatal depression](#); [Summary of findings 2 Sertraline for the prevention of postnatal depression](#)

Comparison 1: nortriptyline versus placebo

One study contributed data to this comparison ([Wisner 2001](#)). Fifty-six participants were randomised in this study and 51 participants were included in their analyses (26 assigned to nortriptyline and 25 assigned to placebo). See also [Summary of findings for the main comparison](#). It was not possible to obtain the necessary data to analyse this study on a 'once randomised, always analyse' basis.

Primary outcomes

1.1 Number of participants who developed depression during the first six months postpartum

[Wisner 2001](#) reported that nortriptyline was not more effective than placebo in preventing postnatal major depressive disorder (RR 0.96, 95% CI 0.36 to 2.59, $P = 0.9381$) after a 17-week treatment period (see [Figure 4](#)). Six out of 26 women in the nortriptyline group developed postnatal depression compared with six out of 25 women in the placebo group. Data from participants who withdrew from the study were censored at the week they withdrew. [Wisner 2001](#) also reported that time to onset of depression did not differ between the nortriptyline and placebo groups (exact log-rank ≤ 0.00 , exact $P = 0.83$). From the serum level tests, the trial authors determined that five women randomised to nortriptyline were non-adherent; censoring these participants at the point of non-adherence did not change the findings of the study.

Figure 4. Forest plot of comparison: 1 Nortriptyline versus placebo, outcome: 1.1 Recurrence of postpartum major depressive disorder.



1.2 Adverse effects experienced by mother and/or foetus or nursing baby

One woman assigned to nortriptyline developed mania within the first week, but no other specific adverse events were reported. The only side effect reported more frequently in the nortriptyline than placebo group was constipation (78% among women taking nortriptyline and 22% among women taking placebo; Fischer's exact test $P < 0.001$). The proportion of women experiencing other side effects was not reported.

Secondary outcomes

1.3 Acceptability of treatment

Acceptability of treatment was not assessed directly. However, information regarding the number of participants dropping out or being lost to follow-up may provide some indication of acceptability. In this study one woman was lost to follow-up from the nortriptyline arm (and one woman in the nortriptyline arm withdrew after developing mania in the first postpartum week) and three withdrew from the placebo arm (owing to side effects, personal reasons and pregnancy). Four participants declined to take the study drug after randomisation.

1.4 Cognitive and emotional development of the infant/child

No data available.

1.5 Overall maternal satisfaction

No data available.

1.6 Improvement in the maternal relationship with the baby

No data available.

1.7 Improvement in the ability of the mother to carry out daily activities and in her social functioning

No data available.

1.8 Establishment or continuation of breastfeeding

No data available.

1.9 Prevention of neglect or abuse of the baby

No data available.

1.10 Effect on marital and family relationships

No data available.

Comparison 2: sertraline versus placebo

One study contributed data for this comparison (Wisner 2004). Twenty-five participants were randomised into this study and 22 were included in their analyses (14 assigned to sertraline and 8 assigned to placebo). See also [Summary of findings 2](#). Three women assigned to sertraline were excluded from the analyses because they did not take the study medication. Additional analyses were conducted on a 'once randomised, always analyse' basis for this review.

Primary outcomes

2.1 Number of participants who developed depression during the first six months postpartum

Wisner 2004 reported that sertraline was more effective than placebo in preventing postnatal major depressive disorder after a 17-week treatment period (see [Figure 5](#)). One (7%) of the 14 women who took sertraline developed depression compared with four (50%) of the eight women taking placebo ($P = 0.04$, Fisher exact test). The difference in rates of postnatal depression was 0.43 (95% exact CI = -0.01 to 0.84). The RR was calculated for this review and provided evidence of a trend but was below the cut-off for statistical significance (RR 0.14, 95% CI 0.02 to 1.07, $P = 0.058$). For this review, we also recalculated the RR on a 'once randomised, always analyse' basis including an additional three participants who were randomised to sertraline but excluded from the trial analyses for never taking the medication. Including these three participants and assuming a negative outcome (i.e. onset of

postnatal depression) for those not included in the original analyses, we calculated the RR to be 0.47 (95% CI 0.16 to 1.42, $P = 0.18$). Assuming a positive outcome for these three participants (i.e. no onset of postnatal depression), we calculated the RR to be 0.12 (95% CI 0.02 to 0.89, $P = 0.038$). Wisner 2004 also reported that the time to recurrence differed between the sertraline and placebo groups (exact Gehan-Wilcoxon $P = 0.02$). The observed hazard ratio for time to recurrence of depression was 0.11 (95% exact CI = 0.02 to 1.02).

