INPLASY

The Efficacy of Zuranolone Versus Placebo in Postpartum Depression and Major Depressive Disorder: A Systematic Review & Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - N/A.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 October 2023 and was last updated on 02 October 2023.

INTRODUCTION

Review question / Objective In this systematic review and meta-analysis, we aim to compare the efficacy of zuranolone versus placebo in the treatment of adults with major depressive disorder and postpartum depression as evidenced by reduction in depressive symptoms.

Rationale The treatment of depression does not provide immediate relief to one's symptoms as soon as they are diagnosed, as many patients find themselves experiencing a long list of adverse effects, lack of remission, and the need to constantly change their treatment regimens to find relief. Currently, many of these existing medications that come with a list of challenges are used to treat both major depressive disorder (MDD) and postpartum depression (PPD), which is a specifier for MDD.
In addition to cognitive behavioral therapy, the current pharmacological standard of care for MDD and PPD is primarily targeted at serotonin and norepinephrine neurotransmitters in the form of selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI), and less commonly tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) due to risk of serious side effects. While SSRIs and SNRIs have a lower side effect profile than the alternatives, they still are far from perfect. Side effects of many treatments include weight gain, loss of libido, and sleep disturbances which may cause medication discontinuation. Additionally, SSRIs may take up to four to six weeks to notice improvement in symptoms. The current antidepressant treatments are also only about 20% effective, when taking the placebo effect into account. All of these factors demonstrate a need for a more effective, efficient, and practical solution for the treatment of MDD and PPD.
Postpartum depression is extremely prevalent in today's society, with 1 in 7 women experiencing PPD in their lifetime, though the number of women

being treated is much less than the number who are suffering. This diagnosis has the potential to not only emotionally and physically cause harm to the mother experiencing it, but the infant, and loved ones around as well. As of 2022, the prevalence of PPD had increased by 24% as compared to pre-pandemic times. Now more than ever, it is crucial to understand the root causes of psychiatric conditions, such as PPD and MDD, to help facilitate effective diagnosis and treatment to improve the lives of those living with treatable illnesses. In an effort to find a solution to these debilitating conditions, there is a new emerging drug that may be effective in treating both, known as zuranolone. This systematic review and meta-analysis will delve into this new drug and the hope it may bring to those battling with MDD and PPD.

Condition being studied Major Depressive Disorder (MDD) is one of the most common mental health disorders in the United States, affecting 21.0 million, or 8.3% of people in 2021. MDD is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) as a two-week period containing at least five symptoms where one of the symptoms is either depressed mood or anhedonia. Other symptoms for diagnosis include either weight loss or weight gain, inability to sleep or sleeping too much, agitation or slowed movements, fatigue, worthlessness, guilt, inability to concentrate, and thoughts of death or suicide.
Postpartum Depression (PPD) affects 10-15% of new mothers, though it is suspected the true number of mothers experiencing PPD is much higher, as it is highly underdiagnosed, due to both stigma and lack of screening. The DSM-V defines postpartum depression as a specifier for major depressive disorder when the onset of symptoms occurs anytime throughout the pregnancy or within 4 weeks after delivery, and includes at least five out of nine possible symptoms for at least a two week period, in which one of the symptoms must be anhedonia or depressed mood. While each individual will experience a unique range of symptoms, common symptoms across the board include persistent sadness, difficulty concentrating, feelings of worthlessness or guilt, insomnia or hypersomnia, irritability, poor bonding with the infant, distancing self from family and/or loved ones, and recurrent thoughts of death, suicide, and in severe forms, harm to the patient or their newborn.

METHODS

Search strategy A systematic literature review was performed on September 2, 2023 using EBSCOhost to search Academic Search Premier, APA PsycArticles, APA PsycInfo, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL Ultimate, and MEDLINE with Full Text simultaneously. Using the Boolean/Phrase search mode, the following terms were searched with assistance from the Sacred Heart University health sciences librarian: ("Zuranolone" OR "Zurzuvae" OR "SAGE-217") AND ("Postpartum depression" OR "PPD" OR "Post-partum depression" OR "Postnatal depression" OR "PND" OR "Post-natal depression" OR "Major Depressive Disorder" OR "MDD" OR "Depression" OR "Major Depression" OR "Unipolar major depression") AND ("Randomized controlled trials'' OR "RCT" OR "Randomised controlled trials" OR "Randomized clinical trial"). The search was limited to only randomized controlled or clinical trials as there are no non-randomized controlled trials available due to the novelty of Zuranolone. Additional searches were completed on PubMed, Nursing and Allied Health Premium, and a grey literature search on BioRxiv and MedRxiv, using similar search terms. All searches were limited to articles written in English, those that were published within the past six years, and those that had been peer reviewed. The search was limited to the past 6 years since the drug first appeared in trials starting in 2018. The search results were then exported to Zotero citation manager, then subsequently exported to Covidence systematic review manager to assess for eligibility.

