Antidepressants for depression during pregnancy

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Antidepressants for depression during pregnancy (Protocol)

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Antidepressants for depression during pregnancy

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Editorial group: Cochrane Common Mental Disorders Group.


ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the safety of antidepressant use, compared with placebo or psychological therapy, for the treatment of pre-existing and antenatal depression during pregnancy.

To assess the effectiveness of antidepressant use, compared with placebo or psychological therapy, for the treatment of pre-existing and antenatal depression during pregnancy.

BACKGROUND

Description of the condition

Depression is a highly prevalent mood disorder associated with social, human and economic costs, and public health impact worldwide. According to the World Health Organization (WHO), depression is estimated to affect more than 350 million people globally (WHO 2010a). The life-time risk of developing depression is 10% to 20% in females and slightly less in males (WHO 2010a). Despite the seriousness of depression as a disease and the availability of effective treatments, less than half of cases worldwide receive appropriate care (WHO 2010a).

Current theories on the causes of depression remain controversial, however, genetic predisposition, chronic disease and disability, environmental factors, an individual’s ability to cope with difficult situations, direct biochemical changes in the brain and early childhood experiences have all been shown to potentially contribute to the onset of depression (beyondblue 2013; Black Dog Institute 2013; Passer 2008).

Depression can be diagnosed by a psychologist, psychiatrist or primary health care provider, usually in conjunction with symptom related scales such as the Beck Depression Inventory (BDI) (Beck 1961), or the Edinburgh Postnatal Depression Scale (EPDS) (also used to assess antenatal depression) (Cox 1994). However, symptom scales alone cannot be used as a direct diagnostic tool although for research purposes these tools are often used to assess improvements or decline in depressive symptoms.

Depression is one of the most common complications of the prenatal period (Gaynes 2005). Rates of depression during pregnancy range from between 7.4% and 12% and rise from the first trimester, to the second and third trimester (Bennett 2004; Gaynes 2005).

The morbidity of depression during pregnancy, as well as the neg-
Ative effects of depression on subsequent fetal, infant and child development and on the family and community as a whole, have been extensively recognised (Cooper 1998; Cox 1982; Grote 2010; O’Connor 2007; O’Hara 1990; Marcus 2009a; Marcus 2009b). Antenatal depression has been associated with maternal substance use and increased risk of preterm birth and low birthweight (Grote 2010; Marcus 2009a; Marcus 2009b; Woods 2010). Prenatal depression also results in reduced total sleep time, night time awakenings, and sleep problems being identified at 6, 18, and 30 months of age in subsequent infants and is related to severity, with higher levels of prenatal maternal depression predictive of more sleep problems at 18 and 30 months (O’Connor 2007), possibly as a result of modifications to neurodevelopmental programming (Ponder 2011). In addition, disturbed infant sleep has been shown to further contribute to postnatal depression (PND) (Dennis 2005).

There is a well-established relationship between antenatal depression and the development of PND, with antenatal depression being the strongest predictor of PND (Beck 1996; Beck 2001; O’Hara 1996). PND is a debilitating and costly condition, has an immediate primary effect on child well-being, parenting efficacy, use of safe parenting practices and marital conflict. Secondary effects of increased problematic behaviours and poorer cognitive development in childhood may occur due to poorer attachment and reduced maternal engagement (Murray 1996). Moreover, it is increasingly recognised that some women who become depressed postnatally have, in retrospect, been depressed during the antenatal period (Evans 2001; Kumar 1984). Large studies have shown that rates of depression in late pregnancy in particular, are as high, or higher, than rates of postpartum depression (DaCosta 2000; Evans 2001; Josefsson 2001; Zuckerman 1989). It is therefore important to detect and treat symptoms of antenatal depression to reduce the incidence of PND.

Depressed mood during pregnancy has also been associated with poor attendance at antenatal clinics (Phillippi 2009). Despite this potential for poor antenatal attendance, the antenatal period provides an opportunity for prevention and management of depression as a result of frequent contact with health professionals. Adequate management of antenatal depression has the potential to reduce maternal substance use, prevent preterm birth and low birthweight as well as PND and its associated consequences. This information in combination with the ineffective treatment of depression, highlights a need to focus recommendations for clinical practice to treat depression in this vulnerable population of pregnant women (Muzik 2009a; Muzik 2009b).

