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Antidepressant treatment for postnatal depression (Protocol)

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[Intervention Protocol]

Antidepressant treatment for postnatal depression

Jennifer Valeska Elli Brown[1,2], Claire A Wilson[3], Karyn Ayre[3], Emily South[4], Emma Molyneaux[3], Kylee Trevillion[3], Louise M Howard[3], Hind Khalifeh[3]

[1]Mental Health and Addiction Research Group, Department of Health Sciences, University of York, York, UK. [2]Cochrane Common Mental Disorders, University of York, York, UK. [3]Section of Women's Mental Health, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. [4]Centre for Reviews and Dissemination, University of York, York, UK

Contact address: Hind Khalifeh, Section of Women's Mental Health, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. hind.khalifeh@kcl.ac.uk.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of antidepressant drugs in comparison with any other treatment (psychological, psychosocial, or pharmacological), placebo, or treatment as usual for PND.

BACKGROUND

Description of the condition

Postnatal depression (PND), which is depression that occurs after a woman has given birth, is an important and common disorder that can have short- and long-term adverse impacts on the mother, her child, and the family as a whole (Howard 2014a; Stein 2014). Perinatal suicide, which is closely linked to PND, is an important contributor to maternal mortality (Grigoriadis 2017; Khalifeh 2016). PND is associated with impaired maternal-infant attachment, and with internalising and externalising problems in children of mothers who have PND, particularly where the depression is severe and persistent and there are familial co-morbidities (Stein 2014). PND has a similar epidemiology and clinical presentation to depression in the general population (Howard 2014a; Stewart 2019). It is characterised by persistent low mood and loss of pleasure or interests, occurring with associated symptoms such as changes in appetite and energy levels, disturbed sleep, and low self-confidence (Howard 2014a; WHO 2018). The 11th revision of the International Classification for Diseases (ICD-11) and the 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) recommend the use of generic (non-perinatal) mood disorder diagnostic categories for depression occurring in the postnatal period, in recognition of the absence for clear evidence of a distinct postnatal depressive clinical syndrome (APA 2013; O'Hara 2013; WHO 2018). However, they allow for the use of a secondary perinatal diagnostic category (in ICD-11) or specifier (in DSM-5) for depression occurring in pregnancy or within four to six weeks after childbirth.

In the UK and internationally, research and clinical practice has most commonly defined PND as that occurring within a year of childbirth (Howard 2014a; NICE 2014; Stewart 2016; Stewart 2019), and this is the definition used in this review. However, there is no clear consensus on a definitive timeframe, and past research, practice guidelines, and diagnostic classifications have variably defined PND as depression occurring within four weeks to 12 months of delivery (O'Hara 2013; Stewart 2019). In the absence of a consensus, it has been helpfully proposed that the relevant timeframe is likely to vary according to study aim, with shorter timeframes being most relevant for biological studies and longer timeframes for prevention or treatment studies (O'Hara 2013).

A recent systematic review of prevalence and incidence of perinatal (i.e. antenatal and postnatal) depression estimated a pooled prevalence for PND of 9.5% (95% CI 8.9 to 10.1) in high-income settings and 18.7% (95% CI 17.8 to 19.7) in low- and middle-income settings, with no significant difference between studies using diagnostic tools (for example, a standardised structured diagnostic interview based on DSM criteria versus those using symptom scales (such as the Edinburgh Postnatal Depression Scale (EPDS)) (Woody 2017). There are few incidence studies (Woody 2017), and contradictory evidence on whether depression is more likely to occur in the postnatal period than at other times in a woman's life (Munk-Olsen 2006; Silverman 2019; Stewart 2019); with some evidence that the risk is elevated specifically for more severe illness requiring admission (Munk-Olsen 2009; Munk-Olsen 2016). Recent evidence suggests that of women who experience PND, around a third also had depression in pregnancy, and a third had pre-pregnancy depression (Wisner 2013).

Most women with postpartum depression recover within a few months but about 30% of episodes last beyond the first postpartum year (Goodman 2004). Women who have had PND also have a high risk (about 40%) of both postnatal and non-postnatal relapse (Cooper 1995; Wisner 2004).

It is important to distinguish postpartum depression from less severe short-lived conditions, such as the 'baby blues' which occurs in around 50% of women and resolves spontaneously within a few days (Howard 2014a; Stewart 2019). On the other end of severity spectrum, it is important to recognise the severe psychiatric emergency of postpartum psychosis, a rare condition affecting 1 to 2 women per 1000 in the general population, where admission is recommended to mitigate risks to mother and baby (Jones 2014). Clinically, PND is often co-morbid with other conditions, particularly anxiety disorders (Stewart 2019).

