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[Intervention Protocol]

Brexanolone and related neurosteroid GABA(A) positive allosteric modulators for postnatal depression

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ABSTRACT

Objectives

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

To assess the effectiveness and safety of brexanolone and related neurosteroid $GABA_A$ positive allosteric modulators in comparison with any other treatment (pharmacological, psychological, or psychosocial), placebo, or treatment as usual for postnatal depression (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 2014; Stein 2014). Perinatal suicide, which is closely linked to PND, is an important contributor to maternal mortality (Grigoriadis 2017; Khalifeh 2016; Knight 2019). 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 comorbidities (Stein 2014). PND has a similar clinical presentation to depression in the general population (Howard 2014; 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 2014; 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 United Kingdom (UK) and internationally, research and clinical practice have most commonly defined PND as that occurring within a year of childbirth (Howard 2014; NICE 2020; 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 time frames being most relevant for biological studies and longer time frames 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). Among women who experience PND, around a third have also had depression in pregnancy, and a third have 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 2014; Stewart 2019). On the other end of the severity spectrum, it is important to recognise the severe psychiatric emergency of postpartum psychosis, a rare condition affecting one to two women per 1000 in the general population, where admission is recommended to mitigate risks to mother and baby (Jones 2014). Clinically, PND is often comorbid 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 2020). Selective serotonin reuptake inhibitors (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).

However, many antidepressants are associated with a limited response or an extended time to response and/or remission (Brown 2021). These antidepressants do not directly relate to the putative pathophysiology of PND. GABA is gamma-aminobutyric acid and is an inhibitory neurotransmitter in the central nervous system. Pre-clinical and clinical studies in PND have highlighted the potential role of dysfunctional GABAergic signalling, suggesting that positive allosteric modulation of $GABA_A$ receptors may provide a promising mechanism of action for emerging pharmacotherapy in PND (Meltzer-Brody 2020). Such insights into the role of GABAergic signalling in PND have led to the development of a number of drugs to treat PND that act as allosteric modulators of $GABA_A$ receptors. These include an intravenous infusion of a neuroactive steroid, allopregnanolone, known as brexanolone (also known as Zulresso or SAGE-547). In 2019, the United States' Food and Drug Administration (FDA) approved the use of brexanolone for the treatment of PND in adult women, making it the first medication approved specifically for the treatment of PND. However, it is not yet approved for use in the UK. Brexanolone is administered intravenously over 60 hours with close monitoring, due to concerns about the risk of excessive sedation. Inhibitory neurosteroids other than allopregnanolone are also in development. These include ganaxolone (also known as CCD-1042), also administered intravenously, and zuranolone (also known as SAGE-217), which can be administered orally.

The safety of medication for PND whilst breastfeeding is also an important consideration for any PND treatment. PND has potential adverse effects for mother and baby (Howard 2014; Stein 2014), and these need to be weighed against the risks of medication exposure via breast milk, which are sometimes uncertain (McAllister-Williams 2017). For example, while there appears to be limited transfer of intravenous allopregnanolone into breast milk, there is as yet little

evidence on long-term outcomes for exposed infants (Hoffman 2019; Howard 2014; McAllister-Williams 2017; Stein 2014).

How the intervention might work

While there are some possible similarities in the pathophysiology of PND and depression occurring outside of the perinatal period, such as dysregulation of the hypothalamic-pituitary (HPA) axis (Maguire 2019), there are physiological changes unique to pregnancy and evidence to support a unique pathophysiology of PND (Meltzer-Brody 2020). A number of neuroendocrine changes have been observed in PND, including changes in GABAergic signalling. In human and animal models of PND, alterations in levels of allosteric modulators of $GABA_A$ have been noted across the perinatal period (Meltzer-Brody 2020). One such $GABA_A$ modulator is allopregnanolone, which is a metabolite of progesterone. Levels of allopregnanolone mirror that of progesterone in the perinatal period, in that they rise during pregnancy and fall after childbirth (Luisi 2000; Paoletti 2006). Women up to six months postpartum have been observed to have lower levels of allopregnanolone than non-pregnant women, although not all studies have found a difference in allopregnanolone levels between depressed and non-depressed postnatal women (Epperson 2006; Maguire 2019). However, postpartum allopregnanolone levels have been observed to be positively correlated with altered functional connectivity in the brains of women with PND, further supporting a relationship between allopregnanolone levels and PND (Deligiannidis 2019). Brexanolone is an intravenous formulation of allopregnanolone and there are other synthetic analogues of allopregnanolone under development, which serve as positive allosteric modulators of $GABA_A$.

Why it is important to do this review

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 2014; Khalifeh 2016; Stein 2014). There is an urgent need for updated high-quality evidence to inform treatment for the growing number of women accessing help for PND.

Many women who are pregnant or postnatal have a preference for psychological therapy over medication, and may be anxious about the potential adverse effects of medication use on the unborn or breastfeeding baby (O'Mahen 2008). However, 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 2020). Nevertheless, some women may not respond to antidepressant medication, necessitating the development of alternative pharmacological intervention. Brexanolone (also known as Zulresso or SAGE-547) and related neurosteroid $GABA_A$ positive allosteric modulators have been developed from the current understanding of PND's pathophysiology as promising new treatments for PND. However, their effectiveness and safety have not yet been reviewed.