Description of the intervention

Antidepressants are commonly prescribed to treat depression (Centre for Disease Control 2011). They include monoamine oxidase inhibitors, tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and others (e.g. bupropion). Based on data from the United States, antidepressant use during pregnancy has increased from 2% of pregnancies in 1996 to 7.6% of pregnancies in 2005 (Andrade 2008). Antidepressants can be used alone or more commonly in conjunction with psychosocial and psychological therapies such as behavioural therapy (includes behavioural activation), cognitive behaviour therapy, mindfulness-based cognitive behavioural therapy (including acceptance commitment therapy), and psychodynamic, humanistic (including motivational interviewing) and integrative therapies (includes interpersonal therapy) (Arroll 2009; Cipriani 2009; Cipriani 2010; Guaiana 2007; Magni 2013; NICE 2007). Patient responses vary markedly to different classes of antidepressants and therefore this will influence the type of antidepressant drug that is prescribed for an individual. Dosage regimes differ between the different classes of antidepressants, and also with the severity of depression. Antidepressants are typically taken daily, with the type of antidepressant determining whether or not night time or morning dosing is appropriate. The length of time antidepressants are taken for may vary, ranging from several months to several years, or lifetime use (FDA 2010; Elsevier 2013).

As with the general population, antidepressants during pregnancy can be used alone or in combination with psychological therapies (NICE 2007). Psychological therapy alone can in some cases be appropriate for some women, but others may need pharmacological treatment (NICE 2007; Yonkers 2009). Decisions surrounding the use of antidepressants during pregnancy are incredibly complex, requiring a careful balance of optimising maternal health while minimising potential risks to the developing fetus. However, data concerning the immediate risks of antidepressants to the fetus are limited, and little is known about the potential long-term risks.

There is much debate concerning the potential increased risk of congenital malformations following the use of paroxetine during pregnancy (Berard 2010; Scali 2010; Wurst 2010), as well as for the remainder of antidepressants (despite a lack of clear evidence that they are teratogenic); due to study designs used there can be no determination of causality (Ellfolk 2010; Nguyen 2010; Pedersen 2009; Udechuku 2010). However, there is evidence that antidepressant use during pregnancy may be associated with an increased risk of a range of adverse pregnancy outcomes including spontaneous abortion (Berard 2010a; Nakhai-Pour 2010), preterm birth (Lund 2009), and low birth weight (Lattimore 2005), but separating these outcomes from the effects of depression itself during pregnancy has been challenging (Ellfolk 2010; Nguyen 2010; Udechuku 2010). Furthermore, exposure to antidepressants during late gestation is associated with an increased risk of admission to special care nurseries and neonatal intensive care units as a result of neonatal abstinence syndrome and/or poor neonatal adaptation, which are usually mild and self-limiting (Coste 2002; Heikkinen 2003; Kallen 2004; Laine 2003; Lattimore 2005; Nguyen 2010; Udechuku 2010; Zeskind 2004). Other perinatal complications

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include the reported increased risk of persistent pulmonary hypertension of the newborn following prenatal exposure to selective serotonin reuptake inhibitors in particular, with the greatest risk attributed to those exposed later in pregnancy (Chambers 2006; Nguyen 2010; Udechuku 2010). Finally, based on the small number of studies available, antidepressant use during pregnancy does not appear to adversely influence developmental outcomes in the offspring; however, major differences in study design, patterns of antidepressant use, age at follow-up, outcome measures used and adjustment for confounding make it difficult to reach any strong conclusions (Ellfolk 2010; Gentile 2011; Nguyen 2010; Udechuku 2010).

**How the intervention might work**

Antidepressants exert their action in a number of different ways depending on the specific type of antidepressant. However, all have an underlying mechanism whereby they effect monoamine transmitter deficits within the brain (Rang 2007).

Antidepressants are organised into classes for the purposes of this review as follows. Tricyclic antidepressants exert their actions through inhibiting uptake of noradrenaline, and or serotonin. Selective serotonin reuptake inhibitors exert their actions through inhibiting uptake of serotonin. Serotonin norpinephrine reuptake inhibitors exert their actions through inhibiting uptake of noradrenaline and serotonin. Noradrenergic and specific serotonergic antidepressants exert their actions through blocking the action of noradrenaline and serotonin at their receptors. Monoamine oxidase inhibitors and reversible inhibitors of monoamine oxidase A exert their actions through inhibition of one or both forms of the enzyme monoamine oxidase.