Description of the intervention

UK national perinatal guidance recommends treatment for PND within a stepped-care model, with antidepressant treatment being recommended for women with more severe depression, with or without combined treatment with psychological therapy (McAllister-Williams 2017; NICE 2014). The guidance emphasises the higher threshold for antidepressant use in the perinatal period (given the uncertain risks of medication use during pregnancy and whilst breastfeeding, see below), and the importance of taking into account the woman's preferences, illness severity, past response to treatment, and relative benefits and risks of different treatment options for mother and baby (Howard 2014b). Antidepressant drugs are commonly divided into the classes of specific serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), with some additional antidepressants that fall outside these classes (e.g. venlafaxine, which is a serotonin and noradrenaline reuptake inhibitor (SNRI), and mirtazapine, which is a noradrenergic and specific serotonergic antidepressant (NaSSA)). Antidepressants across different classes have a similar efficacy, so choice of antidepressant is generally guided by past response and side effect and safety profile. Additionally, in the perinatal period, choice is guided by the extent of safety data available for mothers and babies. In the general population, SSRIs are considered the first-line antidepressant choice because they are relatively well-tolerated and less dangerous in overdose than TCAs. In the past decade, SSRIs have been the most commonly prescribed antidepressants during pregnancy and the postnatal period, and have a relatively favourable reproductive safety profile (McAllister-Williams 2017).

The safety of antidepressants whilst breastfeeding is an important consideration in PND treatment. Antidepressants - and often their metabolites - are lipid soluble and are transferred in breast milk. However, exposure to antidepressants in breastfed infants is considerably lower (five- to 10-fold) than exposure in utero (Berle 2011). In general, passage of antidepressants into breastmilk is low and most antidepressants are not contraindicated whilst breastfeeding (McAllister-Williams 2017; Stewart 2019). Breastfeeding of premature or ill infants requires care and warrants discussion with paediatricians. There is some evidence from case reports that the less commonly used doxepin and bupropion may be associated with short-term adverse effects on breastfed infants (McAllister-Williams 2017; Stewart 2019). For all antidepressants, there is little evidence on long-term outcomes for exposed infants (Orsolini 2015).

Due to the limitations and scarcity of the existing evidence, most manufacturers' data sheets carry warnings that antidepressants should be avoided in breastfeeding mothers. Some physicians, including general practitioners (GPs), general psychiatrists, or obstetricians, may advise women not to breastfeed when taking an antidepressant, prescribe reduced and potentially ineffective doses, or delay pharmacotherapy until after breastfeeding. However, PND has potential adverse effects for mother and baby (Howard 2014a; Stein 2014), and these need to be weighed against the uncertain but most likely small risks of medication exposure via breast milk. The choice of medication is usually guided not only by safety data but also past treatment response. Recent guidance recommends that if a mother was successfully treated for depression during her pregnancy, the same medication should be used in the postpartum period while breastfeeding, as discontinuing or switching an antidepressant treatment could lead to relapse (McAllister-Williams 2017).

In terms of active comparators, evidence-based psychological interventions for PND include cognitive behavioural therapy (CBT) and interpersonal therapy (IPT), whilst psychosocial interventions include peer support and non-directive counselling (Dennis 2007). These interventions were found to be effective when compared to usual care (Dennis 2007).

How the intervention might work

There is substantial evidence showing the effectiveness of antidepressants for depression, particularly as severity of depression increases (Cipriani 2018). The 2014 Cochrane Review on antidepressants for PND concluded that antidepressants were more effective than placebo, but highlighted the very limited evidence base on this, with high risk of bias (Molyneaux 2014). In the general population, the exact mechanism by which antidepressants have their effect is unclear. Antidepressants enhance the functional availability of monoamine transmitters (serotonin, adrenaline and dopamine) through a variety of mechanisms, including inhibition of serotonin reuptake, deactivation of monoamine oxidase and antagonism at some serotonin receptors. However, their therapeutic action is delayed relative to these pharmacological effects, and research suggests that antidepressants may act through effects on synaptic plasticity, and through functional and structural changes in brain circuits related to emotional processing (Harmer 2017; Ma 2015). PND is likely to comprise heterogeneous disorders, and it is hypothesised that most women with PND have depression that is aetiologically similar to depression outside the perinatal period, whereas a small subgroup have depression related to specific vulnerability to postnatal risk factors, such as altered sensitivity to reproductive hormonal changes (Stewart 2019). Therefore, antidepressants are expected to largely work in a similar way for PND as for non-perinatal depression. Recently, the US Food and Drug Administration (FDA) licensed a new pharmacological treatment specifically developed for PND (the neuromodulator brexanolone) and this is the focus of a separate Cochrane Review (Khalifeh in press).

Why it is important to do this review

This review will update the 2014 Cochrane Review on antidepressants for PND (Molyneaux 2014). PND is a common problem that can have adverse short- and long-term effects on the mother, her child, and the wider family; including maternal suffering, problems with mother-infant attachment, emotional and behavioural problems in children, and rarely maternal suicide (Howard 2014a; Khalifeh 2016; Stein 2014). In general, women who are pregnant or postnatal have a preference for psychological therapy over medication, and are often anxious about the potential adverse effects of antidepressant use on the unborn or breastfeeding baby (O'Mahen 2008). Antidepressants are recommended for the treatment of severe PND, the treatment of moderate PND that has not responded to psychological therapy, and for preventing relapse among women with a history of severe depressive illness (NICE 2014). However, there is only limited evidence on antidepressant efficacy and safety for PND (Molyneaux 2014). The 2014 Cochrane Review identified six RCTs comparing antidepressants for PND to placebo or other treatment, with high risk of bias (particularly due to drop-out), very limited data comparing antidepressants to psychological therapy, and lack of safety data on child outcomes among breastfeeding mothers (Molyneaux 2014). Since Molyneaux 2014, there has been a considerable growth in perinatal mental health research and services in the UK and internationally, with the UK government investing heavily in the development of community and inpatient perinatal mental health services. There is an urgent need for updated high-quality evidence to inform treatment for the growing number of women accessing help for postnatal mood disorders.