Figure 5. Forest plot of comparison: 2 Sertraline versus placebo, outcome: 2.1 Recurrence of postpartum major depressive disorder.



2.2 Adverse effects experienced by mother and/or foetus or nursing baby

One woman taking sertraline experienced a hypomanic episode. The first two participants experienced severe headaches causing them to withdraw from the study which led to the original dosage of sertraline being reduced from 50 mg to 25 mg (see [Description of studies](#)). Two side effects were found to be significantly more frequent in the group taking sertraline: eight (57%) of the women taking sertraline and one (13%) of the women taking placebo experienced dizziness ($P = 0.05$ Freeman-Halton extension of Fisher's exact test); and drowsiness was also found to be more frequent in the sertraline arm, in which it was experienced by 14 women (100%), compared with 4 women (50%) in the placebo arm ($P = 0.02$; Freeman-Halton extension of Fisher's exact test).

Secondary outcomes

2.3 Acceptability of treatment

Wisner 2004 did not report a direct measure of acceptability; however no difference was found between the antidepressant and placebo groups in the number of women withdrawing from the study ($P = 0.35$, Fisher's exact test).

2.4 Cognitive and emotional development of the infant/child

No data available.

2.5 Overall maternal satisfaction

No data available.

2.6 Improvement in the maternal relationship with the baby

No data available.

2.7 Improvement in the ability of the mother to carry out daily activities and in her social functioning

No data available.

2.8 Establishment or continuation of breastfeeding

No data available.

2.9 Prevention of neglect or abuse of the baby

No data available.

2.10 Effect on marital and family relationships

No data available.

Subgroup analyses

We were unable to conduct the planned subgroup analyses due to the small number of included studies.

Sensitivity analyses

We were unable to conduct the planned sensitivity analyses due to the small number of included studies.

Reporting bias

There were insufficient studies to assess reporting bias.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Sertraline for the prevention of postnatal depression						
Patient or population: women with a history of postnatal depression Intervention: sertraline Comparison: placebo						
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	Selective serotonin re-uptake inhibitors				
Postnatal depression (17 weeks)	500 per 1000	70 per 1000 (10 to 535)	RR 0.14 (0.02 to 1.07)	22 (1 study)	⊕○○○ very low ^{2,3}	
Adverse effects experienced by mother and/or fetus or nursing baby				22 (1 study)	⊕○○○ very low ^{2,3}	1 woman taking sertraline had a hypomanic episode. 2 side effects (dizziness and drowsiness) were more common among women taking sertraline than women taking placebo
Acceptability of treatment (17 weeks)				22 (1 study)	⊕○○○ very low ^{2,3}	Acceptability of treatment was not assessed directly but no difference was found between the antidepressant and placebo groups in the number of women withdrawing

		from the study (P = 0.35, Fisher's exact test)
Overall maternal satisfaction (17 weeks)	No data available	
Improvement in the maternal relationship with the baby (17 weeks)	No data available	
Establishment or continuation of breastfeeding (17 weeks)	No data available	
<p>*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</p>		
<p>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.</p>		

¹Assumed risk calculated as the proportion of women on placebo with the outcome (postnatal depression) multiplied by 1000

²Downgraded due to high risk of bias in 1 domain (incomplete outcome data)

³Downgraded twice due to imprecision (only 1 small study available for this comparison)

DISCUSSION

Summary of main results

We included two RCTs examining the effectiveness of antidepressants for the prevention of postnatal depression in this review. All participants in both studies had a history of postnatal depression and were not taking antidepressant medication at baseline. There were insufficient studies to conduct a meta-analysis. The first study provided no evidence that nortriptyline was more effective than placebo in preventing postnatal depression (see [Summary of findings for the main comparison](#)). The second study found some evidence that sertraline may be effective in preventing postnatal depression (see [Summary of findings 2](#)) but the sample size was extremely small and the risk ratio, calculated for this review, was just below statistical significance. The low statistical power of this study means that we cannot exclude the possibility that sertraline is no different from placebo in its effectiveness for preventing postnatal depression, but we also cannot exclude the possibility that sertraline has a substantial preventative effect. It is not possible to draw conclusions about the effectiveness of antidepressants for the prevention of postnatal depression until more studies are conducted including greater number of participants.