OBJECTIVES

To assess the effectiveness and safety of brexanolone and related neurosteroid $GABA_A$ positive allosteric modulators in comparison with any other treatment (pharmacological, psychological, or psychosocial), placebo, or treatment as usual for postnatal depression (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 enrolled into a trial. The eligible period of treatment onset will be from delivery to 12 months postpartum.

Diagnosis

We will use a broad definition of PND to include all women 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). We will include trials 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.

Comorbidities

We will include studies that enrolled participants with comorbid physical conditions or other psychological disorders (e.g. anxiety) provided the comorbidity 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

Brexanolone (also known as Zulresso or SAGE-547) or related neurosteroid $GABA_A$ positive allosteric modulators (i.e. those inhibitory neurosteroids that are structurally similar to the naturally occurring inhibitory neurosteroid allopregnanolone, including but not limited to, ganaxolone (also known as CCD-1042) and zuranolone (also known as SAGE-217)), given at any dose, alone or in combination with another treatment, initiated in at least one trial arm.

Comparator intervention

1. Placebo.
2. Other pharmacological interventions (e.g. antidepressants).

3. Any other treatment, including:
   a. 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)
   b. psychological interventions (e.g. CBT or interpersonal therapy)
   c. psychosocial interventions (e.g. peer support or non-directive counselling)

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 participants with a reduction of at least 50% on the total score of a standardised depression scale. Remission is typically measured by the number of participants 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

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. Quality of life (e.g. measured using the 36-item Short Form (SF-36) (Ware 1992))
4. Parenting-related and child-related outcomes (e.g. maternal relationship with the baby and the establishment or continuation of breastfeeding)

Timing of outcome assessment

1. Early phase: between 0 and 5 weeks from commencement of treatment
2. Acute phase: between 5 and 12 weeks from commencement of treatment
3. Continuation phase: more than 12 weeks from commencement of treatment

The primary outcome of interest is the acute phase treatment response (between 5 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 brexanolone (Zulresso or SAGE-547), ganaxolone (CCD-1042), zuranolone (SAGE-217), and any other related neurosteroid $GABA_A$ positive allosteric modulators for the treatment of PND.

Electronic searches

The Cochrane Common Mental Disorders (CCMD) Information Specialist will search the following biomedical databases using relevant keywords, subject headings (controlled vocabularies), and search syntax, appropriate to each resource (Appendix 1).

1. Cochrane Central Register of Controlled Trials (CENTRAL) (all years, current issue).
2. MEDLINE Ovid (1946 onwards).
3. Embase Ovid (1980 onwards).
4. PsycINFO Ovid (all available years).

We will search the international trial registers (ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)) using drug terms only.

Although brexanolone only received regulatory approval from the FDA in March 2019 and the other compounds are not yet approved, we will not apply any date restrictions to the search to ensure we capture all earlier (pre-regulatory) studies. We will also not apply any restrictions on language, publication status or study design in the searches.

Searching other resources

Regulatory documents

We will search for relevant regulatory approval documents (reviews) submitted by Sage Therapeutics Inc, to the US Food and Drug Administration, by searching Drugs@FDA: FDA-Approved Drugs for Zulresso (NDA 211371).

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 additional data where necessary, or information on ongoing or completed but unpublished trials from the following sources.

1. Sage Therapeutics Inc (developers of brexanolone (Zulresso) and zuranolone (SAGE-217)).
2. Marinus Pharmaceuticals (developers of ganaxolone (CCD-1042)).
3. Any other pharmaceutical company or research institute involved in any of the included trials (as funder, sponsor or trialist).
4. Authors of included trials published within the last five years.
5. 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 review authors (CW, JB, KA, or LR)

will independently inspect abstracts retrieved from the search. We will obtain the full-text articles for any publication that is potentially relevant. Two review authors (CW, JB, KA, or LR) will independently assess the full-text 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 be 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, time since delivery at commencement of treatment, time of onset of current depressive symptoms, 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 review authors (CW, JB, KA, or LR) will independently extract data from included studies. We will resolve any disagreements through 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 for two separate groups of neurosteroid $GABA_A$ positive allosteric modulators administered intravenously and neurosteroid $GABA_A$ positive allosteric modulators administered orally:

1. Neurosteroid $GABA_A$ positive allosteric modulators versus placebo.
2. Neurosteroid $GABA_A$ positive allosteric modulators versus other pharmacological intervention.
3. Neurosteroid $GABA_A$ positive allosteric modulators versus any other intervention (e.g. treatment as usual, psychological or psychosocial intervention).

Assessment of risk of bias in included studies

Two review authors (CW, JB, KA, or LR) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We will resolve any disagreements through 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 (Bland 2000).

If dichotomous data on those who did or did not fulfil criteria for depression are not available, where possible we will attempt to convert outcome measures to dichotomous data using cut-off points on rating scales. In sensitivity analyses, these data will be excluded to examine the impact on effect estimates.