This is a protocol for an update of the review published in 2014 (Molyneaux 2014). We have made minor changes to the Methods, which are highlighted below. They reflect either changes between the previous protocol (Hoffbrand 2001) and the 2014 review (Molyneaux 2014), or a change in understanding of the clinical context in the scientific literature. The key objectives remain unchanged to Molyneaux 2014.

OBJECTIVES

To assess the effectiveness and safety of antidepressant drugs in comparison with any other treatment (psychological, psychosocial, or pharmacological), placebo, or treatment as usual for PND.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published and unpublished randomised controlled trials (RCTs) and cluster-RCTs. We will include trials employing a cross-over design but will exclude all other study designs, including quasi-randomised studies and non-randomised studies.

Types of participants

Participant characteristics

Women of any age with PND who were enrolled into a trial and were not taking any antidepressant medication at the trial start. Following a discussion of the recent scientific literature, we extended the eligible period of treatment onset from six months after giving birth (as used in the 2014 review, Molyneaux 2014) to 12 months after giving birth.

Diagnosis

We will use a broad definition of PND to include all women who were depressed during the first 12 months postpartum, regardless of time of onset of depression (i.e. including women whose depression started during or before pregnancy). Trials will be included in which women met criteria for depression by any of the following: use of a validated screening measure, for example, the EPDS (Cox 1987), use of standard observer-rated depression diagnostic instrument, by a recognised diagnostic scheme (e.g. DSM-5 (APA 2013) or the ICD-11 (WHO 2018), or by other standardised criteria, for example, the Research Diagnostic Criteria (RDC) (Spitzer 1978). The threshold scores we will use for the respective scales will be those used by the trial investigators.

Co-morbidities

We will include studies that enrolled participants with co-morbid physical conditions or other psychological disorders (e.g. anxiety) provided the co-morbidity was not the focus of the study.

Setting

We will not assign any restrictions to the type of study setting.

Types of interventions

Experimental intervention

Antidepressant medication alone or in combination with another antidepressant or treatment, initiated in at least one trial arm.

We will organise antidepressants into classes for the purposes of this review, for example:

1. SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.
2. TCAs: amitriptyline, clomipramine, desipramine, dothiepin, doxepin, imipramine, lofepramine, nortriptyline, protriptyline, trimipramine.
3. MAOIs: irreversible: izocarboxazid, phenelzine, tranylcipromine; reversible: brofaramine, moclobemide, tyrima.
4. SNRIs: duloxetine, milnacipram, venlafaxine.
5. Other antidepressants.

Our primary analyses will focus on SSRIs, as these are the most commonly used antidepressants for treatment of perinatal depression in recent routine clinical practice (McAllister-Williams 2017; Yonkers 2014), and are the recommended first line antidepressant treatment in recent clinical guidance (McAllister-Williams 2017; NICE 2014).

We will only include those trials in which treatment was started after the birth. Trials in which treatment started antenatally (regardless of gestation) will be excluded. If trials include both women who started treatment before the birth and those who started after, we will include the trial only if we can extract data on the women who started treatment postnatally.

Comparator intervention

Any other treatment, placebo, or treatment as usual (including, but not limited to, 'watch and wait', regular visits with a care-coordinator, or interventions aimed at addressing social risk factors). For 'any other treatment' we will include psychological interventions (e.g. CBT or interpersonal therapy), psychosocial interventions (e.g. peer support or non-directive counselling), or other pharmacological interventions (e.g. another antidepressant).

Types of outcome measures

We will include studies that meet the above inclusion criteria regardless of whether they report the following outcomes. We will describe narratively any studies that report outcomes not included here.

Primary outcomes

1. Response or remission of depression, using dichotomous response or remission measures as reported in the individual studies and defined by the study authors. Response is typically measured by the number of patients with a reduction of at least 50% on the total score of a standardised depression scale. Remission is typically measured by the number of patients whose scores fall below a pre-defined threshold on a standardised depression scale. We will report the trial authors' definitions in the full review.
2. Adverse events (or side effects) experienced by:
   a. mother;
   b. nursing baby.

We will extract all adverse events and data from side effect scales recorded in the trial reports and summarise them narratively. We will also report overall proportions of participants experiencing adverse effects by trial arm where possible.

