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

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REVIEW ARTICLE

The efficacy of zuranolone versus placebo in postpartum depression and major depressive disorder: a systematic review and meta-analysis

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Abstract

Background Zuranolone, an oral version of allopregnanolone and neurosteroid, is a novel drug for the treatment of major depressive disorder (MDD) and postpartum depression (PPD).

Aim The purpose of this systematic review and meta-analysis was to assess the efficacy of zuranolone in the treatment of MDD and PPD.

Method A systematic search was conducted using EBSCOhost to simultaneously 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. Two independent reviewers screened the articles and completed a full-text review using Covidence. The quality of each study was assessed using the Cochrane Risk of Bias tool for randomized trials (RoB 2). A meta-analysis was then conducted using Review Manager (RevMan v5.4) software.

Results The initial search yielded 127 results, with 6 articles fitting our inclusion and exclusion criteria. All 6 studies, comprising 1707 participants, had an overall low risk of bias. There was a significant decrease in HAM-D scores for MDD at 15 days versus placebo (MD −2.40, 95% CI −3.07 to −1.63; $p < .001$). When pooling data for PDD, there was an overall significant decrease in HAM-D scores at 15 days versus placebo (MD −4.06, 95% CI −4.25 to −3.87; $p < .001$).

Conclusion The results suggest that zuranolone can improve symptoms of PPD at 15 days; however, results were not clinically significant for MDD. Future research is needed to evaluate the long-term efficacy of zuranolone in PPD and the treatment efficacy in MDD.

Keywords Allopregnanolone · Brexanolone · Depression · Depressive disorder · Major · Neurosteroid · Postpartum · Pregnanolone · Zuranolone

Impact statements

- The available antidepressant treatments are not always effective for the treatment of major depressive disorder (MDD) and postpartum depression (PPD), demonstrating a need for a more effective, efficient, and practical solution.
- The novel drug zuranolone, an oral version of allopregnanolone and neurosteroid, is currently being studied in the treatment of MDD and PPD.
- This systematic review and meta-analysis suggests that in patients with MDD or PPD, a 14-day course of once-daily zuranolone causes a statistically significant reduction of HAM-D; however, these outcomes are only considered clinically significant for PPD.
- The future direction of neurosteroid research is open for exploration as to how this class of medications can fit into the treatment regimens of other mental and neurological disorders.

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Introduction

The treatment of both major depressive disorder (MDD) and postpartum depression (PPD) 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 [1, 2]. However, there is a new drug that may be effective in treating both, known as zuranolone [3].

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, and about 6.5% of the European population [4, 5]. Globally, the COVID-19 pandemic played a significant role in the increase of MDD. Populations with higher rates of COVID-19 infections and decreased mobility due to lockdowns showed increased rates of depression between 2020 and 2021 [6]. In the wake of the post-COVID-19 pandemic, MDD is more important than ever to address. People diagnosed with MDD are at an increased risk of mortality, partially due to the risk of suicide, but MDD also is a comorbidity of many mental and physical disorders [2].

In addition to cognitive behavioral therapy, the current pharmacological standard of care for MDD is primarily targeted at serotonin and norepinephrine neurotransmitters in the form of selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), and less commonly due to the risk of adverse effects, tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) [7]. Adverse effects of many treatments include weight gain, loss of libido, and sleep disturbances, which may cause medication discontinuation [8]. Additionally, SSRIs may take up to 6 weeks to notice improvement in symptoms [8]. The current antidepressant treatments are thought to improve symptoms in approximately 20% of patients [9], demonstrating a need for a more effective, efficient, and practical solution for the treatment of MDD.

Postpartum depression

One of the most common complications of childbirth is postpartum depression (PPD), affecting 10–15% of people who recently gave birth. However, it is suspected the true number of those experiencing PPD is much higher, as it is highly underdiagnosed due to both stigma and lack of screening [10]. As of 2022, the prevalence of PPD had increased by 24% as compared to pre-pandemic times [11].

The treatment of PPD is multifactorial and multidisciplinary, as the condition is both medical and psychiatric. For those suffering from severe symptoms of PPD, SSRIs may not work; therefore, other classes of antidepressants, such as SNRI, TCA, and atypicals such as bupropion, may be trialed, which carry greater concern for safety during breastfeeding [12]. Electroconvulsive therapy (ECT) may also be an option for severe treatment-resistant PPD [13].

Allopregnanolone

Allopregnanolone, a neurosteroid and progesterone metabolite, is a potent positive allosteric modulator that binds to synaptic and extrasynaptic $GABA_A$ receptors [14]. In patients with depression, allopregnanolone levels are decreased in the cerebrospinal fluid [15]. In addition, the increase of progesterone is directly related to the increase in serum allopregnanolone throughout pregnancy, especially in the third trimester [16]. In the postpartum period, serum progesterone and, therefore, allopregnanolone levels drop rapidly [14].