Overall completeness and applicability of evidence

This review includes two trials comparing antidepressants with placebo but we identified no studies comparing antidepressants with other preventative interventions or with standard care. Both trials examined a 17-week treatment period with primary outcomes assessed immediately post treatment, meaning that it is not possible to draw conclusions about the optimal duration of antidepressant treatment for the prevention of postnatal depression. In addition, neither study addressed any of the secondary outcomes of this review regarding the effect of antidepressants on the infant or other family members, or secondary outcomes for the mother such as social functioning. In addition, neither study reported on the severity or course of depressive episodes, which means it is not possible to examine whether antidepressant use was associated with a milder symptom profile and course among women who did develop postnatal depression.

Recruitment rates were low and, where reported in [Wisner 2001](#), under half of the women eligible for the study took part. This reflects many women's reluctance to take antidepressants in the perinatal period, observed in other studies and systematic reviews ([Turner 2008](#); [Molyneux 2014](#)), which may be particularly the case for prevention rather than treatment of depression. This issue was also highlighted by one trial identified through the searches of ClinicalTrials.gov which would have been eligible for this review but was terminated due to slow recruitment ([NCT02235064](#)).

In both of the studies that we included in this review, women were only eligible if they had a history of postnatal depression. This is unlikely to be a major limitation to the applicability of this evidence to clinical practice, as prophylactic antidepressant use in the postnatal period is most likely to be considered for this group of women. No studies were identified for this review in which antidepressants were started during pregnancy as a preventative intervention. Many women will be very unwilling to start antidepressants in pregnancy if they are not currently depressed; however, some women with a recent history of major depressive episodes may stay on their antidepressants throughout pregnancy and the postnatal period to prevent relapse.

This update of the review identified no new studies, despite the last published version of this review being completed over a decade ago. This suggests significant barriers to the completion of research in this area which may, for example, be related to the difficulties in recruiting pregnant women to randomised trials and the reluctance of many women to take antidepressants during pregnancy and breastfeeding. In addition, the lack of recent trials in this area is likely to reflect the fact that research and clinical practice is moving away from a specific focus on the prevention of postnatal depression to also consider the prevention and treatment of antenatal depression, including the continuation of antidepressants throughout pregnancy to prevent relapse of depression during pregnancy or the postnatal period. For example, one ongoing study is comparing continuation of antidepressants throughout pregnancy with preventative cognitive therapy and gradual discontinuation of antidepressants ([Molenaar 2016](#)). This pragmatic study would not meet the inclusion criteria for this systematic review, but should provide important data on whether continuation of antidepressants throughout pregnancy prevents relapse of depression. To maximise the clinical utility of future systematic reviews in this area, we recommend that reviews should examine the effectiveness of antidepressants for the prevention of perinatal depression more broadly (i.e. antenatal as well as postnatal), and should include trials investigating the effectiveness of the continuation of antidepressant use for the prevention of perinatal depression. Future studies should also consider the severity of women's previous depression episodes, potentially stratifying by this in their randomisation and analyses. As described in [Agreements and disagreements with other studies or reviews](#), evidence suggests that recurrence of depression after discontinuation of antidepressants may be more likely for women with a history of severe, or recent, episodes of depression.

Quality of the evidence

The studies included in this review do not allow a robust examination of the effectiveness of antidepressants in preventing postnatal depression. Only two eligible studies were identified, which included 73 participants in total in their main analyses. Both studies were generally well conducted, with effective double-blind-

ing for example; however neither trial was analysed on a 'once randomised, always analyse' basis as women who dropped out of the study after randomisation before taking any medication were excluded from the analyses. There was also drop-out from both studies and, although the numbers dropping out were not high, this may have influenced results owing to the small overall sample sizes. Wisner 2001 stated that their results (that nortriptyline was not effective in preventing postnatal depression) were inconsistent with a pilot trial they had conducted on this topic that was unblinded and not randomised, which highlights the importance of high-quality study methodology in this field. There was also inconsistency between the findings in Wisner 2001 and in Wisner 2004. Finally, both studies were conducted by the same research team, which is a limitation of the evidence base to date. Overall, the results of the studies included in this review do not allow conclusions to be drawn about the effectiveness of antidepressants for postnatal depression, but do highlight that it may be important to consider the effectiveness of different antidepressants separately.

Potential biases in the review process

We minimised potential bias in the selection of studies by employing consistent and predefined eligibility criteria. In order to reduce potential biases we also predefined our methods for extracting data and conducting risk of bias assessment; and conducted them in accordance with guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For example study screening, data extraction and risk of bias assessment were performed by two review authors independently. Publication bias may have influenced the findings of this review, as we did not search the grey literature and studies may be more likely to be published if they find that antidepressants are effective in preventing postnatal depression. However, we did search clinical trials' registries, which enabled us to identify relevant unpublished RCTs; this should limit any impact of publication bias. Overall, the review process is unlikely to have been biased, but it was limited by the extremely small number of relevant studies identified.