Secondary outcomes

1. Severity of depression based on rating scales (continuous data; either self-reported, such as the EPDS (Cox 1987), or clinician-rated, such as the Hamilton Rating Scale for Depression (HDRS) (Hamilton 1967).
2. Acceptability of treatment both as assessed directly by questioning trial participants and indirectly by the dropout rates.
3. Child-related outcomes:
   a. neurodevelopment of the infant/child (e.g. cognitive development measured using age-appropriate observer-rated or parent-reported standardised rating scales);
   b. neglect or abuse of the baby (e.g. using the Parent-Report Multidimensional Neglectful Behavior Scale (Kantor 2004)).
4. Parenting-related outcomes:
   a. maternal relationship with the baby (e.g. improved mother-infant interactions measured using the CARE-Index (Crittenden 1988));
   b. overall maternal satisfaction and confidence;
   c. the establishment or continuation of breastfeeding.
5. Quality of life (e.g. measured using the 36-item Short Form (SF-36) (Ware 1992))

Timing of outcome assessment

1. Early phase: 0 to < five weeks.
2. Acute phase: five to <= 12 weeks.
3. Continuation phase: > 12 weeks.

The primary outcome of interest is the acute phase treatment response (between five and 12 weeks). Where this is reported,

we will use any additional reported early and continuation phase responses as secondary outcomes.

Search methods for identification of studies

We will identify all studies that might describe RCTs of antidepressants for PND from the specialised registers of the Cochrane Common Mental Disorders (CCMD) Group and the Cochrane Pregnancy and Childbirth Group. We will supplement these with further searches of the key biomedical databases.

Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

The CCMD Group maintains an archived specialised register of RCTs: the CCMD Controlled Trials Register (CCMDCTR). This register contains over 40,000 reference records (reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm, and other mental disorders within the scope of this Group. The CCMDCTR is a partially studies-based register with more than 50% of reference records tagged to around 12,500 individually PICO-coded study records. Reports of studies for inclusion in the register were collated from (weekly) generic searches of key bibliographic databases to June 2016, which included: MEDLINE (1950 onwards), Embase (1974 onwards), PsycINFO (1967 onwards), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), and review-specific searches of additional databases. Reports of studies were also sourced from international trials registries, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies (used to identify RCTs) are on the Group's website, with an example of the core MEDLINE search displayed in Appendix 1.

The CCMDCTR is hosted and maintained on the new Cochrane Register of Studies (CRS). The CCMDCTR fell out of date in June 2016 when the CCMD editorial group moved from the University of Bristol to the University of York.

(Note: the CCMD Group was previously called the Cochrane Collaboration Depression, Anxiety and Neurosis (CCDAN) review group. The Group changed its name in 2015 and the re-naming of the specialised register from CCDANCTR to CCMDCTR reflects this change).

Electronic searches

The CCMD Information Specialist will search the following biomedical databases using relevant keywords, subject headings (controlled vocabularies) and search syntax, appropriate to each resource (Appendix 2).

1. CCMDCTR (all years to June 2016).
2. Cochrane Pregnancy and Child Birth's Controlled Trials Register (CPC) (all years).
3. Cochrane Central Register of Controlled Trials (CENTRAL) (all years, current issue).
4. OVID MEDLINE (2014 onwards).
5. OVID Embase (2014 onwards).
6. OVID PsycINFO (2014 onwards).

We will apply no restrictions on date, language, or publication status to the searches.

We will search searched the international trial registers (ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)) using terms for postnatal/postpartum depression.

Searching other resources

Reference lists

We will perform forward and backward citation tracking of all included studies to identify additional studies missed from the original electronic searches (for example, unpublished or in-press citations).

Personal communication

We will request information on additional ongoing or completed trials from the following sources.

1. Any pharmaceutical company involved in any of the included trials (as funder, sponsor, or involvement in the research).
2. Manufacturers of the antidepressant(s) used in any of the included trials.
3. Authors of included trials published within the last five years.
4. The International Marcé Society for Perinatal Mental Health.

Data collection and analysis

Selection of studies

We will manage records retrieved by the literature search in Covidence (Covidence). Two of three review authors (JB and KA or CW) will independently inspect abstracts retrieved from the search. We will obtain the full-text articles for any publication that is potentially relevant. Two of three review authors (JB and KA or CW) will independently assess the full articles for inclusion based on the defined inclusion criteria. We will resolve any disagreements through discussion or by recourse to another review author (HK).

We will record reasons for exclusion of ineligible studies. We will ensure that we collate multiple reports that relate to the same study, so that each study rather than each report will the unit of interest in the review. The study selection process will be recorded and included in the final review as a PRISMA flowchart, and we will report details of all included studies.

Data extraction and management

Using Covidence (Covidence), we will extract the following data from the included studies.

1. Methods: date of study, study design, study setting, details of blinding/allocation concealment, total duration of study, details of any 'run-in' period, number of study centres and location, and withdrawals.
2. Participants: total number and number of each group, inclusion and exclusion criteria, mean age, age range, severity and duration of condition, diagnostic criteria, physical and mental health comorbidities.
3. Interventions: number of intervention groups, type of interventions and comparisons, duration of intervention and key details (e.g. dosage, adherence, quality of delivery), concomitant medications, and excluded medications.
4. Outcomes: details of measures used to assess outcomes (e.g. details of validation), primary and secondary outcomes

specified and collected, time points reported, and adverse events.
5. Analysis: statistical techniques used, unit of analysis for each outcome, subgroup analyses, number of participants followed up from each condition.
6. Notes: publication type, funding for trial, and notable conflicts of interest of trial authors.

Two of three review authors (JB, ES, or CW) will independently extract data from included studies. We will resolve any disagreements in discussion or by recourse to another review author (HK).