The Food and Drug Administration (FDA) approved a parenteral version of the neurosteroid allopregnanolone, brexanolone (Zulresso), for the treatment of PPD in March 2019 [17]. While effective, brexanolone requires a 60-h infusion time in the hospital, making it inconvenient and expensive for the medication and the required hospital stay [18]. Recently, in August 2023, zuranolone, an oral version of allopregnanolone, was FDA-approved for the treatment of PPD, with once-daily dosing for 14 days, demonstrating the ability to provide symptomatic relief in as soon as 3 days [19].

Aim

This systematic review and meta-analysis aimed to compare the efficacy of zuranolone versus placebo in the treatment of adults with MDD and PPD, as evidenced by a reduction in depressive symptoms on the Hamilton Depression Rating Scale (HAM-D). An ethics statement is not applicable because this study is based exclusively on published literature.

Method

Search strategy

A systematic literature review was performed 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

from inception until September 2, 2023. The University Health-Sciences librarian assisted in developing a comprehensive Boolean-based search strategy (See Supplement 1). Additional searches were completed on PubMed, Nursing and Allied Health Premium, and a grey literature search on BioRxiv and MedRxiv, using similar search terms.

Study selection

The inclusion criteria were defined as peer-reviewed, English language reports of adults ≥ 18 years old, randomized, placebo-controlled trials, and those diagnosed with either postpartum depression or major depressive disorder as defined by the DSM-5. Two independent reviewers used covidence.org (M.W. and E.W.) to screen the titles and abstracts for eligibility, followed by a full-text review with any conflicts resolved by discussion or a third-party reviewer (S.R.) [20]. Data were independently extracted from the retained articles for analysis. This study protocol had been registered to the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) register, registration number INPLASY2023100007; available at doi.org/https://doi.org/10.37766/inplasy2023.10.0007.

Risk of bias assessment

The risk of bias of each included study was evaluated using the Cochrane Risk of Bias tool for randomized trials (RoB 2) by the 2 independent reviewers assessing for bias through five domains and reported as low risk, some concerns, or high-risk [21].

Meta-analysis

Review Manager (RevMan v5.4) software was used to conduct a DerSimonian and Laird random-effects meta-analysis to account for heterogeneity [22]. A p-value of < 0.05 indicated statistical significance, and heterogeneity was considered when $I^2 > 50\%$.

Results

Search results

The database search yielded 127 results, with 49 duplicate records removed. After title and abstract screening, a full-text review of the remaining 35 records was completed, and 28 reports were excluded, 26 of which were excluded based on insufficient data, most of which were poster presentations without complete data sets. A total of 6 randomized controlled trials (RCT), comprised of 1707 participants, are included in the review (see Fig. 1 PRISMA Flow Diagram) [19, 23–28].

Study characteristics

The 6 studies included in this systematic review were double-blinded, randomized controlled trials [19, 23–27]. Of the 6 studies, 2 focused on the efficacy of zuranolone in treating PPD [26, 27], while the other 4 focused on zuranolone in treating MDD [19, 23, 24, 27]. The primary outcome of all six RCTs was a change in HAM-D scores from baseline to day 15 [19, 23–27]. To capture those with moderate to severe MDD or PPD, all studies required baseline HAMD-17 scores of ≥ 22 [19, 23], ≥ 24 [24], or ≥ 26 [25, 26]. Kato et al. [27] included participants with baseline HAM-D scores < 25 and ≥ 25. Patient demographics and baseline HAM-D scores were comparable among experimental and control groups. In addition to HAM-D scores, all six studies analyzed multiple rating scales as sources of secondary outcomes (Table 1).

The treatment period for all studies was 14 days, in which one dose of either zuranolone or the placebo was given each night with fat-soluble foods to maximize absorption [19, 23–27]. Multiple dosing strategies included: 2 experimental groups, one taking a 20 mg dose and the other taking a 30 mg dose [19, 27]; 50 mg doses of zuranolone [24, 26]; and 30 mg doses of zuranolone only [23, 25]. The treatment drug was self-administered in five studies [19, 24–27], and inpatient for the first week to monitor for adverse effects in one study [23]. Participants on antidepressants prior to the study were permitted if they were on a stable regimen for at least 60 days [19, 24], or 30 days [23, 25, 26] in which doses could not be titrated during the active trial. Kato et al. [27] excluded any individuals from their study who had used an antidepressant within 14 days of beginning the trial.