It may also be speculated that antidepressants exert some of their antidepressant effects through their negative immunoregulatory capacities (Maes 2001). Much of the research investigating the effects of antidepressants on inflammation has focused on the selective serotonin reuptake inhibitors, in particular fluoxetine. Animal studies have shown that fluoxetine may be a therapeutic agent to manage inflammatory bowel disease by significantly inhibiting activated nuclear factor kappa B signals and the up-regulated expression of interleukin-8 in intestinal epithelial cells (Koh 2011). Sluzewska 1995 reported changes in serum levels of interleukin-6 as well as levels of C-reactive protein, alpha1-acid glycoprotein and its degree of microheterogeneity before and after treatment with fluoxetine 20 mg daily over an eight-week period. Following treatment of selective serotonin reuptake inhibitors for major depression over a four-week period, O’Brien 2006 also observed a significant drop in C-reactive protein concentrations whether or not the depression resolves. These findings indicate that antidepressants can induce an anti-inflammatory response independent of antidepressant action.

**Why it is important to do this review**

The decision to begin, maintain or discontinue antidepressant treatment after a pregnancy is confirmed should take into account the severity of depression, the risk of relapse, and the specific drug safety data available. However, it has been shown that two-thirds of women whose depression was well stabilised and who interrupted, or discontinued their antidepressant treatment before conception, relapsed during pregnancy, compared to one quarter of women who maintained their treatment (Cohen 2006). This highlights the need to undertake, and or, continue antidepressant treatment for those women who develop depression in the antenatal period, and those women who already have a pre-existing depressive disorder prior to conception, respectively. However, with a lack of certainty in this area, a systematic review needs to be undertaken to assess the safety and efficacy of antidepressant use during pregnancy to determine potential side effects and the most effective pharmacological intervention to manage depressive symptoms in this population.

While Cochrane systematic reviews have been undertaken in the area of treatment strategies for mental health problems during pregnancy (Dennis 2007), there are currently no systematic reviews listed that address the use of pharmacological interventions to treat depression during pregnancy. This includes pre-existing depression (i.e. the mother was depressed prior to conception) and antenatal depression (i.e. the mother became depressed following conception). Cochrane systematic reviews have been presented that focus on and discuss antidepressant use for the prevention and treatment of postnatal depression (Hoffbrand 2001; Howard 2005); however, there are no reviews that target depression in the antenatal period. The proposed systematic review aims to focus on this area in particular.

Other non-Cochrane reviews that assess the use of antidepressants during pregnancy have been published. However, these tend to focus on one type of antidepressant alone. While, those that have been performed assessing all types of antidepressants appear to be lacking in their approach and are of poor quality (Simoncelli 2010).

Lack of high quality evidence surrounding the safety (as defined in this instance as a lack of adverse events) and efficacy of antidepressants during pregnancy increases therapeutic uncertainty, making it difficult to accurately balance the risks and benefits associated with treatment. This may result in decisions to cease antidepressant use during pregnancy, even in situations where treatment is considered necessary. We are however aware of the potential ethical implications of conducting randomised controlled trials during pregnancy which may impact on the ability to identify these types of studies during pregnancy. As such we have acknowledged this by expanding inclusion of studies to be assessed in this review to include non-randomised studies.

Therefore, a systematic review of the safety and efficacy of antidepressants during pregnancy is required to bring together the relevant evidence for people wishing to make a well-informed deci-
This would enable strengthened safety data, support medication use during pregnancy when necessary and allow healthcare professionals and women to be adequately informed of the true risks and benefits associated with treatment.

OBJECTIVES

To assess the safety of antidepressant use, compared with placebo or psychological therapy, for the treatment of pre-existing and ante-natal depression during pregnancy.

To assess the effectiveness of antidepressant use, compared with placebo or psychological therapy, for the treatment of pre-existing and ante-natal depression during pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies
All published and unpublished randomised controlled trials, and non-randomised controlled prospective and retrospective studies including cohort and case control studies.

Types of participants
Women of all ages who are pregnant and:
- who have a diagnosis of depression based on established diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) or the International Classification of Disease (ICD10) (APA 2000; WHO 2010b);
- who had pre-existing depressive symptoms prior to pregnancy conception;
- who have developed depressive symptoms in the antenatal period.