We will import data into Review Manager 5 (RevMan 5) or RevMan Web for analysis (Review Manager 2014; RevMan Web 2019).

Main comparisons

The main planned comparisons are as follows.

1. Antidepressants versus placebo.
2. Antidepressants versus treatment as usual.
3. Antidepressants versus psychological intervention.
4. Antidepressants versus psychosocial intervention.
5. Antidepressants versus other pharmacological intervention.

We will analyse and present findings per antidepressant class (SSRIs, TCAs, SNRIs, MAOIs, other). We do not plan to pool findings across studies of different antidepressant classes, since the different classes are not sufficiently homogenous and are likely to have distinct adverse effects.

For our main analyses we will focus on SSRI studies (i.e. studies that compare SSRIs versus each of the five comparison groups above). The primary focus is SSRIs because these are the most commonly used antidepressants in the perinatal period in recent clinical practice (McAllister-Williams 2017; Yonkers 2014), and are recommended first line treatment for perinatal women in recent national guidance (McAllister-Williams 2017; NICE 2014). We anticipate that the majority of the included studies will focus on SSRIs, as was found in the previous version of this Cochrane Review (Molyneaux 2014).

If there are studies that report findings on a mixture of antidepressant classes (and where data on individual classes are unavailable), we will present their findings separately.

Assessment of risk of bias in included studies

Two of three review authors (JB, ES, or CW) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a). We will resolve any disagreements in discussion or by recourse to another review author (HK).

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), funding source, conflicts of interest.

We will use RevMan 5 or RevMan Web to produce risk of bias figures based on our assessment of each domain as low, high, or unclear risk (Review Manager 2014; RevMan Web 2019). We will try to minimise the use of the unclear category by contacting trial authors for further information as needed.

Measures of treatment effect

Dichotomous data

We will calculate the risk ratio (RR) and its 95% confidence interval (CI) for primary outcome dichotomous data. It has been shown that RR is more intuitive than odd ratios (ORs) and that OR tend to be interpreted as RR by clinicians (Bland 2000). This misinterpretation then leads to an overestimate of the impression of the effect.

Where possible, we will attempt to convert 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.

Continuous data

If a meta-analysis can be conducted for continuous data, we will analyse this by calculating the mean difference (MD) between groups, if studies use the same outcome measure for comparison. If studies use different outcome measures to assess the same outcome, we will calculate standardised mean difference (SMD) and 95% CIs.

Where studies report a combination of change from baseline and endpoint data, this can lead to bias when using SMDs. Therefore when using SMDs, we will convert data onto the same scale (i.e. change from baseline or endpoint). We anticipate this would require estimating or imputing the endpoint or change from baseline standard deviation (SD). If so, we will use methods reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a).

When trial authors present standard errors (SE) instead of standard deviations (SD), we will convert the former to SDs. If trial authors do not report SDs and we cannot calculate these values from available data, we will ask trial authors to supply the data. In the absence of data from trial authors, we will use the mean SD from other studies.

Where trial arm level data is unavailable, we will use mean differences and their SE in meta-analyses using the generic inverse variance method.

Unit of analysis issues

Cluster-randomised trials

It is important to ensure that the data analysed from cluster-RCTs take into account the clustered nature of the data. If any cluster-RCTs meets the inclusion criteria for this review, we will deal with them as follows. We will extract the intra-cluster correlation coefficient (ICC) for each trial; where no such data are reported, we will request the information from study authors. If this information is unavailable, in line with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), we will use estimates from similar studies in order to 'correct' data for clustering where this had not been done. We will use generic inverse variance methods to meta-analyse results from cluster-RCTs (Higgins 2019a).

Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). Both of these effects are very likely in PND; if any cross-over trials are identified for inclusion we will only use data from the first randomised treatment period.

Studies with multiple treatment groups

Trials that have more than two arms (e.g. pharmacological intervention (A); psychological intervention (B); and control (C)) can cause issues with regards to pair-wise meta-analysis. In line with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), if we identify any studies with two or more active treatment arms, then we will take the following approach, dependent on whether the outcome is dichotomous or continuous.

For a dichotomous outcome: we will combine active treatment groups into a single arm for comparison against the control group (in relation to the number of people with events and sample sizes), or the control group will be split equally.

For a continuous outcome: we will pool means, SDs, and the number of participants for each active treatment group across treatment arms as a function of the number of participants in each arm to be compared against the control group.

Dealing with missing data

At some degree of loss of follow-up, data must lose credibility (Xia 2009). The protocol for the review published in 2014 determined that studies with more than 50% loss to follow-up would be excluded (Molyneaux 2014). However, owing to the small evidence base, the authors decided to include studies with greater than 50% drop-out. In the interest of consistency, we will take this approach for this review update. We will assess the impact of data lost to follow-up in sensitivity analyses.

In the case where included trials present binary outcome data for women who were lost to follow-up, we will report the data. We will present data on a 'once-randomised always-analyse' basis, assuming an intention-to-treat (ITT) analysis. We will assume that women lost to follow-up had a negative outcome, with the exception of the outcome of death. For example, for the outcome of remission of depression, we will assume that this had not occurred for any of the women lost to follow-up.