All studies measured HAM-D scores and secondary outcomes at different predetermined intervals (See Fig. 2). Zuranolone or the placebo was given once daily from day 1 to day 14 of the trials, with the observational period beginning on day 15 for all studies included (See Table 2). Observation was continued through the measurement of primary and secondary outcome scores until day 42 [23, 24], 45 [25, 26], 57 [27], or 182 [19]. While Kato et al. [27] required participants to complete observation and subsequent HAM-D reports, participants were given the choice to voluntarily continue observation through HAM-D scores on days 71 and 99.

Risk of bias

Risk of bias was assessed through five domains using the Cochrane Risk of Bias tool (2.0) [21]. All 6 RCTs in this systematic review had overall low risks of bias.

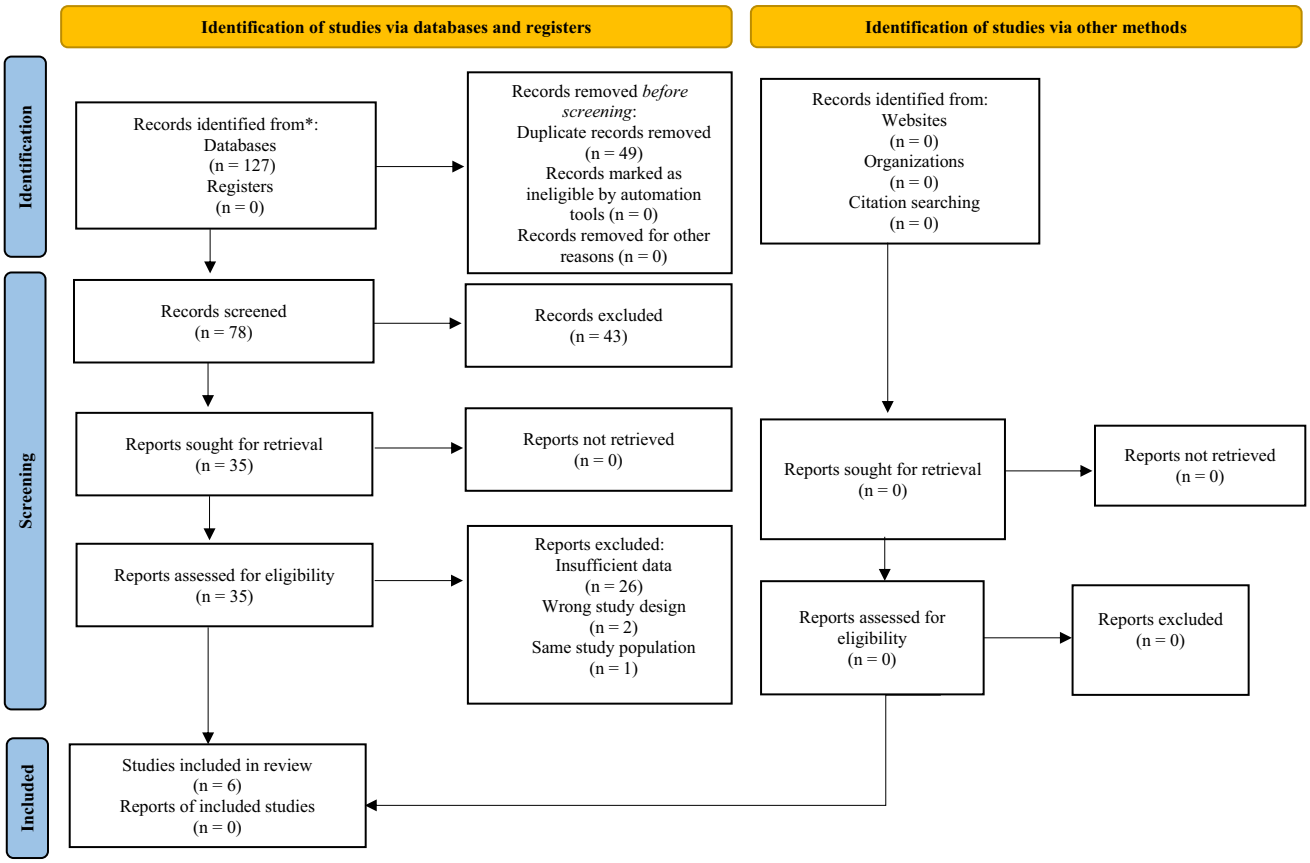

Fig. 1 PRISMA flow diagram

MDD pooled analysis

When pooling data from the 4 studies (See Fig. 3) that evaluated efficacy in MDD (with Clayton et al. & Kato et al. investigating both 20 and 30 mg doses), there was an overall significant decrease in HAM-D scores at 15 days versus placebo (MD −2.40, 95% CI −3.07 to −1.63; $p < 0.001$). When pooling data from the 2 studies (See Fig. 4) that evaluated efficacy in PDD, there was an overall significant decrease in HAMD-17 scores at 15 days versus placebo (MD −4.06, 95% CI −4.25 to −3.87; $p < 0.001$). There was a high degree of heterogeneity between MDD studies (I^2 of 99%), whereas there was a low heterogeneity ($I^2 = 0\%$) in the PPD studies.