We will use depression screening tools and scales e.g. EPDS (Cox 1994), estimates of depression by recognised diagnostic schemes, or by other standardised criteria, including the Research Diagnostic Criteria (RDC), as an indicator of depression severity. The threshold scores used for the respective scales will be those used by the investigators in the trials as discussed in previous Cochrane Reviews in relation to assessment of antidepressants (Hoffbrand 2001). We will include all women that had been taking antidepressants of any kind during their pregnancy. Women taking other psychoactive substances, and/or with co-morbidities (for example diabetes, asthma), and/or taking medication for these respective conditions will not be excluded, however, these will be analysed and discussed separately at the time of analysis.

We will exclude women prescribed antidepressants as a preventative intervention.

Types of interventions

Experimental interventions (used alone or in combination)
We will include the following types of antidepressants (all dose ranges and preparations).
- Tricyclic antidepressants: amitriptyline, imipramine, trimipramine, doxepin, desipramine, protriptyline, nortriptyline, clomipramine, dothiepin, isoepinazapine.
- Selective serotonin re-uptake inhibitors: zimelidine (worldwide ban), fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram.
- Serotonin-norepinephrine reuptake inhibitors: venlafaxine, milnacipram, duloxetine.
- Noradrenergic and specific serotonergic antidepressants: mirtazapine.
- Monoamine oxidase inhibitors: (a) irreversible: phenelzine, tranylcipromine, izocarboxazid; (b) reversible: brofamine, moclobemide, tyrina.
- Other antidepressants:
  - noradrenaline reuptake inhibitors: reboxetine, atomoxetine;
  - norepinephrine-dopamine reuptake inhibitors: amineptine, bupropion;
  - serotonin antagonist and reuptake inhibitors: trazodone;
  - unclassified: agomelatine, vilazodone;
  - other heterocyclic antidepressants: mianserin, amoxapine, maprotiline.

Comparator interventions
- Placebo.
- Psychological therapies (e.g. behavioural therapy (including behavioural activation)), cognitive behavioural therapy, mindfulness-based cognitive behavioural therapy (including acceptance commitment therapy), and psychodynamic, humanistic (includes motivational interviewing) and integrative therapies (including interpersonal therapy).

Types of outcome measures

Primary outcomes
Maternal outcomes

1. Safety
   - Maternal mortality and serious morbidity including self-harm and suicide attempts.
   - Maternal complications of pregnancy (i.e. pre-eclampsia).
   - Spontaneous abortion / miscarriage.

2. Effectiveness
   Clinical response to antidepressant as observed by a reduction and or improvement in depression (as defined in individual studies according to validated scales used to assess depression (e.g. the Beck Depression Inventory (Beck 1961), the Edinburgh Postnatal Depression Scale (Cox 1994), and their subsequent scoring and cut off protocols). Effectiveness can be measured as "responded" versus "not responded".

Neonatal outcome

3. Safety
   - Neonatal mortality (death of neonate).
   - Neonatal morbidity (adverse events not including mortality (e.g. congenital malformations (as defined by individual studies)).

Neonates are defined as infants of four weeks of age or less.

Secondary outcomes

Maternal outcome

4. Effectiveness
   - Clinical response to antidepressant as observed by a reduction and or improvement in depression (as defined in individual studies according to validated scales used to assess depression (e.g. BDI (Beck 1961), EPDS (Cox 1994), and their subsequent scoring).
   - Effectiveness will be assessed in this instance on a continuous scale of increasing or decreasing score.
   - Improvement in the ability of the mother to carry out daily activities and social functioning e.g. Global Assessment of Functioning (GAF) (APA 2000).
   - Acceptability and maternal satisfaction of treatment both as assessed directly by questioning trial participants and indirectly by the drop-out rates.
   - Maternal/neonate attachment.

Neonatal outcome

5. Safety
   - Neonatal abstinence syndrome.
   - Gestational age at birth (preterm delivery).
   - Birth weight (small-for-gestational age).
   - Neonatal development both physical and cognitive (as variously defined and measured).

- Mother/neonate attachment.

Search methods for identification of studies

The Cochrane Depression, Anxiety and Neurosis Review Group’s Specialised Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CC-DAN) maintain two clinical trials registers at their editorial base in Bristol, UK: a references register and a studies based register. The CCDANCTR-References Register contains over 31,500 reports of RCTs in depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-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 CCDAN Trials Search Coordinator for further details. Reports of trials for inclusion in the Group’s registers are collated from routine (weekly), generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-); 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 trials registers c/o 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 CCDAN’s generic search strategies (used to identify RCTs) can be found on the Group’s website.

