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Efficacy and safety of zuranolone in major depressive disorder and postpartum depression: A meta-analysis of meta-regression and dose-response analysis

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Corresponding author:
Chih-Wei Hsu

harwicacademia@gmail.com

Author Affiliation:
Kaohsiung Chang Gung Memorial Hospital.

Lin, YW[1]; Tu, YK[2]; Hung, KC[3]; Liang, CS[4]; Tseng, PT[5]; Lin, PY[6]; Lai, ECC[7]; Hsu, CW[8].

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202360087

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 June 2023 and was last updated on 26 July 2023.

INTRODUCTION

Review question / Objective PICO (Patient, Intervention, Comparison, and Outcome) questions for our study were as follows: (1) Patient: Individuals diagnosed with a major depressive episode of major depressive disorder; (2) Intervention: Administration of a complete regimen of zuranolone; (3) Comparison: Placebo treatment; and (4) Outcome: Alterations in the severity of depression and anxiety, and dropout and adverse event incidence rates.

Condition being studied Zuranolone, also known as SAGE-217, is a synthetic neurosteroid being developed as a potential treatment for major depressive disorder and postpartum depression. It acts as a positive allosteric modulator of GABA-A receptors in the brain, aiming to provide rapid relief of depressive symptoms without the side effects associated with traditional antidepressants.

METHODS

Search strategy A systematic literature search was conducted across PubMed, EMBASE, Cochrane CENTRAL, Web of Science, ProQuest, Clinical Key, ScienceDirect, ClinicalTrials.gov database, and grey literature from database inception until August 20, 2023, using keywords such as (depress* OR “affective” OR “mood”) AND (“zuranolone” OR ”SAGE-217” OR ”S-812217”).

Participant or population Individuals diagnosed with a major depressive episode of major depressive disorder, with or without postpartum onset.

Intervention Zuranolone.

Comparator Placebo or different dose of zuranolone.

Study designs to be included RCT.

Eligibility criteria Inclusion criteria were as follows: (1) Randomised controlled trials (RCTs) incorporating a placebo control group; (2) Diagnosis of major depressive disorder, with or without postpartum onset, according to accepted diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders); and (3) quantification of depression severity using a valid scale, both pre- and post-zuranolone regimen administration. Exclusion criteria were as follows: (1) non-randomised trials, including literature reviews and case studies or series; (2) letters to the editor or editorial commentary; and (3) RCTs lacking a placebo control group.

Information sources PubMed, EMBASE, Cochrane CENTRAL, Web of Science, ProQuest, Clinical Key, ScienceDirect, ClinicalTrials.gov database, and grey literature from database inception until August 20, 2023.

Main outcome(s) Changes in depression severity scores on the 17-item Hamilton Rating Scale for Depression (HAMD-17). If the included studies did not employ the HAMD-17 for assessing depression, we selected the primary outcome scale utilised in the relevant studies to assess depression as an alternative, such as the 21-item HAMD or Montgomery Asperger Depression Rating Scale.

Additional outcome(s) There were five secondary outcomes. First, the response and remission rates of depressive symptoms. They were defined as a reduction in depression scores by more than 50% and a fall in depression scores below a specific cut-off point, respectively. In cases where depressive symptoms were assessed using the HAMD-17, a score of 7 was classified as remission. Second, changes in anxiety severity scores on the Hamilton Anxiety Rating Scale (HAM-A). If the included studies did not employ the HAM-A for assessing anxiety, we selected the outcome scale utilised in the relevant studies to assess anxiety as an alternative, such as the anxiety subscale of the HAMD-17. Finally, dropout and side effect rates. Dropouts were defined as participants who did not complete the study for any reason. Regarding side effects, we included any treatment-emergent adverse events recorded during the treatment period, regardless of their severity. Dropout and side effect rates were calculated by dividing the number of dropouts or side effects, respectively, by the total number of random participants.

Quality assessment / Risk of bias analysis The appraisal for the risk of bias among our included studies was independently performed by two authors, following the risk of bias tool in the Cochrane Handbook.

Strategy of data synthesis In the meta-analysis of continuous variables, such as the severity of depression or anxiety, we calculated effect sizes based on between-group differences (treatment and placebo) in changes in depression and anxiety scores (pre- and post-value), utilising the standardised mean difference (SMD) with 95% confidence intervals (CIs). If all included studies used a consistent measurement tool, such as HAMD-17, we conducted a sensitivity analysis using the mean difference (MD) as a measure. For dichotomous outcomes, such as depression response or remission rate, incidence of side effects, and dropout rate, we used the odds ratio (OR) as a measure. Given the potential heterogeneity among various studies, we conducted a meta-analysis using a random-effects model. Moreover, we performed a leave-one-out sensitivity analysis to identify RCTs that might be a potential source of heterogeneity. Given that we were interested in the potential differences in the effect of zuranolone on MDD and postpartum-onset MDD, we performed a subgroup analysis specifically for these two diagnoses. Additionally, we conducted a meta-regression analysis to identify potential confounding factors, including pre-treatment depression severity, age, and sex.
We also conducted a one-stage, random-effects, dose-response meta-analysis. We defined the dose for each zuranolone category based on the therapeutic dose utilised in the included studies (i.e., 0 mg for placebo; 30 mg for zuranolone). To discern the relationship between exposure dose and outcomes, we applied the methodologies proposed by Orsini, which facilitated the exploration of nonlinear trends. In our analysis, restricted cubic splines with three knots at fixed percentiles (10, 50, and 90%) of the distribution of zuranolone in the included studies were used to model the dose-response relationship. The model was then estimated using a generalised least squares estimator accounting for the correlation between effect sizes (SMD or OR) in each study. The choice of three knots and fixed percentiles of 10, 50, and 90% were based on recommendations from previous research and the limited dose categories of zuranolone observed in the current studies. Additionally, we performed a sensitivity analysis at fixed percentiles (10, 75, and 95%) of the zuranolone distribution.

Subgroup analysis Major depressive disorder or postpartum depression.

Sensitivity analysis There were three sensitivity analyses. First (meta-analysis), if all included studies used a consistent measurement tool, such as HAMD-17, we conducted a sensitivity analysis using the mean difference (MD) as a measure. Second (dos-response meta-analysis), we performed a sensitivity analysis at fixed percentiles (10, 75, and 95%) of the zuranolone distribution. Third (publication bias), if publication bias was statistically significant, we further applied trim-and-fill approaches to potentially impute missing studies.

Language restriction No.

Country(ies) involved Taiwan.

Keywords depression, DRMA, MDD, postpartum, SAGE-217, zuranolone.

Contributions of each author

Author 1 - Yu-Wei Lin.
Author 2 - Yu-Kang Tu.
Author 3 - Kuo-Chuan Hung.
Author 4 - Chih-Sung Liang.
Author 5 - Ping-Tao Tseng.
Author 6 - Pao-Yen Lin.
Author 7 - Edward Chia-Cheng Lai
Author 8 - Chih-Wei Hsu.