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Efficacy and Safety of Zuranolone in the Treatment of Major Depressive Disorder: A Meta-Analysis

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ADMINISTRATIVE INFORMATION

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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 29 November 2023 and was last updated on 29 November 2023.

INTRODUCTION

Review question / Objective This study aimed to conduct a systematic review to assess the efficacy and safety of zuranolone for the treatment of major depressive disorder (MDD).

Rationale We conducted electronic searches of databases including PubMed, Embase, Cochrane, and Web of Science to identify randomized controlled trials of zuranolone for the treatment of MDD from the inception of the studies up to September 15, 2023. Two independent reviewers screened the studies, extracted data, and evaluated the quality of the included studies. We then used R 4.2.2 to perform a meta-analysis.

Condition being studied This is the first study to systematically review and analyze the efficacy and safety of zuranolone in the treatment of patients with MDD. In this meta-analysis of four randomized, double-blind, placebo-controlled studies of zuranolone for patients with MDD, we investigated the rapid efficacy of zuranolone by including the most recent high-quality research, surpassing the scope of a previous meta-analysis. Our efficacy study revealed that zuranolone led to a significant improvement in HAM-D, HAM-A, and MDARS scores. This underscores the potential efficacy of zuranolone in ameliorating depression.

METHODS

Search strategy Even before the emergence of the coronavirus disease 2019 (COVID-19) pandemic, major depressive disorder (MDD) ranked among the leading global causes of health burden.The advent of the COVID-19 pandemic has exacerbated many determinants of poor mental

health. Studies estimate an additional 53.2 million cases of MDD globally attributable to the COVID-19 pandemic. MDD is a mental health disorder characterized by a depressed mood, loss of interest or pleasure in activities, and other symptoms. It affects over 3.8% of the global population, making it a significant health concern. Recent research indicates that depression is associated with impaired neuronal activity in brain networks, such as the central executive network [CEN], default mode network [DMN], and salience network [SN]. It is hypothesized that improving depressive symptoms may involve restoring balance in the brain networks that regulate mood.

Participant or population Inclusion criteria for MDD were as follows: (1) randomized controlled trials (RCT); (2) Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [15], and 17-item Hamilton Depression Rating Scale (HAM-D) scores [16]; (3) intervention: zuranolone was administered to the experimental group while the control group received a placebo [17].Exclusion criteria were as follows: (1) studies with inconsistent subject-object relationships; (2) studies with duplicated data; (3) unavailability of full text or complete data; and (4) studies focusing on MDD subtypes (such as severe postpartum depression or severe post-stroke depression); (5) non-English articles; and (6) publication in the form of letters, conference reports, editorials, case reports, animal studies, basic studies, or systematic reviews.

Intervention Zuranolone.

Comparator Placebo.

Study designs to be included We conducted electronic searches of databases including PubMed, Embase, Cochrane, and Web of Science to identify randomized controlled trials of zuranolone for the treatment of MDD from the inception of the studies up to September 15, 2023. Two independent reviewers screened the studies, extracted data, and evaluated the quality of the included studies. We then used R 4.2.2 to perform a meta-analysis.

Eligibility criteria Inclusion criteria for MDD were as follows: (1) randomized controlled trials (RCT); (2) Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [15], and 17-item Hamilton Depression Rating Scale (HAM-D) scores [16]; (3) intervention: zuranolone was administered to the experimental group while the control group received a placebo [17].Exclusion criteria were as follows: (1) studies with inconsistent subject-object relationships; (2) studies with duplicated data; (3) unavailability of full text or complete data; and (4) studies focusing on MDD subtypes (such as severe postpartum depression or severe post-stroke depression); (5) non-English articles; and (6) publication in the form of letters, conference reports, editorials, case reports, animal studies, basic studies, or systematic reviews.

Information sources In this study, we conducted electronic searches in English databases, primarily sourcing relevant literature from PubMed, Embase, Cochrane, and the Web of Science. The search period spanned from the inception of the databases to September 15, 2023. Two researchers (SYW and ZL) independently assessed the titles and abstracts of the studies identified during the search, excluding those that were not pertinent. For the remaining studies, we thoroughly examined both the full texts and supplementary materials to ascertain whether they contained the necessary information. Any disagreements in the study selection process were resolved by referring to the original article and reaching a consensus with the senior investigator (WHL).

Main outcome(s) HAM-D Score on Day 15.

Quality assessment / Risk of bias analysis To evaluate the quality of the studies, the Cochrane Handbook of Systematic Reviews [18] was employed, which consisted of the following seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The level of bias risk for each item was graded as low, unclear or high.

Strategy of data synthesis Heterogeneity was evaluated using the chi-square test (P 50%). When both P 50% were met, it indicated substantial heterogeneity among the studies, leading to the adoption of a random effect model. In the analysis of overall effects, we used weighted mean difference (WMD), odds ratio (OR), and 95% confidence interval (95% CI) as the effect indicators. As the number of included studies was <10, the funnel plot and Egger's test were used to examine the potential presence of publication bias. A significance level of P <0.05 was considered to be statistically significant.

Subgroup analysis Subgroup analyses of the primary outcomes were conducted, and the results showed that most subgroups yielded consistent results. There were no significant differences among the subcategories within each subgroup.

Sensitivity analysis Sensitivity analysis was performed on the HAM-D scores and the clinical efficacy of the zuranolone intervention for MDD. The sensitivity analyses indicated the robustness of all the findings. Consequently, one article was excluded, and a meta-analysis was conducted on the remaining articles. The combined results from the remaining studies remained statistically significant, underscoring the robustness of the findings and confirming that the exclusion had no impact on the final results.

Country(ies) involved China.

Keywords Depression; MDD; SAGE-217; Zuranolone.

Contributions of each author

Author 1 - Shuyu Wang, as the principal author, had full access to all the data in the study and takes responsibility for the accuracy of the data analysis and the integrity of the data. Additionally, She contributed to the conception and design, as well as the acquisition and interpretation of the date.
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Author 2 - Wenxing Zhang contributed to both the conception and design, as well as the data acquisition and interpretation.
Author 3 - Zhang Liu contributed to data acquisition and interpretation.
Author 4 - Tian Zhnag contributed to the draft of the manuscript.
Author 5 - Yi Wang contributed to the draft of the manuscript.
Author 6 - Weihong Li contributed to revise of the article and final approval.