Agreements and disagreements with other studies or reviews

Previous systematic reviews of RCTs have shown that psychological and psychosocial interventions can be effective in preventing postnatal depression (Morrell 2016); and that antidepressants can reduce the risk of relapse among non-pregnant adults with recent episodes of depression (Geddes 2003). There is also evidence from a Cochrane Review that antidepressants can be effective for treating postnatal depression (Molyneux 2014). However, there have been very few trials of antidepressant prevention of postnatal depression and only two eligible RCTs were identified for this review. One of these trials suggested that antidepressants may be effective

in preventing postnatal depression whereas the other trial found no evidence for this.

Related observational studies examining relapse following discontinuation of antidepressants during pregnancy have also had inconsistent findings. One prospective cohort study found a significantly higher rate of relapse among women who discontinued antidepressant medication during pregnancy than women who continued antidepressants (hazard ratio (HR) 5.0, 95% CI 2.8 to 9.1) (Cohen 2006). In contrast, another prospective cohort study found no association between antidepressant discontinuation and rate of relapse of depression during pregnancy or the first two months after delivery (adjusted HR 0.88, 95% CI 0.51 to 1.50) (Yonkers 2011). The difference in findings between these two studies may reflect differing severity of depression among participants. Yonkers 2011 recruited from obstetricians and general hospital settings, and found no difference in the rate of relapse related to antidepressant discontinuation. In contrast, Cohen 2006 recruited from specialist mental health centres and participants are therefore likely to have had more severe disorders (and were more likely to relapse following discontinuation of antidepressants). The importance of ensuring that treatment needs are met for women with severe depression or other mental disorders during pregnancy and the postnatal period was also highlighted in a recent study using UK data from women in contact with psychiatric services, which found that suicides in the perinatal period are more likely to occur among women not receiving any treatment at the time of death (Khalifeh 2016).

This Cochrane Review is an update and did not include any additional studies beyond the previous version of this review, published in 2005. The overall conclusion of the original version of this review remains: it is not possible to conclude whether or not antidepressants are effective in preventing postnatal depression.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review only identified two completed studies of antidepressant prevention of postnatal depression. All participants in both studies had a history of postnatal depression, and were therefore at higher risk of experiencing postnatal depression again. It is not possible from these two studies to draw conclusions about the effectiveness of antidepressants in preventing postnatal depression. Decisions around the use of antidepressants for preventing postnatal depression need to be made through individual risk-benefit analyses which take into account the preferences of the woman as well as severity and recency of previous episodes of depression.

Implications for research

RCTs with larger sample sizes and longer-term follow-up are needed. It is critical that future trials assess side effects of antide-

pressant use for the fetus or infant, as well as for the mother. Both of the trials eligible for this review compared antidepressants with placebo, and studies comparing the effectiveness of antidepressants with evidence-based psychological or psychosocial preventative interventions are also needed (such as cognitive behavioural therapy or interventions based on a person-centred approach; Morrell 2016). No new studies were eligible for this update of the review, despite the last published version being completed over a decade ago. Future reviews in this area could broaden their scope to examine the effectiveness of antidepressants for the prevention of perinatal depression (i.e. antenatal as well as postnatal depression), and include trials investigating the effectiveness of the continuation of antidepressant use for the prevention of relapse of depression during the perinatal period.