Electronic searches

The CCDANCTR-Studies Register will be searched using the following terms:

Diagnosis = (depress* or dysthymi*) and Concomitant Condition = pregnancy
OR
Diagnosis = "Depression, Antenatal" or "Depression, Perinatal" AND
Intervention = antidepress* or anti-depress* or "anti depress*" or MAO* or RIMA* or "monoamine oxidase inhibit*" or ((serotonin or norepinephrine or noradrenaline or neurotransmitt* or dopamin*) and (uptake or reuptake or re-uptake or "re uptake")) or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or pharmacotherap* or psychotropic* or "drug therapy") or (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Beflaxatone or Benactyzine or Binospirone or Brofaromine or (Bupropion or Amfebutamone) or Butriptyline or Caroxazine or Cinopramine or Cibolamine or Cimoxatone or Citalo-

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pram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramin* or Pertofrane) or Desvenlafaxine or Dibenzepin or Dilofensine 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 Fluvaxamine or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Ioscarboxazid* or Levomilnacipran or Lofepramin* or ("Lu AA21004" or Vortioxetine) or "Lu AA24530" or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Nortriptylin* or Nortriptyline or Nortriptyline* or Nioxiprin* or Oxpipamol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Phenofoxazine or Pirilindole 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 Tranlylcypromin* or Trazodone or Trimipramine or Venlafaxine or Vloxazine or Vilazodone or Vipazine or Zimelidine)

The CCDANCTR-References Register will be searched using similar terms in the title, abstract and keywords fields.

Additional searches will be conducted on the ‘Specialized register’ of the Cochrane Pregnancy and Childbirth Review Group, MIDIRS Midwifery Database, CINAHL, LILACS, PSYNDEX and Open SIGLE.

The WHO Trials portal (ICTRP) together with ClinicalTrials.gov will also be searched to identify any unpublished or ongoing studies.

A cited reference search, of reports of all included studies, will be conducted on the Web of Science to identify any outstanding reports of trials.

**Searching other resources**

**Handsearches**

1. Reference lists of identified studies
2. Relevant book chapters and their bibliographies
3. Conference proceedings

**List of book titles:**

- Pregnant on Prozac: The Essential Guide to Making the Best Decision for You and Your Baby (Bennett 2009);
- Pregnancy Blues: What Every Woman Needs to Know about Depression During Pregnancy (Misti 2006);
- The New Antidepressants and Antianxieties (Appleton 2004);
- Medication Safety in Pregnancy and Breastfeeding (Koren, Medication Safety in Pregnancy and Breastfeeding) (Koren 2006);
- A Deeper Shade of Blue: A Woman’s Guide to Recognizing and Treating Depression in Her Childbearing Years (Nonacs 2006);
- What Am I Thinking? Having a Baby After Postpartum Depression (Kleiman 2005);
- Psychiatric Disorders in Pregnancy and the Postpartum: Principles and Treatment (Current Clinical Practice) (Hendrick 2010);
- When Baby Brings the Blues: Solutions for Postpartum Depression (Dalfen 2008);
- Depression in New Mothers: Causes, Consequences, and Treatment Alternatives (Kendall-Tackett 2010).

**List of conference proceedings:**

- Perinatal Society of Australia and New Zealand;
- Australian College of Midwives;
- International Confederation of Midwives.

**Personal communication**

- We will contact pharmaceutical companies directly for any relevant unpublished data. Companies include:
  - We will also contact authors of identified trials and with experts in the field including a search for non-English material.

**Data collection and analysis**

**Selection of studies**

Abstracts of studies identified in the above search will be examined by all four authors. We will obtain the full-text reports of studies that are potentially relevant; trials under consideration will be assessed for whether they fulfil the inclusion criteria and methodological quality without regard to their results. Where the authors disagree, the matter will be discussed until agreement is reached.
Where two authors disagree on the inclusion of a study, a third author will be invited to determine the inclusion of the study. Where necessary the matter will be discussed with all authors until agreement is reached. As four authors are to be included on this review, where a situation occurs where there is no majority decision or a split in the decision to include a study, the Cochrane Depression, Anxiety and Neurosis Group will be contacted for further consultation.

The process of study selection will be documented and reported using a PRISMA flow diagram.

Data extraction and management

We will design data extraction forms for the purpose of recording descriptive information, summary statistics of the outcome measures, the quality scale ratings, and associated commentary. Once extracted, we will enter the data into the Cochrane Collaboration's statistical software, Review Manager 2013, to conduct any meta-analysis. Where information is missing, we will contact investigators by email in an attempt to obtain this information.