Reduction in montgomery-Åsberg depression rating scale (MADRS) and Hamilton anxiety rating scale (HAM-A) scores

Of the 5 studies that examined depressive symptoms using the MADRS scale, all found statistically significant reductions in MADRS scores from baseline, 2 for PPD and 3 for MDD [19, 23–26]. Anxiety symptoms, assessed using the HAM-A, were significantly improved in three of the six RCTs, 2 for PPD and 1 for MDD [24–26]. However, for both, clinical significance was not consistently demonstrated.

Discussion

Statement of key findings

To the best of the authors' knowledge, this is the first systematic review and meta-analysis that evaluated the efficacy of zuranolone for both PPD and MDD. Overall, data analysis exhibits a statistically significant reduction of HAM-D scores; however, the clinical significance was mixed. Generally, a 50% reduction in HAM-D scores is considered a response to an intervention, and scores of < 7 are considered remission [29]. Unfortunately, only half of the studies on MDD yielded a response. According to Hengartner and Ploderl, the minimal clinical important difference (MCID) for the HAM-D is 3–5 points [30]. The HAM-D overall mean difference of −2.40 suggests there likely is not a clinically significant improvement in the treatment of MDD.

In contrast, both studies in the PPD analysis individually yielded a clinically significant response to zuranolone, and

Table 1 Study characteristics table

Baseline study characteristics												
Author(s)	N	Study design	Age (years)	Gender (M/F) (n)	Country	Depressive disorder	Intervention	Comparison	Concurrent antidepressant use	Primary outcomes	Secondary outcomes	Risk of bias
Clayton et al. [24]	537	RCT	18–64	185/352	USA	MDD	Zuranolone (50 mg) for 14 days	Placebo	Yes, if patients were on a stable dosage for 60 days prior to day 1 and agreed to continue on the stable dosage through day 42 29.5% of treatment group and 30.1% of placebo group used antidepressants	Change in HAM-D from baseline to day 15	CGI-S, CGI-I, MADRS, HAM-A	Low
Clayton et al. [19]	482	RCT	18 -65	143/339	USA	MDD	Zuranolone (20 mg or 30 mg) for 14 days	Placebo	Yes, if were on a stable dose for at least 60 days prior to day 1 and agreed to continue on the stable dose through day 42 28.3% of 30 mg treatment group, 28.9% of the 20 mg group and 31.2% of placebo group used antidepressants	Change in HAM-D from baseline to day 15	CGI-S, MADRS, HAM-A, CSFQ-14	Low

Table 1 (continued)

Baseline study characteristics												
Author(s)	N	Study design	Age (years)	Gender (M/F) (n)	Country	Depressive disorder	Intervention	Comparison	Concurrent antidepressant use	Primary outcomes	Secondary outcomes	Risk of bias
Deligiannidis et al. [25]	153	RCT	18–45	0/153	USA	PPD	Zuranolone (30 mg) for 14 days	Placebo	Yes, if taking a stable dose for more than 30 days prior to day 1 and delay the start/alteration of psychotropic treatment regimens until after the treatment period and day 15 assessments were completed 21% of the treatment group and 18% of the placebo group used antidepressants	Change in HAM-D from baseline to day 15	MADRS, HAM-A, CGI-I, BIMF	Low
Kato et al. [27]	250	RCT	18–75	106/143	Japan	MDD	Zuranolone (20 mg or 30 mg) for 14 days	Placebo	NO, patients were excluded if they used antidepressants within 14 days prior to the study	Change in HAM-D from baseline to day 15	HAM-A, CGI-S, PGI-I, PHQ-9 Bech-6*, Maier*	Low
Deligiannidis et al. [26]	196	RCT	18–45	0/196	USA	PPD	Zuranolone (50 mg) for 14 days	Placebo	Yes, if patients were on a stable for at least 30 days prior to the first study treatment dose 15.3% of the treatment group and 15.3% of the placebo group used antidepressants	Change in HAM-D from baseline to day 15	CGI-S, MADRS, HAM-A, EPDS, PHQ-9	Low

Table 1 (continued)

Baseline study characteristics												
Author(s)	N	Study design	Age (years)	Gender (M/F) (n)	Country	Depressive disorder	Intervention	Comparison	Concurrent antidepressant use	Primary outcomes	Secondary outcomes	Risk of bias
Gunduz-Bruce et al. [23]	89	RCT	18–65	34/55	USA	MDD	Zuranolone (30 mg)	Placebo	Yes, if receiving stable doses of antidepressants for at least 30 days prior to the first study treatment dose.27% of the treatment group and 23% of the placebo group used antidepressants	Change in HAM-D from baseline to day 15	MADRS, Bech-6*, HAM-A, CGI-I	Low