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Disclaimer

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Wisner 2001

Methods	Study design: randomized controlled trial. Method of randomisation not described	
Participants	<p>Inclusion criteria: ≤ 35 weeks gestation, aged 21 to 45 years, history of at least 1 episode of postpartum major depressive disorder with onset of symptoms within 3 months of a live birth (beginning within 5 years prior to study enrolment).</p> <p>Exclusion criteria: depression during the index pregnancy (i.e. not meeting the research diagnostic criteria for major depression); antidepressant use after the first trimester of the index pregnancy; meeting criteria for another axis 1 diagnosis (except generalised anxiety disorder or panic disorder); meeting criteria for antisocial or borderline personality disorder; history of bipolar disorder or psychosis; continuing use of psychotherapy or other psychotropic medications</p> <p>121 women were eligible and 56 women participated. 5 withdrew after randomisation (1 developed mania in 1st week postpartum and was withdrawn, 4 refused medication) . 51 women were included in the main analyses (26 randomised to nortriptyline, 25 to placebo)</p>	
Interventions	<p>Participants were randomly assigned to either:</p> <p>(1) Nortriptyline Treatment protocol: bedtime dose of 3 capsules given as soon as possible after birth, ideally within 24 hours, increase daily for 1 week postpartum, 20, 30, 40, 50, 60, 70 mg/day and 75 mg to day 21. Serum level from day 14 determined dose from then on to achieve 50 mg/ml to 150 mg/ml serum level. Dose tapered from week 17 at 33% per week and discontinued at week 20 postpartum</p> <p>(2) Placebo Duration: same protocol for placebo as nortriptyline to help maintain blinding</p>	
Outcomes	<p>Timepoints for assessment: primary outcomes assessed post-treatment (17 weeks after randomisation)</p> <p>Primary outcome: postnatal depression (recurrence and time to recurrence)</p>	
Notes	<p>Funding source: National Institute of Mental Health (NIMH)</p> <p>Declarations of interest among the primary researchers: Dr Wisner has received honoraria from Pfizer and Solvay.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

<p>Blinding (performance bias and detection bias) All outcomes</p>	<p>Low risk</p>	<p>Quote: “the primary study staff (nurse, mood symptom rater, coordinator, and principal investigator) were blind to medication assignment. The medication monitoring function (nurse) was separate from (and blind to the mood-symptom monitoring.” “We monitored the adequacy of the blind. Except for the nurse who monitored side effects, none of the other personnel were more successful than chance at identifying the drug assignment”</p>
<p>Blinding of participants and personnel (performance bias) All outcomes</p>	<p>Low risk</p>	<p>Quote: “double-blind conditions” “The remainder of the protocol ... was identical in the nortriptyline and placebo groups.” “The primary study staff (nurse, mood symptom rater, coordinator, and principal investigator) were blind to medication assignment. The medication monitoring function (nurse) was separate from (and blind to the mood-symptom monitoring.” “We monitored the adequacy of the blind. Except for the nurse who monitored side effects, none of the other personnel were more successful than chance at identifying the drug assignment”</p>
<p>Blinding of outcome assessment (detection bias) All outcomes</p>	<p>Low risk</p>	<p>Quote: “the primary study staff (nurse, mood symptom rater, coordinator, and principal investigator) were blind to medication assignment. The medication monitoring function (nurse) was separate from (and blind to) the mood-symptom monitoring.” “We monitored the adequacy of the blind. Except for the nurse who monitored side effects, none of the other personnel were more successful than chance at identifying the drug assignment”</p>
<p>Incomplete outcome data (attrition bias) All outcomes</p>	<p>High risk</p>	<p>Quote: “of the 56 subjects, 4 declined to take the study drug after randomization. One subject (randomly assigned to nortriptyline) developed mania in the first postpartum week. Data for the clinical trial are derived from 51 subjects: 26 who received nortriptyline and 25 who received placebo. Four subjects withdrew from the protocol. Three subjects assigned</p>

Wisner 2001 (Continued)

		to placebo withdrew because of side-effects, personal reasons and pregnancy at 4, 10 and 14 weeks, respectively. One subject assigned to nortriptyline was lost to follow-up at week 14. There was no difference in time to withdrawal of subjects in the nortriptyline or placebo groups (exact Savage test = 0.005, P = 0.91, df = 1)."
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting for important trial outcomes
Other bias	Low risk	Quote: "five subjects who took nortriptyline were defined as noncompliant (serum nortriptyline level < 50ng/mL). Censoring of these subjects at the time of noncompliance did not change the results of the recurrence analysis (exact log-rank < 0.00, P = 0.83)."