We will present and compare studies under two separate headings: (1) randomised trials; and (2) non-randomised trials (e.g. cohort and case control trials), with the analyses presented separately for each subgroup.

We will collate the following information from randomised trials.

1. Description of the trials, including the primary researcher, the year of publication, and the source of funding.
2. Characteristics of the interventions, including the number of participants randomised to the treatment and control groups, the number of total drop-outs per group as well as the number that dropped out due to adverse effects, the dose of medication and the period over which it was administered, and the agents used for treating depression. Details of any psychological therapy used in the comparator group will be recorded.
3. Characteristics of trial methodology, including the diagnostic (e.g. DSM-IV-TR) and exclusionary criteria employed (APA 2000), the screening instrument used (e.g. the Structured Clinical Interview for DSM-IV) for diagnosis of depression (Spitzer 1996), the use of a placebo, whether a minimal severity criterion was employed, the number of centres involved.
4. Characteristics of participants, including gender distribution and mean and range of ages, mean length of time since diagnosis with depression, whether they have been treated with medication in the past (treatment naïveté), the number of participants in the sample with depression, and the baseline severity of the disorder, as assessed by the study's primary outcome measure or another commonly employed scale.
5. Outcome measures employed, and a summary of continuous (means and standard deviations) and dichotomous (frequencies and percentages) data provided. Additional information will be included, such as whether data reflected the intent-to-treat with last observation carried forward or completer/observed cases sample, and the minimal period required for inclusion of participants in the last observation carried forward analyses. Other methods of estimating the outcome for participants who dropped out of the study, such as the mixed-effects model, will also be recorded.
6. Quality assessment, including the number of randomised participants who were not included in the analysis (lost to follow-up), whether blinding occurred for the assessor(s), patients, or those who administered medication, as well as whether the allocation of medication was randomised and the allocation sequence was concealed (the methods used in implementing these respective bias reduction measures will also be documented).

The following information will be collated from non-randomised trials.

1. Description of the studies, including the primary researcher, the year of publication, and the source of funding.
2. Characteristics of the study, including the number of participants (per group if groups identified), the number of total drop-outs per as well as the number that dropped out due to adverse effects, the dose of medication and the period over which it was administered, and the agents used for treating depression. Details of any psychological therapy used in the comparator group (if any) will be recorded.
3. Characteristics of study methodology, including the diagnostic (e.g. DSM-IV-TR) and exclusionary criteria employed (APA 2000), the screening instrument used (e.g. the Structured Clinical Interview for DSM-IV (SCID)) for diagnosis of depression (Spitzer 1996), whether a minimal severity criterion was employed, the number of centres involved.
4. Characteristics of participants, including gender distribution and mean and range of ages, mean length of time since diagnosis with depression, whether they have been treated with medication in the past (treatment naïveté), the number of people in the sample with depression and/or other MH disorders and the baseline severity of the disorder, as assessed by the study’s primary outcome measure or another commonly employed scale.
5. Outcome measures employed, and a summary of continuous (means and standard deviations) and dichotomous (frequencies and percentages) data provided. Other methods of estimating the outcome for participants who dropped out of the study, such as the mixed-effects model, will also be recorded.
6. Quality assessment, including: sample size, clear description of treatment, representative source of subjects, adequately selected controls (for case-control studies), use of diagnostic criteria or inclusion criteria, length of follow-up, loss to follow-up, whether any form of blinding occurred, outcome measures described and the use of validated instruments methods used in implementing these respective bias reduction measures will also be documented).
Main planned comparisons
- Antidepressant versus placebo.
- Antidepressant plus one or more additional antidepressants versus placebo.
- Antidepressant versus psychological therapy.
- Antidepressant plus one or more additional antidepressants versus psychological therapy.

We will stratify antidepressants in the analyses according to the categories as laid out in the Types of interventions section, so that we do not combine drugs from different classes in analyses. The group ‘Other antidepressants’ will be presented together, but again only drugs of the same class will be combined to produce a pooled effect, e.g. duloxetine and venlafaxine.