RCT = randomized controlled trial, MDD = major depressive disorder, PPD = postpartum depression, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery–Åsberg Depression Rating Scale, BIMF = Barkin Index of Maternal Functioning, EPDS = Edinburgh Postnatal Depression Scale, HAM-A = Hamilton Anxiety Rating Scale, CSFQ-14 = Changes in Sexual Functioning Questionnaire, HAM-S = Hamilton Somatization Rating Scale, SF-36v2 = Short Form-36v2 Health Survey, CGI-S = Clinical Global Impression—Severity Scale, CGI-I = Clinical Global Impression—Improvement Scale, PHQ-9 = Patient Health Questionnaire, PGI-I = Patient Global Impression of Improvement

*Bech-6 and Maier are subscales of the HAMD-17

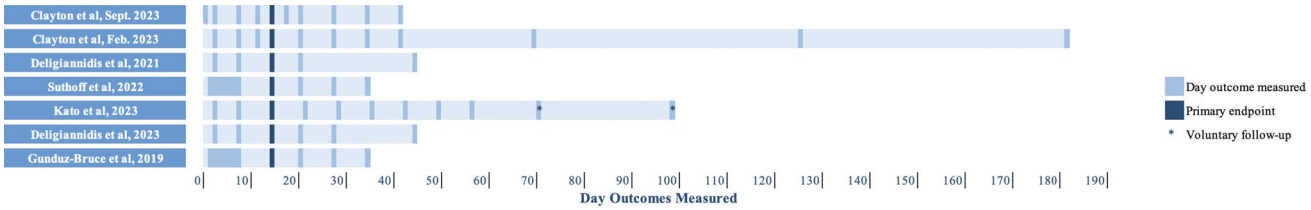

Fig. 2 Time intervals of primary and secondary outcome collection

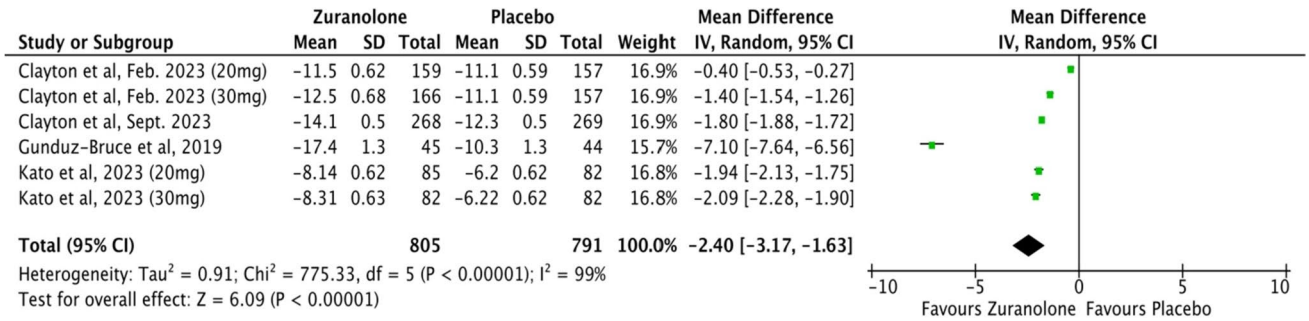

Fig. 3 Forest plot of change in HAM-D score from baseline to day 15 for MDD

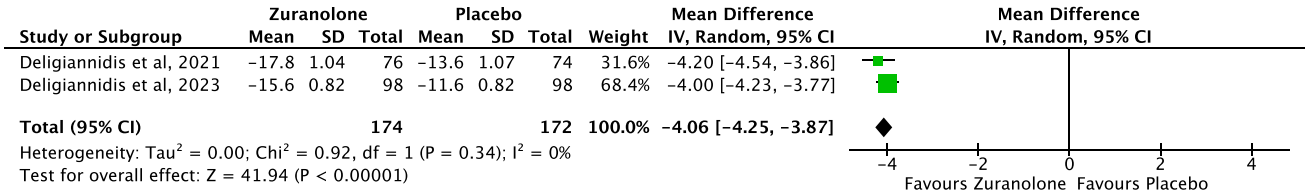

Fig. 4 Forest plot of change in HAM-D score from baseline to day 15 for PPD

the pooled mean difference of -4.06 indicates a clinically meaningful difference compared to placebo. While these pooled results have not yet been published, it is unsurprising to see why the United States Food and Drug Administration approved zuranolone for PPD but rejected its approval for MDD [31]. It is not clear why the repletion of allopregnanolone would be more effective in improving HAM-D scores in PDD versus MDD, though some have speculated there is a physiological difference in disease processes [16].