We will use ITT analysis when available. We anticipate that some studies will have used a variety of imputation methods including: last observation carried forward (LOCF), multiple imputation, mixed-effect models. All imputation methods require assumptions which introduce uncertainty about the reliability of the results.

Therefore, we will indicate where studies have used imputation (and which methods) in this review. We will present ITT analysis for all primary outcomes. Where ITT analyses are unavailable for secondary outcomes, we will report this in the relevant section of the results.

Assessment of heterogeneity

If there are sufficient data for a meta-analysis, we will assess statistical heterogeneity visually by studying the degree of overlap of the CIs for individual studies in a forest plot. We will also carry out more formal assessments using the I^2 statistic. The I^2 statistic only provides an approximate estimate of the variability due to heterogeneity so the following overlapping bands will be used to guide our interpretation of the I^2 statistic, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a).

1. 0% to 40% might not be important;
2. 30% to 60% may represent moderate heterogeneity.
3. 50% to 90% may represent substantial heterogeneity.
4. 75% to 100% represents considerable heterogeneity.

Assessment of reporting biases

If there are more than 10 studies included in any meta-analysis, we will generate funnel plots and inspect them visually for asymmetry. Asymmetry in the plot might be attributable to publication bias; however, there are other causes of funnel plot asymmetry (heterogeneity unrelated to publication bias) that we will also take into consideration.

Data synthesis

We plan to conduct a random-effects meta-analysis to synthesise data from studies with comparable methods (using the same class of antidepressants and the same comparison group, e.g. placebo, listening visits) if three or more studies are identified for each comparison. As far as possible, we will use RevMan 5 or RevMan Web for meta-analysis (Review Manager 2014; RevMan Web 2019). In case more complex analyses are needed, we will use a suitable statistics software package.

Subgroup analysis and investigation of heterogeneity

We plan to perform the following subgroup analyses to assess the effectiveness of the intervention in the following groups.

1. Women with mild to moderate depressive disorder (as defined by diagnostic interview or a validated scale) versus women with severe depressive disorder (as defined by diagnostic interview or a validated scale).
2. Women with chronic depression (onset pre-pregnancy) versus women with onset in pregnancy versus new-onset postpartum depression.
3. Interventions lasting eight weeks or less versus interventions lasting more than eight weeks.

Subgroups will be compared using the formal Test for Subgroup Differences in RevMan (Review Manager 2014; RevMan Web 2019).

We will explore and comment on any observed clinical heterogeneity, for example due to different definitions of PND or use of different diagnostic tools, in the 'Discussion' section of the review.

Sensitivity analysis

We are planning to conduct a priori sensitivity analyses (if sufficient data were identified) to explore the robustness of pooled estimates

to decisions made in the systematic review. We will assess the effect 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 trial studies that were unblinded.
3. Attrition:
   a. excluding studies with more than 20% attrition; and
   b. excluding studies with greater than 50% attrition.
4. Validation: excluding outcomes based on non-validated scales from the analyses.

For outcomes with both skewed data and non-skewed data, we will investigate the effect of combining all data and if there is no substantive difference we will leave the potentially skewed data in the analyses.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' tables, where we will summarise findings of studies comparing SSRIs with each of the five comparison groups (i.e. placebo; treatment as usual; psychological interventions; psychosocial interventions and other pharmacological interventions). A separate 'Summary of Findings' table will be presented for each comparison group. We will include the following outcomes: depression response, depression remission, adverse events (mother), adverse events (baby), depression severity, acceptability of treatment and child-related outcomes (where possible data for 'child cognitive development' will be presented). Where possible, data for the acute phase treatment response (between 5 and 12 weeks) will be presented in this Summary of Findings table. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019), using GRADEpro software (GRADEpro GDT 2015). We will justify all decisions to downgrade the certainty of the evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Two review authors (JB, ES, or CW) will independently assess the certainty of the evidence, and will resolve disagreements through discussion or by consulting a third review author (HK). Judgements will be justified, documented, and incorporated into reporting of results for each outcome.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research and outline what are the remaining uncertainties in the research area.

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APPENDICES

Appendix 1. Specialised Register: CCMD's core MEDLINE search strategy

The search strategy listed below is the weekly OVID MEDLINE search used to inform the Cochrane Common Mental Disorders (CCMD) Group's Specialised Register. It is based on a list of terms for all conditions within the scope of the CCMD Group plus a sensitive RCT filter.

1. *[MeSH Headings]:*
eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. *[Title/ Author Keywords]:*
(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. *[RCT filter]:*
(controlled clinical trial.pt. or randomised controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomised controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs were tagged to the appropriate study record.