Participant or population Adult patients (18 years or older) diagnosed with major depressive disorder or postpartum depression as defined by the DSM-5.

Intervention Zuranolone.

Comparator Placebo.

Study designs to be included Randomized Controlled Trials.

Eligibility criteria The following inclusion criteria were defined as: adults ≥ 18 years old, randomized controlled trials, and those diagnosed with either postpartum depression or major depressive disorder as defined by the DSM-5. The study selection excluded participants younger than 18 years old, studies that were not placebo-controlled, studies with the same patient population, and studies performed on animals.

Information sources A systematic literature review was performed on September 2, 2023 using EBSCOhost to search Academic Search Premier,

APA PsycArticles, APA PsycInfo, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL Ultimate, and MEDLINE with Full Text simultaneously. Additional searches were completed on PubMed, Nursing and Allied Health Premium, and a grey literature search on BioRxiv and MedRxiv, using similar search terms.

Main outcome(s) Reduction in Hamilton Depression Rating Scale (HAMD-17) from baseline to day 15 following a once daily dose of zuranolone or placebo for 14 days.

Additional outcome(s) Reduction in Hamilton Anxiety Rating Scale (HAM-A) from baseline to day 15 following a once daily dose of zuranolone or placebo for 14 days.
Reduction in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to day 15 following a once daily dose of zuranolone or placebo for 14 days.

Data management Two independent reviewers (M.W. & E.W.) screened the titles and abstracts using Covidence for eligibility with respects to the inclusion and exclusion criteria. A full-text review was then completed independently by the two reviewers (M.W. & E.W.), with any conflicts being resolved by discussion or a third-party reviewer (S.R.). Data extracted from the articles deemed eligible by the reviewers was then utilized in the systematic review.

Quality assessment / Risk of bias analysis The quality of each randomized controlled trial included in the systematic review was evaluated using the Cochrane Risk of Bias tool for randomized trials (RoB 2) by two independent reviewers (M.W. & E.W). The Cochrane RoB 2 tool assesses for bias through five domains, which includes bias from randomization such as allocation concealment and blinding, deviations from the intended interventions, missing data, measurement error, and selective outcome reporting. The risk of bias is then reported as low risk, some concerns, or high risk.

Strategy of data synthesis The data from the systematic review was then used to generate a meta-analysis. Data from the eligible articles in Covidence was input into Review Manager (RevMan v5.4) software and analyzed. Heterogeneity across studies was accounted for using the DerSimonian and Laird random-effects and fixed-effects models for the meta-analyses. Significance was determined by a p-value of 50% was determined to be statistically significant.

Subgroup analysis Subgroup analyses are not planned for this review.

Sensitivity analysis After data synthesis, we plan to conduct sensitivity analysis by excluding studies one-by-one to observe whether there is a significant change in the overall result.

Language restriction English.

Country(ies) involved United States.

Keywords Major depressive disorder; postpartum depression; Zuranolone; allopregnanolone; neurosteroid; systematic review; meta-analysis.

Dissemination plans We aim to publish this systematic review and meta-analysis to provide consolidated and evidence-based research to medical providers in practice to manage the treatment of major depressive disorder and postpartum depression.

Contributions of each author
Author 1 - Mackenzie Winslow - Mackenzie Winslow, PA-S, drafted the manuscript.
Author 2 - Emily White - Emily White, PA-S, drafted the manuscript.
Author 3 - Elijah Salzer - Elijah Salzer, DMSc, PA-C, NYSAFE, C-EMF, served as an expert in the field.
Author 4 - Suzanne Rose - Suzanne Rose, MS, PhD, CCRC, FACRP, read, provided feedback, and approved the final manuscript.