There are not yet any studies that directly compare zuranolone to brexanolone; however, the pooled reduction in HAM-D was similar to outcomes reported by Meltzer-Brody et al. [17]. The benefit of zuranolone is the simplicity of oral administration compared to an inpatient stay in the postpartum period. The other significant benefit is the rapid onset of its antidepressant effect, compared to the traditional first-line use of SSRI, where outcomes are typically measured 8–12 weeks after initiation [32].

While the aim of this review was not to compare zuranolone to other existing treatments for PPD, it is important to be mindful of these treatments and their limitations. Although those with moderate symptoms respond well to psychological treatments, such as Cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT), drawbacks include the time commitment required for regular therapy sessions and the potential for financial strain if not covered by insurance [12]. In addition, as previously noted, SSRIs and SNRIs have well-described side effect profiles, but their full impact can be delayed for 4–6 weeks, and treatment may not always be effective with lactation safety considerations, as well [8–10]. Finally, in regard to ECT, while it may be considered a treatment option for severe and refractory cases of PPD, more research is needed to understand better its efficacy, safety, and appropriate role in the management of this condition. It should be approached cautiously and only after careful consideration of all available treatment options and potential risks [13].

Table 2 Change from baseline to day 14 in HAMD-17

Change from baseline to day 15 in HAMD-17 score									
Author(s) and year	Depressive disorder	Baseline HAMD-17 (M ± SD)		Day 15 HAMD-17 (LSM [SE])		LSM Difference	95% CI	*P*-value	Result
		P	Z	P	Z				
Clayton et al. [24]	MDD	26.9 ± 2.7	26.8 ± 2.6	− 12.3 [0.5]	− 14.1 [0.5]	− 1.8	− 3.0 to–0.1	$p = 0.01$	Significantly lowered HAM-D score with Zuranolone compared to placebo
Clayton et al. [19]	MDD	25.8 ± 3.1	30 mg: 25.9 ± 2.9 20 mg: 25.8 ± 2.8	− 11.1 [0.59]	30 mg: − 12.5 [0.68] 20 mg: − 11.5 [0.62]	30 mg: − 1.4 20 mg:− 0.4	30 mg:− 0.40 to 0.06 20 mg: − 0.26 to 0.20	30 mg: $p = 0.116$ 20 mg: $p = 0.664$	HAM-D score was not significantly lowered in either Zuranolone 20 mg or 30 mg
Deligiannidis et al. [25]	PDD	28.8 ± 2	28.4 ± 2	− 13.6 [1.07]	− 17.8 [1.04]	− 4.2	− 6.9 to − 1.5	$P = 0.003$	Significantly lowered HAM-D score with Zuranolone compared to placebo
Kato et al. [27]	MDD	24.5 ± 2.1	30 mg: 24.6 ± 2.2 20 mg: 24.8 ± 2.4	− 6.22 [0.62]	30 mg: − 8.31 [0.63] 20 mg: − 8.14 [0.62]	30 mg: − 2.09 20 mg: − 1.92	30 mg:− 3.83 to − 0.35 20 mg: − 3.65 to − 0.19	30 mg: $p = 0.0190$ 20 mg: p = 0.0296	Significantly lowered HAM-D scores with both Zuranolone 20 mg and 30 mg compared to placebo
Deligiannidis et al. [26]	PPD	28.8 ± 2.3	28.6 ± 2.5	− 11.6 [0.82]	− 15.6 [0.82]	− 4.0	− 6.3 to − 1.7	$p = 0.001$	Significantly lowered HAM-D score with Zuranolone compared to placebo
Gunduz-Bruce et al. [23]	MDD	25.7 ± 2.4	25.2 ± 2.6	− 10.3 [1.3]	− 17.4 [1.3]	− 7.0	− 10.2 to − 3.9	$p < 0.001$	Significantly lowered HAM-D score with Zuranolone compared to placebo

M = mean, SD = standard deviation, LSM = least squares mean, SE = standard error, P = placebo, Z = Zuranolone

Strengths and weaknesses

A common limitation across all the studies included in the systematic review were small sample sizes, ranging from 89 to 537 participants, and overall short durations of the studies, ranging from 45 to 182 days in length [19, 23–27]. Due to the novelty of zuranolone, the long-term efficacy and safety of the drug are currently unknown, warranting trials with longer durations. The RoB2 tool deemed all six RCTs to have a low risk of bias. However, it is also important to consider conflicts of interest, as five of the RCTs received funding from zuranolone manufacturer

Sage Therapeutics, each with multiple authors working for and holding stock within the company [19, 23–26].