Assessment of risk of bias in included studies

Assessing quality of non-randomised studies
We are aware of the various limitations of non-randomised studies. Where the systematic review identifies non-randomised trials, the quality of the non-randomised selected studies will be assessed using the guidance from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will consider whether or not confounding factors (e.g. parity, gravida, planned or unplanned pregnancy, single mother) were noted or considered and whether confounding was taken into account by the study design or analysis. Details of whether or not the baseline characteristics of the groups being compared was reported will be considered and a description of how confounding factors were measured, or fitted as covariates in regression models (e.g. as a continuous, ordinal, or grouped categorical variable) will also be provided. The authors will identify what researchers did to control for selection bias, including design features of the studies (e.g. matching or restriction to particular subgroups) and the methods of analysis (e.g. stratification or regression modelling with propensity scores or covariates). An additional table will be created listing the pre-stated confounders as columns, the studies as rows, and indicating whether each study:
- restricted participant selection so that all groups had the same value for the confounder (e.g. restricting the study to first time mothers);
- demonstrated balance between groups for the confounder;
- matched on the confounder; or
- adjusted for the confounder in statistical analyses to quantify the effect size.

Assessing quality of randomised studies
Risk of bias for all randomised studies will be assessed using the Cochrane Collaboration’s tool for assessing risk of bias (Higgins 2011). This tool addresses the following domains:
1. selection bias (random sequence generation, allocation concealment);
2. performance bias (blinding of participants and personnel);
3. detection bias (blinding of outcome assessment);
4. attrition bias (incomplete outcome data);
5. reporting bias (selective outcome reporting);
6. other sources of bias.

We will assess sample size, clear description of treatment (e.g. length of treatment), representative source of subjects, use of diagnostic criteria or inclusion criteria, outcome measures described and the use of validated instruments. We will also assess the possibility of attrition bias due to non-equivalent drop-out rates in the medication and comparison groups as part of the risk of bias approach. We will judge each of the six risk of bias domains using the categories “low risk”, “high risk” or “unclear risk” of bias for all randomised trials, and non-randomised trials for appropriate areas of assessment of bias (i.e. description of randomisation will not be applicable for non-randomised trials). All four authors will independently assess the methodological quality of the trials. Any disagreements about methodological quality will be resolved by consultation amongst all authors.

Measures of treatment effect
For continuous variables, we will calculate the mean difference (MD) or standardised mean difference (SMD) with 95% confidence intervals (CIs). We will combine dichotomous and continuous variables using the standard Cochrane procedure \((\text{InOR} = \frac{\text{MD}}{\pi \sqrt{3}})\) (Higgins 2011). We will calculate the number needed to treat (NNT) and risk difference (RD) where appropriate; odds ratio (OR) will be calculated and converted to an approximate risk ratio (RR) with 95% CIs for interpretation.

Unit of analysis issues

Studies with multiple treatment groups
In trials comparing the efficacy of multiple medications in treating depression, we will split the shared comparison group (e.g. placebo or psychological therapy) equally between the medication arms as comparison groups.

Cross-over trials
We will only include cross-over trials in the calculation of the outcomes of interest when it is: (a) possible to extract medication and placebo/comparator data from the first treatment period; or (b) when the inclusion of data from both treatment periods is justified through a wash-out period of sufficient duration as to minimise the risk of carry-over effects. An adequate wash-out period is defined in accordance with clinical practice as at least two weeks.
for all agents with the exception of fluoxetine, for which a minimum wash-out period of four weeks will be required, given the long plasma half-life of this agent. For trials in which the washout period is regarded as adequate, data from both periods will only be included when it is possible to determine the standard error of the mean difference in response between groups (Elbourne 2002). The summary statistics required to derive the standard error of interest will be obtained from the trial report, or for trials for which this information is missing, will be imputed through averaging the relevant statistic from other included crossover trials with comparable control conditions.

Dealing with missing data

All analyses of dichotomous data will be intention-to-treat. This will be achieved by including the total number of participants randomised to the different comparison groups as the denominator in comparisons of treatment response. We will only include data from trials which provide information on the original group size (prior to drop-outs) in the analyses of treatment response. Preference will be given to the inclusion of summary statistics for continuous outcome measures derived from mixed-effects models, followed by last observation carried forward and observed cases summary statistics (in that order). This is in line with evidence that mixed-effects models are more robust to bias than last observation carried forward analyses (Verbeke 2000).

Assessment of heterogeneity

We will assess heterogeneity of treatment response and symptom severity visually from the forest plot of relative risk. This will help determine whether the differences between the results of trials were greater than would be expected by chance alone. We will also assess heterogeneity by means of the chi-squared test of heterogeneity. If the chi-squared test has a P value of less than 0.10, given the low power of the chi-square statistic when the number of trials is small, this will be interpreted as evidence of heterogeneity (Higgins 2011).