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% confidence intervals (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 2019).

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. If trial authors have appropriately adjusted for clustering in their analyses, we will use generic inverse variance methods to meta-analyse these data from cluster-RCTs (Higgins 2019). If these data are not available, we will conduct 'approximately correct' analyses taking into account the intra-cluster correlation coefficient (ICC) and an estimate of cluster size 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 2019), we will use estimates of ICC from similar studies (Higgins 2019)

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 2019), 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 to follow-up, data must lose credibility (Xia 2009). However, due to the small evidence base, we decided to include studies with greater than 50% dropout. 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, and 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 2019).

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 with data on the primary outcomes 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 comparison group, e.g. placebo) 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.

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.

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. Different times of onset of depression in the postnatal period.
4. Different classes of antidepressants to which the drug under study may be compared (e.g. selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or other antidepressants).
5. Women co-prescribed antidepressants while also receiving the drug under study versus women not receiving antidepressants.
6. By individual drug or compound.

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 plan to conduct a priori sensitivity analyses (if sufficient data are 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 more 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 summary of findings tables, where we will summarise findings of studies comparing intravenous and oral neurosteroid $GABA_A$ positive allosteric modulators, with each of the three comparison groups (i.e. placebo, other pharmacological intervention, or any other intervention). We will present a separate summary of findings table 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, quality of life, and parenting-related and child-related outcomes. Where possible, we will present data for the acute phase treatment response (between 5 and 12 weeks) in these summary of findings tables. 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 (CW, JB, KA, or LR) 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. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL) (current issue)

#1 (Brexanolone or Zulresso or SAGE-547 or Ganaxolone or CCD-1042 or Zuranolone or SAGE-217)
#2 Allopregnanolone
#3 ((neurosteroid* or "neuro* steroid*" or "neuroactive steroid*" or "positive allosteric modulat*" or PAM or PAMs) and ((GABA* or "gamma aminobutyric acid") and receptor*))
#4 (#2 or #3)
#5 ((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*") and (depress* or dysthymi* or "adjustment disorder*" or "mood disorder*" or "affective disorder*" or "affective symptom*")))
#3 (#1 or (#4 and #5))

****

Ovid MEDLINE(R) ALL <1946 onwards>
Search Strategy:
---
1 (Brexanolone or Zulresso or SAGE-547 or Ganaxolone or CCD-1042 or Zuranolone or SAGE-217).mp.
2 Allopregnanolone.mp.
3 ((neurosteroid* or neuro* steroid* or neuroactive steroid* or positive allosteric modulat* or PAM?) and ((GABA* or gamma aminobutyric acid) and receptor*)).mp.
4 or/1-3
5 ((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*) and (depress* or dysthymi* or adjustment disorder* or mood disorder* or affective disorder* or affective symptom*)).mp.
6 (4 and 5)
7 exp animals/ not humans.sh.
8 (6 not 7)

****

Ovid Embase <1980 onwards>
Search Strategy:
---
1 Brexanolone/
2 Ganaxolone/
3 Zuranolone/
4 (Brexanolone or Zulresso or SAGE-547 or Ganaxolone or CCD-1042 or Zuranolone or SAGE-217).mp.
5 Allopregnanolone.mp.
6 ((neurosteroid* or neuro* steroid* or neuroactive steroid* or positive allosteric modulat* or PAM?) and ((GABA* or gamma aminobutyric acid) and receptor*)).mp.
7 exp 4 aminobutyric acid A receptor stimulating agent/
8 *GABAergic receptor affecting agent/
9 or/1-8
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 ((animal or nonhuman) not human).de.
15 (13 not 14)

****

Ovid APA PsycInfo <all available years>
Search Strategy:
---

1 (Brexanolone or Zulresso or SAGE-547 or Ganaxolone or CCD-1042 or Zuranolone or SAGE-217).mp.
2 Allopregnanolone.mp.
3 ((neurosteroid* or neuro* steroid* or neuroactive steroid* or positive allosteric modulat* or PAM?) and ((GABA* or gamma aminobutyric acid) and receptor*)).mp.
4 (2 or 3)
5 ((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*") and (depress* or dysthymi* or "adjustment disorder*" or "mood disorder*" or "affective disorder*" or "affective symptom*")).mp.
6 (4 and 5)
7 (1 or 6)

****

Appendix 2. A note regarding the use of the term 'woman'

'Woman' has been used to refer to all those who could find themselves pregnant and in the postnatal period. It is recognised that this could include individuals with diverse gender identities.

CONTRIBUTIONS OF AUTHORS

Claire A Wilson (CW), Lindsay Robertson (LR), Jennifer Valeska Elli Brown (JB), Karyn Ayre (KA) and Hind Khalifeh (HK) developed the protocol.
All authors approved the final protocol prior to publication.

DECLARATIONS OF INTEREST

CW: no conflicts of interest.
LR: no conflicts of interest.
JB: no conflicts of interest.
KT: no conflicts of interest.
HK: no conflicts of interest.

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