Appendix 2. Database search strategy

Cochrane Common Mental Disorders Controlled Trials Register (CMDCTR-Studies and Reference Registers) (all available years) & Cochrane Central Register of Controlled Trials (CENTRAL) % CRS (all years)

#1 MESH DESCRIPTOR Antidepressive Agents EXPLODE ALL AND INREGISTER

#2 MESH DESCRIPTOR Neurotransmitter Uptake Inhibitors EXPLODE ALL AND INREGISTER

#3 MESH DESCRIPTOR Monoamine Oxidase Inhibitors EXPLODE ALL AND INREGISTER

#4 (Antidepressant Agent):EMT AND INREGISTER

#5 ("Serotonin Receptor Affecting Agent" or "Serotonin Uptake Inhibitor" or "Serotonin Noradrenalin Reuptake Inhibitor" or "Triple Reuptake inhibitor"):EMT AND INREGISTER

#6 ("Dopamine Receptor Affecting Agent" or "Dopamine Uptake Inhibitor/"):EMT AND INREGISTER

#7 ("Adrenergic Receptor Affecting Agent" or "Noradrenalin Uptake Inhibitor"):EMT AND INREGISTER

#8 ("Neurotransmitter Uptake Inhibitors"):EMT AND INREGISTER

#9 ("Monoamine Oxidase Inhibitor"):EMT AND INREGISTER

#10 (antidepress* or "anti depress*" or MAOI* or "monoamine oxidase inhibit*" or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or "anti adrenergic" or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*) AND INREGISTER

#11 Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Bupropion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or Lorpiprazole or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Mepiprazole or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or (Tryptophan not depletion) or Venlafaxine or Viloxazine or Vilazodone or Vortioxetine or Viqualine or Zimelidine AND INREGISTER

#12 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #11)

#13 (postpartum or post-partum or "post partum" or postnatal* or post-natal* or "post natal*" or perinatal* or peri-natal* or "peri natal*" or puerp* or intrapartum or intra-partum or "intra partum" or antepartum or ante-partum or "ante partum") AND INREGISTER

#14 (pregnan* or maternity or birth) and depress* AND INREGISTER

#15 (#13 OR #14)

#16 (#12 AND #15)

Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

<RCTs 2014 onwards> <Systematic Reviews (all years)>

Search Strategy:

---

1 exp Antidepressive Agents/

2 exp Neurotransmitter Uptake Inhibitors/

3 exp Monoamine Oxidase Inhibitors/

4 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).ti,ab,kf.

5 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Bupropion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or Lorpiprazole or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Mepiprazole or Metapramine or Mianserin or Milnacipran or Minaprine

or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or (Tryptophan not depletion) or Venlafaxine or Viloxazine or Vilazodone or Vortioxetine or Viqualine or Zimelidine).mp.

6 or/1-5

7 Depression, Postpartum/

8 ((postpartum* or post partum* or postnatal* or post natal* or perinatal* or peri natal* or puerp* or intrapartum* or intra partum* or antepartum* or ante partum*) adj3 (depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder* or affective symptom*)).ti,ab,kf.

9 (7 or 8)

10 (6 and 9)

11 controlled clinical trial.pt.

12 randomized controlled trial.pt.

13 clinical trials as topic/

14 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf.

15 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kf.

16 placebo.ab,ti,kf.

17 trial.ti.

18 (control* adj3 group*).ab.

19 (control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw.

20 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf.

21 double-blind method/ or random allocation/ or single-blind method/

22 or/11-21

23 exp animals/ not humans.sh.

24 (22 not 23)

25 (10 and 24)

26 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).yr,dt,ed,ep.

27 (25 and 26)

28 (systematic or structured or evidence or trials or studies).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)

29 (0266-4623 or 1469-493X or 1366-5278 or 1530-440X or 2046-4053).is.

30 meta-analysis.pt. or (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).ti,ab,kf,hw.

31 ((systematic or meta) adj2 (analys* or review)).ti,kf. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).ti,ab,kf,sh. or (quantitativ$ adj5 synthesis$).ti,ab,kf,hw.

32 (integrative research review* or research integration).tw. or scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.) or (evidence adj3 review*).ti,ab,kf.

33 review.pt. and ((medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,hw. or (retraction of publication or retracted publication).pt.)

34 or/28-33

35 (10 and 34)

36 (26 and 35)

****

Ovid Embase

<RCTs 2014 onwards> <Systematic Reviews (all years)>
Search Strategy:
---
1 exp Antidepressant Agent/
2 Serotonin Receptor Affecting Agent/ or Serotonin Uptake Inhibitor/ or Serotonin Noradrenalin Reuptake Inhibitor/ or Triple Reuptake inhibitor/
3 Dopamine Receptor Affecting Agent/ or Dopamine Uptake Inhibitor/
4 Adrenergic Receptor Affecting Agent/ or Noradrenalin Uptake Inhibitor/
5 Neurotransmitter Uptake Inhibitors/
6 exp Monoamine Oxidase Inhibitor/
7 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*).ti,ab,kw.
8 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Bupropion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or Lorpiprazole or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Mepiprazole or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or (Tryptophan not depletion) or Venlafaxine or Viloxazine or Vilazodone or Vortioxetine or Viqualine or Zimelidine).mp.
9 (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8)
10 postnatal depression/
11 ((postpartum* or post partum* or postnatal* or post natal* or perinatal* or peri natal* or puerp* or intrapartum* or intra partum* or antepartum* or ante partum*) adj3 (depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder* or affective symptom*)).ti,ab,kw.
12 (10 or 11)
13 (9 and 12)
14 randomized controlled trial/
15 randomization.de.
16 controlled clinical trial/ and (Disease Management or Drug Therapy or Prevention or Rehabilitation or Therapy).fs.
17 *clinical trial/
18 placebo.de.
19 placebo.ti,ab.
20 trial.ti.
21 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kw.
22 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kw.
23 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp.
24 (control* and (study or group?) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kw,hw.
25 or/14-24
26 ((animal or nonhuman) not (human and (animal or nonhuman))).de.