Wisner 2004

Methods	Study design: randomized controlled trial. Method of randomisation: randomised in a 2:1 ratio for sertraline vs placebo; other details not given
Participants	Inclusion criteria: pregnant women age 21 to 45, healthy with normal thyroid studies and blood count, < 35 weeks gestation at recruitment, at least 1 episode of postpartum major depression fulfilling DSM-IV criteria within 5 years of study enrolment. Exclusion criteria: depression during index pregnancy, use of psychotherapy or psychotropic medication after 1st trimester, other Axis 1 diagnoses (except general anxiety or panic disorder), antisocial or borderline personality disorder, or had psychosis or bipolar disorder 38 eligible women screened, 25 consented to participate, 3 women randomised to sertraline never took the medication and were excluded from the analysis. 22 were participants included in the main analysis (14 randomised to sertraline and 8 randomised to placebo)
Interventions	Sertraline - single post-breakfast dose in 2 identical opaque gelatin capsules. Same protocol for placebo to help maintain blinding
Outcomes	Timepoints for Assessment: primary outcomes assessed post-treatment (17 weeks after randomisation) Primary outcome: postnatal depression (recurrence and time to recurrence)
Notes	Funding source: National Institute of Mental Health (NIMH) Declarations of interest among the primary researchers: Dr Wisner is on the speaker's bureau for Pfizer Inc, and the sertraline used in this study was donated by Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "the blind was continued until all subjects completed the protocol" "Sertraline or placebo was given as a single post-breakfast dose in two identical opaque gelatin capsules" "None of the personnel or subjects was more successful than chance at identifying the drug assignment. The rates of agreement with the assigned condition ranged from 38% (for the blinded mood assessors) to 71% (for the side effects monitors), which did not differ significantly from the expected 44%-57% (Fisher's exact test, P = 0.14-0.53)." "If the subject had a Hamilton depression scale score of 15 or higher on two occasions 1 week apart, she was evaluated by a blinded psychiatrist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the blind was continued until all subjects completed the protocol" "Sertraline or placebo was given as a single post-breakfast dose in two identical opaque gelatin capsules" "None of the personnel or subjects was more successful than chance at identifying the drug assignment. The rates of agreement with the assigned condition ranged from 38% (for the blinded mood assessors) to 71% (for the side effects monitors), which did not differ significantly from the expected 44%-57% (Fisher's exact test, P = 0.14-0.53)."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "if the subject had a Hamilton depression scale score of 15 or higher on two occasions 1 week apart, she was evaluated by a blinded psychiatrist"
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "there was no difference in the number of women who withdrew from the

Wisner 2004 (Continued)

		study (P = 0.35, Fisher's exact test) or in the time to withdrawal (P = 0.85, Freeman-Halton extension of Fisher's exact test) between subjects in the sertraline and placebo groups... In the 14 women assigned to sertraline, the one recurrence became manifest at week 17. Two women withdrew rapidly because of headaches, which resulted in the dose change already described. One subject was removed because of hypomania, and nine women completed the randomized clinical trial without recurrence."
Selective reporting (reporting bias)	Unclear risk	No evidence of selective reporting for important trial outcomes
Other bias	Low risk	Quote: "the women in the study were compliant, as evidenced by ranges of maternal serum sertraline and N-desmethylsertraline levels of 23-48 and 36-66 ng/ml, respectively, across samples from the 8 weeks of collection."

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Appleby 1997	Treatment study
Epperson 1996	Treatment study
Heath 2000	Treatment study
NCT02235064	Terminated early due to slow recruitment; no available data
Sharp 2004	Treatment study

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

[NCT00276900](#)

Trial name or title	
Methods	Double-blind, placebo-controlled randomised controlled trial
Participants	Estimated enrolment: 300
Interventions	Sertraline or placebo
Outcomes	Primary outcome: depressive symptoms (measured at 24 and 52 weeks postpartum). Secondary outcome: functioning (measured at 24 and 52 weeks postpartum)
Starting date	
Contact information	
Notes	This study is led by Katherine Wisner in the USA. The ClinicalTrials.gov record states that data collection is completed but it was not possible to obtain additional information about this study from the lead researcher

DATA AND ANALYSES

Comparison 1. Nortriptyline versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence of postpartum major depressive disorder	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 2. Sertraline versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence of postpartum major depressive disorder	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

WHAT'S NEW

Last assessed as up-to-date: 13 February 2018.

Date	Event	Description
13 February 2018	New search has been performed	The searches were updated on 13 February 2018
15 September 2016	New citation required but conclusions have not changed	Review updated

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 2, 2005

Date	Event	Description
1 November 2008	Amended	Converted to new review format.
31 January 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

This is an update of a previous Cochrane Review. EM and LT undertook the selection of studies, data extraction, quality appraisal and interpretation of the data. All review authors contributed to the final draft of the review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Health Services Research Dept, Institute of Psychiatry, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Protocol methods were updated from the previous version of this review to reflect current guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), for example to replace the CCDAN quality rating scale with the Cochrane 'Risk of bias' tool. Additional detail was also added to the original methods for clarity.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Depression, Postpartum [*prevention & control]; Nortriptyline [therapeutic use]; Randomized Controlled Trials as Topic; Sertraline [therapeutic use]

MeSH check words

Female; Humans