Many studies required a minimum HAM-D score as an inclusion criterion, resulting in most participants having severe MDD or PPD in this systematic review and meta-analysis; therefore, limiting the generalizability of the results to those with mild or moderate MDD or PPD [24]. Last, trials studying zuranolone primarily occurred during the COVID-19 pandemic, a time of isolation and increased depression. Due to this, the decrease in HAM-D scores could have been magnified due to participants feeling less isolated during the multiple in-person study visits.

Systematic review limitations

The limitations of this systematic review and meta-analysis are mainly surrounding the paucity of data. Substantially high heterogeneity was found within the MDD pooled analysis. A stepwise removal of studies was performed to identify causes of heterogeneity. Based on a visual inspection of the forest plot, we speculated that Gunduz-Bruce et al. was the likely cause; however, when removed, the I^2 remained at 99%. Additionally, authors pooled data at varying doses (ranging from 20 to 50 mg); however, even when analyzing only the same doses (e.g., 30 mg), the I^2 remained at 99%. Given the overall low risk of bias, we are unsure of the specific cause of heterogeneity. As only 2 relatively small RCTs examined the effect of zuranolone on PPD, it may be difficult to extrapolate data and generalize it to the greater public [25, 26]. An additional limitation was the lack of studies only examining the efficacy of zuranolone without additional antidepressants. Only one study excluded all patients who used psychotropic medications during the study period [27]. The rest included approximately 30% of participants with concomitant use of antidepressants during the study period (See Table 1). The rate of antidepressant use was similar between treatment and placebo; however, results were not stratified to compare potential differences.

Interpretation

While depressive symptoms of PPD are accurately measured by scales such as the HAM-D or MADRS, symptoms that are more specific for PPD can also be assessed by BIMF and EPDS scores. These scores were significantly improved with the treatment of zuranolone through day 45, which suggests a sustained impact on maternal functioning several weeks after the 14-day treatment. Indeed, across all scales measuring symptoms of depression (HAM-D, MADRS), anxiety (HAM-A), and PPD-specific symptoms (BIMF, EPDS), symptoms remained significantly reduced at day 45, indicating that the effect of zuranolone for PPD persists longer than the effect of zuranolone for MDD [25, 26]. Considering that zuranolone is not approved for breastfeeding as it has not been studied for safety; however, it would still preclude breastfeeding for that relatively short 14-day course. As for MDD, the effects of zuranolone were not significantly sustained past the 15-day period [19, 23, 24, 27], which may indicate the need for longer treatment periods or re-dosing strategies.

Adverse effects are frequently an issue in the treatment of depression. Sexual side effects, specifically sexual dysfunction (e.g., anorgasmia or decrease in libido), may cause many to be non-compliant with their recommended antidepressant regimen [33]. One in six women have reported some degree of sexual dysfunction while taking antidepressants, such as SSRIs, SNRIs, TCAs, and atypical antidepressants like bupropion [34]. Clayton et al. [19] analyzed the effect of zuranolone 30 mg on sexual dysfunction among men and women, in which neither sex reported an increase in sexual dysfunction from baseline while taking zuranolone or upon completing the trial. This is an important consideration when a clinician is weighing zuranolone as a treatment option.

Further research

While the 14-day course of zuranolone appears successful in reducing the depressive symptoms of PPD, it remains unknown as to whether the effects will be sustained beyond day 45, guiding future research to help leave those suffering from PPD with lasting remission. While there was marginal improvement for MDD during the treatment period, symptoms returned during the observation period. Due to the brevity of the effect and the lack of clinical significance, further studies examining longer durations or re-dosing strategies are needed to investigate if this is a viable option for MDD. One final limitation is that almost all the studies took place in the United States. Cultural factors play a significant role in the severity of PPD; thus, these results are likely not representative of all cultures [35]. As of February 2024, zuranolone is only commercially available in the United States. Given the global prevalence of postpartum depression and the apparent safety and efficacy of zuranolone, authors speculate that it will be of interest to the international community [36].

Conclusion

This systematic review and meta-analysis concludes that a once-daily, 14-day course of oral zuranolone causes a clinically significant decrease in HAM-D for PPD. Given

the novelty of zuranolone and short follow-up period, further research is needed to confirm these findings.