27 (25 not 26)
28 (13 and 27)
29 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).yr,dc.
30 (28 and 29)
31 systematic review/ or meta analysis/ or network meta-analysis/
32 ((systematic or structured or evidence or trials or studies) and (review or overview or look or examination or update* or summary)).ti.
33 (0266-4623 or 1469-493X or 1366-5278 or 1530-440X or 2046-4053).is.
34 (systematic review? or evidence report* or technology assessment?).jw.
35 (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).ti,ab,kw,hw.
36 ((systematic or meta) adj2 (analys* or review)).ti,kw. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).ti,ab,kw,sh. or (quantitativ* adj5 synthes*).ti,ab,kw,hw.
37 exp "clinical trial (topic)"/ and review.ti,kw,pt.
38 (integrative research review* or research integration).ti,ab,kw. or scoping review?.ti,kw. or (evidence adj3 review*).ti,ab,kw.
39 review.pt. and (medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).ti,ab,kw,hw.
40 review.pt. and ((evidence based adj (medicine or practice)) or (outcome? adj (assessment or research)) or treatment outcome).hw.
41 or/31-40
42 (13 and 41)
43 (29 and 42)

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Ovid PsycINFO

<RCTs 2014 onwards> <Systematic Reviews (all years)>
Search Strategy:
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1 Psychopharmacology/ or Neuropsychopharmacology/
2 "3340".cc.
3 exp Antidepressant Drugs/
4 Neurotransmitter Uptake Inhibitors/ or exp serotonin norepinephrine reuptake inhibitors/ or exp serotonin reuptake inhibitors/
5 exp Monoamine Oxidase Inhibitors/
6 exp Tricyclic Antidepressant Drugs/
7 (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic*).mp.
8 Drug Therapy/
9 (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Bupropion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or Lorpiprazole or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Mepiprazole or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or (Tryptophan not depletion) or Venlafaxine or Viloxazine or Vilazodone or Vortioxetine or Viqualine or Zimelidine).ti,ab,id,hw.
10 or/1-9
11 postpartum depression/ or postnatal period/
12 ((postpartum* or post partum* or postnatal* or post natal* or perinatal* or peri natal* or puerp* or intrapartum* or intra partum* or antepartum* or ante partum*) adj3 (depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder* or affective symptom*)).ti,ab,id.
13 (11 or 12)
14 (10 and 13)
15 clinical trials.sh.
16 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id.
17 (RCT or at random or (random* adj3 (administ* or allocat* or assign* or class* or control* or crossover or cross-over or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or recruit* or split or subsitut* or treat*))).ti,ab,id.

18 (control* and (trial or study or group) and (placebo or waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,hw.
19 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id.
20 trial.ti.
21 placebo.ti,ab,id,hw.
22 treatment outcome.md.
23 treatment effectiveness evaluation.sh.
24 mental health program evaluation.sh.
25 or/15-24
26 (14 and 25)
27 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).yr,an.
28 (26 and 27)
29 (meta analysis or "systematic review").md.
30 meta analysis/
31 ((systematic or structured or evidence or trials or studies) and (review or overview or look or examination or update* or summary)).ti.
32 (meta-analys* or meta analys* or metaanalys* or meta synth* or meta-synth* or metasynth*).ti,ab,id,hw. (31678)
33 ((systematic or meta) adj2 (analys* or review)).ti,id. or ((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)).ti,ab,id,sh. or (quantitativ* adj5 synthes*).ti,ab,id,hw.
34 (integrative research review* or research integration).ti,ab,id. or scoping review?.ti,id. or (evidence adj3 review*).ti,ab,id. (16928)
35 literature review.sh. and (medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).ti,ab,kw,hw.
36 ((systematic or structured or evidence or trials or studies) adj3 review*).ti,ab,id. and (evidence based practice or treatment outcomes or mental health program evaluation).sh.
37 or/29-36
38 (14 and 37)
39 (27 and 38)

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CONTRIBUTIONS OF AUTHORS

Kylee Trevillion (KT), Louise M Howard (LH), and Emma Molyneaux (EM) developed the protocol methodology and background as part of previous versions of this Cochrane Review (Hoffbrand 2001; Molyneaux 2014).
Jennifer Valeska Elli Brown (JB), Hind Khalifeh (HK), Karyn Ayre (KA), Claire Wilson (CW), and Emily South (ES) updated the protocol.
All authors approved the final protocol prior to publication.

DECLARATIONS OF INTEREST

JB: no conflicts of interest.
CW: no conflicts of interest.
KA: no conflicts of interest.
ES: no conflicts of interest.
EM: no conflicts of interest.
KT: no conflicts of interest..
LH: has worked for the National Institute for Health and Care Excellence (NICE) Scientific Advice on pharmacological treatment for postnatal depression.
HK: no conflicts of interest.

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