In addition, we will use the I² statistic to determine differences in effect size across trials that cannot be explained by chance alone (Higgins 2003). An I² statistic of greater than 30% and 50% will arbitrarily be regarded as indicative of moderate and severe heterogeneity, respectively. We will assess differences on continuous measures in medication efficacy between these subgroups by means of Deeks' stratified test of heterogeneity (Deeks 2001). This method subtracts the sum of the chi-square statistics available for each of the subgroups in the study from the chi-squared statistic available for all the trials, to provide a measure (Qb) of heterogeneity between groups. We will determine the differences in treatment response on the Clinical Global Impression - Improvement scale (CGI-I) by whether the CIs for the effect sizes of the subgroups overlap. This method was chosen in preference to the stratified test, due to inaccuracies in the calculation in Review Manager 2013 of the chi-squared statistic for dichotomous measures (Higgins 2011). In recognition of the possibility of differential effects for different medications, we will stratify all of the outcome comparisons (excluding subgroup and sensitivity analyses) by the individual antidepressant used.

Assessment of reporting biases

Publication is not necessarily related to study quality and indeed publication may imply certain biases (Dickersin 1992; Song 2000). We will detect small-sample effects (including publication bias) by visual inspection of a funnel plot of treatment response. However, this method is not robust if there are less than 10 studies and therefore it will only be carried out in this circumstance (Egger 1997a; Egger 1997b; Egger 2003).

Data synthesis

We will obtain categorical and continuous treatment effects from a random-effects model (the random-effects model includes both within-study sampling error and between-studies variation in determining the precision of the confidence interval around the overall effect size, whereas the fixed-effect model takes only within-study variation into account). We will express the outcomes in terms of an average effect size for each subgroup, as well as by means of 95% CIs. In trials that incorporate a follow-up phase, data from the final assessment point will be combined for all outcome measures. We will stratify comparisons of global treatment response and reduction of symptom severity on primary and secondary outcomes by study design (long-term maintenance studies (>14 weeks) acute treatment interventions).

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses in order to assess the degree to which clinical and methodological differences between trials might have systematically influenced differences observed in the primary treatment outcomes.

We will group the trials according to the following clinical sources of heterogeneity (number of trials permitting):

1. pregnancy trimester;
2. maternal age;
3. whether or not the sample included patients diagnosed with other co-morbidities including other mental health issues and chronic diseases;
4. planned versus unplanned pregnancies.

In addition, the following criteria will be used to assess the extent of methodological sources of heterogeneity:

1. the involvement of participants from a single centre or multiple centres. Single-centre trials are more likely to be
associated with lower sample size but less variability in clinician ratings;
2. whether or not trials were industry funded. In general, published trials which are sponsored by pharmaceutical companies appear more likely to report positive findings than trials which are not supported by for-profit companies (Als-Nielsen 2003; Baker 2003);
3. whether or not psychological therapy was implemented concurrently with pharmacotherapy.

Sensitivity analysis
We will conduct sensitivity analyses to determine the robustness of our conclusions to methodological assumptions made in conducting the meta-analysis.

1. A sensitivity analysis will be conducted to determine whether treatment response varies as a function of the use of treatment response versus non-response as an outcome statistic. This comparison may be necessary in the light of evidence that treatment response may result in less consistent outcome statistics than non-response when the control group event rate is higher than 50% (Deeks 2002). This sensitivity analysis will accordingly only be performed if the majority of trials report a control group event rate higher than 50%.

2. A “worst case/best case” analysis will also be conducted to determine the influence of the exclusion of participants who were lost to follow up on the findings of treatment efficacy (Higgins 2011). In the worst case, all the missing data for the treatment group will be recorded as non-responders, whereas in the best case, all missing data in the control group will be treated as non-responders. Should the conclusions regarding treatment efficacy not differ between these two comparisons, it can be assumed that missing data in trial reports do not have a significant influence on outcome.

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* Indicates the major publication for the study

CONTRIBUTIONS OF AUTHORS
Dr Andrea Gordon and Dr Antonina Mikocka-Walus conceived the idea of the review and developed the protocol. Dr Rasika Jayasekara and Dr Luke Grzeskowiak reviewed and provided feedback on the draft version of the protocol.

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The authors are unaware of any interests that need to be declared.
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