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References

1. Batt MM, Duffy KA, Novick AM, et al. Is postpartum depression different from depression occurring outside of the perinatal period? A review of the evidence. Focus (Am Psychiatr Publ). 2020;18:106–19.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
3. Zhang Q, Dai X, Li W. Comparative efficacy and acceptability of pharmacotherapies for postpartum depression: a systematic review and network meta-analysis. Front Pharmacol. 2022;13:950004.
4. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2021 National Survey on Drug Use and Health (HHS Publication No. PEP22-07-01-005, NSDUH Series H-57). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/report/2021-nsduh-annual-national-report. 2022. Accessed 09 Feb 2024.
5. la Torre JA, Vilagut G, Ronaldson A, et al. Prevalence and variability of current depressive disorder in 27 European countries: a population-based study. Lancet Public Health. 2021;6:e729–38.
6. Santomauro DF, Herrera AMM, Shadid J, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021;398:1700–12.
7. Park LT, Zarate CA. Depression in the primary care setting. N Engl J Med. 2019;380:559–68.
8. Machado-Vieira R, Baumann J, Wheeler-Castillo C, et al. The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments. Pharmaceuticals (Basel). 2010;3:19–41.
9. Depression: How effective are antidepressants? Inf. Internet, Institute for Quality and Efficiency in Health Care (IQWiG); 2020.
10. Suryawanshi O 4th, Pajai S. A comprehensive review on postpartum depression. Cureus. 2022;14(12):e32745.
11. DiGregory S, Githere N, Crites K, et al. The impact of COVID-19 on postpartum depression and the responsibility of the healthcare system. Cureus. 2022;14(8):e27805.
12. Stewart DE, Vigod SN. Postpartum depression: pathophysiology, treatment, and emerging therapeutics. Annu Rev Med. 2019;70:183–96.
13. Rundgren S, Brus O, Båve U, et al. Improvement of postpartum depression and psychosis after electroconvulsive therapy: a population-based study with a matched comparison group. J Affect Disord. 2018;235:258–64.
14. Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet. 2017;390:480–9.
15. Agis-Balboa RC, Guidotti A, Pinna G. 5α-reductase type I expression is downregulated in the prefrontal cortex/Brodmann's area 9 (BA9) of depressed patients. Psychopharmacology. 2014;231:3569–80.
16. Meltzer-Brody S, Kanes SJ. Allopregnanolone in postpartum depression: role in pathophysiology and treatment. Neurobiol Stress. 2020;12:100212.
17. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet. 2018;392:1058–70.
18. Treatment for PPD | ZULRESSO® (brexanolone) CIV n.d. https://www.zulresso.com/treatment. Accessed 09 Feb 2024.
19. Clayton AH, Lasser R, Nandy I, et al. Zuranolone in major depressive disorder: results from MOUNTAIN—a phase 3, multicenter, double-blind, randomized Placebo-Controlled Trial. J Clin Psychiatry. 2023;84:22m14445. https://doi.org/10.4088/JCP.22m14445
20. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org. Accessed 09 Feb 2024.
21. Higgins J, Thomas J, Chandler J, et al editors. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Chichester: John Wiley & Sons; 2019.
22. RevMan Web 2020. Rev Manag Web RevMan Web 2020. https://revman.cochrane.org/. Accessed 09 Feb 2024.
23. Gunduz-Bruce H, Silber C, Kaul I, et al. Trial of SAGE-217 in patients with major depressive disorder. N Engl J Med. 2019;381:903–11.
24. Clayton AH, Lasser R, Parikh SV, et al. Zuranolone for the treatment of adults with major depressive disorder: a randomized, placebo-controlled phase 3 trial. Am J Psychiatry. 2023;180:676–84.
25. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. JAMA Psychiat. 2021;78(9):951–9.
26. Deligiannidis KM, Meltzer-Brody S, Maximos B, et al. Zuranolone for the treatment of postpartum depression. Am J Psychiatry. 2023;180:668–75.
27. Kato M, Nakagome K, Baba T, et al. Efficacy and safety of zuranolone in Japanese adults with major depressive disorder: a double-blind, randomized, placebo-controlled, phase 2 clinical trial. Psychiatry Clin Neurosci. 2023;77:497–509.
28. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
29. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry. 1991;48:851–5.
30. Hengartner MP, Plöderl M. Estimates of the minimal important difference to evaluate the clinical significance of antidepressants in the acute treatment of moderate-to-severe depression. BMJ Evid-Based Med. 2022;27:69–73.
31. Mullard A. FDA approves first oral drug for postpartum depression, but rejects it for major depressive disorder. Nat Rev Drug Discov. 2023;22(10):774.
32. Frieder A, Fersh M, Hainline R, et al. Pharmacotherapy of postpartum depression: current approaches and novel drug development. CNS Drugs. 2019;33(3):265–82.
33. Ashton AK, Jamerson BD, Weinstein LW, et al. Antidepressant-related adverse effects impacting treatment compliance: results of a patient survey. Curr Ther Res Clin Exp. 2005;66:96–106.

34. Lorenz T, Rullo J, Faubion S. Antidepressant-induced female sexual dysfunction. Mayo Clin Proc. 2016;91:1280–6.
35. Bina R. The impact of cultural factors upon postpartum depression: a literature review. Health Care Women Int. 2008;29:568–92.
36. Wang Z, Liu J, Shuai H, et al. Mapping global prevalence of depression among postpartum women. Transl Psychiatry. 2021;11:543.